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LAS VEGAS, NEVADA

Scientific Highlights/Abstracts of Original Investigations

Abstracts by Title

Author Index

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Volume 23, Abstract Supplement #2
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14th Annual Meeting of the
Associated Professional Sleep Societies

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The 2000 Annual Meeting abstract supplement unites the Journal SLEEP and the science of the associated sleep professionals in a new and convenient format. As in past years, this special issue will include all abstracts to be presented at the 2000 APSS Annual Meeting, June 17-22, in Las Vegas, Nevada. The supplement will provide all members, including those unable to attend the meeting, a brief glimpse into the new ideas and fresh research, which the APSS Annual Meeting provides. Those who do attend the meeting should bring this supplement with them for use as reference. Additional abstract books will not be provided to members at the meeting.

The benefit of electronic technology allowed authors the advantage of reviewing their abstract submission as a PDF file, enabling them to see the abstract in supplement format and to make necessary edits before publication.

The abstracts listed herein are arranged to follow the final program of the 14th APSS Annual Meeting as closely as permitted. References have returned to the abstract publication with an allowable maximum of three per abstract. The index by author has been increased to include all authors of an abstract, rather than first author only. Abstracts accepted for poster presentation are located at the back of the supplement, arranged by category.

Readers will find two new categories created for this year's abstracts: 1) Molecular biology & genetics, and 2) Sleep disorders-movement disorders. Category designations reflect the abstract's category as follows:

A. Basic neuroscience
B. General physiology
C. Clinical pharmacology
D. Dreams
E. Circadian rhythms
F. Phylogeny
G. Pediatrics
H. Aging
I. Sleep & behavior
J. Sleep deprivation
K. Sleep disorders
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L. Sleep in medical disorders
M. Sleep in psychiatric disorders
N. Instrumentation & methodology
O. Sleep education
P. Molecular biology & genetics

The 14th Annual Meeting moves into the new century with a forum of fascinating research and exciting discoveries. Members of the American Academy of Sleep Medicine and the Sleep Research Society can look forward to great opportunities for sharing the latest ideas and technologies.

Thomas Roth, PhD
Editor-in-Chief

Index of Abstracts by Title

1718.A

Extracellular Single Unit Recordings of Dopaminergic Neurons in the Ventral Tegmental Area in Narcoleptic Dobermans

Nishino S, Honda K, Riehl J, Mignot E

Introduction: Using hypocretin receptor-2 (Hcrtr-2) mutated narcoleptic Dobermans, we have demonstrated that dopaminergic (DA) transmission is critically involved in the regulation of cataplexy and sleepiness.[1,2] Systemic administration or local perfusion into the ventral tegmental area (VTA) and substantia nigra (SN) of dopamine D2/3 agonists significantly aggravates cataplexy. Furthermore, perfusion of D2/3 agonists into the VTA, but not the SN, increases drowsy state.[2] Systemic administration of DA uptake inhibitors significantly promotes wakefulness, but has no effect on cataplexy.[1] The differential effects of DA uptake inhibitors on cataplexy and sleep may suggest that changes in activity in DA neurons are required for the exacerbation of cataplexy, while enhancement of terminal DA transmission is sufficient for mediating alerting effects. In the current study, we therefore recorded extracellular single units in the VTA in narcoleptic dogs during various vigilance states and noted any changes in their response to a D2/3 agonist to test this hypothesis.

Methods: Extracellular single unit recordings of neurons in the VTA were evaluated in 3 genetically narcoleptic Dobermans. Movable microdrives combined with 32 and 64µm microwires were positioned in the VTA (AP=11-13, L=1.5. H=6-8) in narcoleptic dogs implanted with electrodes for EEG, EOG and neck EMG. Dogs were freely-moving, and unit activity was continuously recorded during active wake, quiet wake or drowsy, slow wave sleep (SWS), REM sleep (REM), and cataplexy. Quinpirole (6 µg/kg i.v.), a D2/3 agonist, was administered during the recording in order to carry out pharmacological characterization of the recorded neurons.

Results: Twenty two neurons were recorded in the VTA region. The firing pattern and wave forms of these neurons were used to distinguish DA and non-DA neurons. Neurons showing either a high (>5/sec) or low (< 5/sec) firing rate during wake were observed. The duration of action potentials varied among the 22 neurons recorded. 12 low-firing units had long action potentials (2.47±0.1 versus 1.59±0.2 msec for low versus high firing units), and thus were presumed to be DA neurons. Mean firing rate of 12 DA neurons was slightly lower during drowsy and SWS versus wake or REM sleep, although this change was not statistically significant. In contrast, a consistent reduction (-41.7% from wake) in firing rate was observed during cataplexy. The effect of autoreceptor D2/3 modulation after administration of low doses of Quinpirole (6 µg/kg i.v.) induced a moderate reduction (-35.3% at wake) in the firing rate of neurons both during wake and cataplexy.

Conclusions: Our preliminary results indicate that DA activity in the VTA is reduced during spontaneous cataplexy. After autoreceptor stimulation (low doses of a D2/3 agonist), a manipulation known to trigger cataplexy, DA activity in the VTA was also reduced. In contrast, no significant reduction in firing was observed during REM sleep. Differences in firing during cataplexy and REM sleep, however, are consistent with our recent finding that the mechanism for induction of cataplexy is different from that for REM sleep,[3] and may suggest that the activity of VTA neurons is more specifically involved in the regulation of cataplexy than REM sleep. Hcrtr-2 are abundant in the VTA, while Hcrtr-1 are abundant in the locus coeruleus (Lu, personal communication). A lack of excitatory input to VTA DA neurons mediated by Hcrtr-2 may thus be critical for the induction of cataplexy.

References:

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Research supported by Research supported by NS 27710, NS23724 and MH01600.

1715.A

Microdialysis Perfusion of Histamine in Rat Basal Forebrain Increases Wakefulness

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Introduction: Considerable evidence implicates both the cholinergic and other neurons of the magnocellular regions of the basal forebrain (BF) and histaminergic neurons of the tubero-mammary nucleus (TMN) in the process of cortical activation that occurs during wakefulness. Single unit recording in unanaesthetized, naturally sleeping felines and rodents have shown that both the neurons in the cholinergic BF and the histaminergic neurons of the TMN exhibited highest discharge activity during wakefulness. The cholinergic zone of the BF is known to receive histaminergic projections from the TMN (Panula et al 1989). In vitro studies have shown that histamine excites the cholinergic neurons of the BF (Khateb et al 1995). Microdialysis studies done in our lab suggest that levels of extracellular histamine show alteration across behavioral states in the ventral forebrain region (Strecker et al 1999). It is thus possible that the histaminergic neurons excite the cholinergic and other neurons of the basal forebrain to induce wakefulness and cortical arousal. To test the role of histamine in the activation of the BF cholinergic zone neurons and arousal, we hypothesized that local perfusion of histamine in the cholinergic BF would induce arousal.

Methods: Adult male Sprague-Dawley rats were anesthetized for implantation of two bilateral guide cannulas for microdialysis probe along with standard sleep recording electrodes. These guide cannulas were targeted towards the cholinergic horizontal diagonal band (HDB) at coordinates : AP - 0.40; ML 1.8 and DV 9.0 according to Paxinos and Watson rat brain atlas. After post-operative recovery and habituation to the recording chamber, the microdialysis probe (CMA-11; 1 mm length, 0.24 mm diameter) was lowered through one of the guide cannulas. After 12 h of recovery from probe insertion, the experiments were begun. ACSF was continuously perfused while behavioral states were simultaneously recorded for 6 h (1100 h to 1700 h). The following day same protocol was followed except that histamine was perfused for 2 h (1300 h to 1500 h). Three different doses (100, 500 and 1000 µM) of histamine were used. Behavioral states were classified into 4 different states: active wakefulness (AW), quiet wakefulness (QW), slow wave sleep (SWS) and rapid eye movement sleep (REM). Once the experiment was completed the animals were sacrificed, the brain removed and histological analysis was performed to verify the perfusion site.

Results: Our initial data indicate that 1000 µM histamine perfused in the cholinergic HDB significantly increased both AW ($p < 0.04$) and QW ($p < 0.02$) during the perfusion period as compared with ACSF. There was a significant reduction in SWS ($p < 0.02$). REM showed no change. The analysis for 100 and 500 µM has yet to be completed.

Conclusions: Our data suggests that histamine acting on the BF cholinergic zone may play a role in regulating wakefulness and cortical arousal. This is highly compatible with in vitro work indicating histamine excites BF cholinergic neurons, although, since in vitro work has not yet addressed the question of histamine effects on noncholinergic neurons, we cannot be certain of the specificity of action on the cholinergic BF

population.

References:
(1) Panula P, Pirvola U, Auvinen S, Airaksinen MS: Histamine immunoreactive nerve fibers in the rat brain. Neuroscience 1989;28:585-610.
(2) Khateb A, Fort P, Pegna A, Jones BE, Muhlethaler M: Cholinergic nucleus basalis neurons are excited by histamine in vitro. Neuroscience 1995;69:495-506.
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Research supported by NIMH 39683; Dept vet. Aff.

1297.A

Microdialysis Perfusion of Serotonin into the Hypoglossal Motor Nucleus Increases Genioglossus Muscle Activity Across Sleep-Wake States in Freely Behaving Rats

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Introduction: Decreased genioglossus (GG) muscle activity in sleep predisposes to obstructive apneas, but the central mechanisms underlying the effects of natural sleep-wake states on GG activity are unknown. Serotonin (5-hydroxytryptamine, 5HT) excites hypoglossal motoneurons in neonatal tissue slices and decerebrate animals, and it has been suggested that sleep-related withdrawal of 5HT may reduce GG activity.[1] However, whether 5-HT at the hypoglossal motor nucleus modulates GG activity in natural sleep has not been tested. This study aims to develop an animal model to investigate neuromodulation of the hypoglossal motor nucleus in natural sleep, and test the hypothesis that 5HT applied to this nucleus will increase GG activity.

Methods: Seven rats were implanted with EEG and neck muscle electrodes to record sleep-wake states, and GG and diaphragm wires for respiratory muscle recording. Microdialysis probes were aimed at the hypoglossal motor nucleus with sites verified by histology. Studies were performed >5 days after surgery with probes perfused with artificial cerebrospinal fluid (ACSF, pH=7.4) or 10-50mM 5HT. In two separate rats, 10ul of a 10% solution of the fluorescent tracer tetramethylrhodamine-dextran-lysine was microinjected into the tongue (in the same region as the GG electrodes) for back labeling of hypoglossal motoneurons. Further studies were also performed in urethane-anesthetized, tracheotomized and vagotomized rats while recording EEG, GG and diaphragm activity, blood pressure and end-tidal CO2. In these anesthetized rats, responses to microinjection of 5-HT (100nl in 1 min, 5mM, 5 injections in 3 rats), and saline into the hypoglossal motor nucleus were recorded.

Results: Stereotypical motor acts such as licking, grooming and chewing were associated with phasic GG activation in the behaving rats. However, respiratory-related GG activity was rarely observed in these conscious rats although it was typically recorded at the time of surgery. Nevertheless, retrograde florescent labeling of motoneurons in ventral regions of the hypoglossal motor nucleus confirmed that the GG electrodes were placed at sites innervated by GG motoneurons. During control ACSF perfusion, normal decreases in GG activity occurred in non-REM and REM sleep compared to waking (decreases =56.9 to 75.8 %, $p<0.02$). Marked GG activation occurred in non-REM and REM during 5-HT microdialysis (increases =185.6 to 321.7% compared to ACSF, $p<0.04$). Sleeping GG activity during 5HT was similar ($p>0.27$) to waking levels before 5HT. Responses were specific to GG muscle as diaphragm amplitude was unchanged by 5HT across sleep-wake states ($p>0.57$). Further studies in the anesthetized rats confirmed that 5-HT applied to the hypoglossal motor nucleus caused marked increases in GG activity ($p<0.05$) and that the responses were specific as no change in diaphragm, respiratory rate, end-tidal CO2 or mean blood pressure occurred (all $p>0.240$). Saline microinjections produced no change in the measured parameters.

Conclusions: The results show that 5HT delivery to the hypoglossal motor nucleus increases GG activity in freely behaving rats, and can increase GG activity in sleep to waking levels. The results from anesthetized rats confirmed that the 5HT responses were specific to GG as there were no changes in respiratory pump muscle activity, breathing pattern, CO2 levels or blood pressure. Since loss of GG activity in sleep predisposes to obstructive apneas, this animal model using in-vivo microdialysis of the hypoglossal motor nucleus will be important in determining the neuronal mechanisms underlying control of pharyngeal muscles in natural sleep.

References:
(1) Kubin L, Tojima H, Davies RO, Pack AI. Serotonergic excitatory drive to hypoglossal motoneurons in the decerebrate cat. Neurosci Lett 1992;139:243-8.

Research supported by Medical Research Council of Canada, Canada Foundation for Innovation and Ontario Thoracic Society

1344.A

Serotonergic Dorsal Raphe REM-off Cells Reduce Discharge but do not Shut Off During Cataplexy

Wu MF, John J, Nguyen GB, Siegel JM
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Introduction: Cataplexy, a sudden loss of muscle tone triggered by strong emotions, is one of the defining symptoms of narcolepsy. It has been hypothesized that this is due to the activation of the REM sleep atonia mechanism in waking. Two groups of brainstem neurons, the locus coeruleus (LC) and the raphe nuclei, cease activity specifically in REM sleep. We found that LC neurons cease discharge in cataplexy (Wu et al., 1999), suggesting that at least part of the REM sleep mechanism is recruited in this state. The present study shows that, unlike LC neurons, serotonergic dorsal raphe cells behave differently in cataplexy and REM sleep.

Methods: Cells were recorded from dorsal raphe nucleus of four narcoleptic Doberman Pinschers using microwire recording techniques (Wu et al., 1999). The dogs were free to move around the chamber during the recording. The discharge profile for each cell was established across sleep/wake cycles and during cataplexy. Cells were identified as serotonergic based on the location, REM-off discharge pattern, tonic waking activity, response to 8-OH DPAT and spike waveform (e.g., Fornal & Jacobs, 1988).

Results: One hundred and eight cells have been recorded. Among them, sixteen were "REM-off". These cells had slow and regular activity in waking, reduced activity in non-REM sleep and complete or near complete cessation of discharge in REM sleep. Mean rates were AW: 1.29; QW: 0.90; non-REM: 0.35; REM: 0.09. 8-OH DPAT, a 5HT1A agonist (8 μg/kg, i.v.), greatly reduced (>75%) the spontaneous activity of all REM-off dorsal raphe cells. These cells had longer spike width compared to adjacent cells of different types (1.8±0.1 vs. 1.2±0.1 msec). Unlike the LC neurons, which cease discharge both in REM sleep and cataplexy, dorsal raphe REM-off cells did not shut off during cataplexy,

but rather, maintained an intermediate activity of on average 36% of their active waking level. Prazosin, an α1 antagonist (0.5 mg/kg, p.o.), that exacerbates cataplexy, reduced spontaneous waking activity of these cells by an average of 32%.

Conclusions: Serotonergic neurons in the dorsal raphe have been implicated in arousal, REM sleep and motor control. The fact that serotonergic neurons remain relatively active during cataplexy but cease activity in REM sleep suggests that discharge in these cells is linked to a phenomenon that differs between REM sleep and cataplexy. We have shown that presumed histaminergic REM-off cells in the posterior hypothalamus also maintain activity during cataplexy (John et al., 1998). The continued activity of histaminergic and serotonergic REM-off cells during cataplexy suggests that they may be linked to the maintenance of consciousness or other factors that differ in REM sleep and cataplexy.

References:
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(2) John J, Wu M-F, Phan B, Siegel JM: Cataplexy related neurons in the posterior hypothalamus of the narcoleptic dog. Soc. Neuro. Abst. 1998; 24:14.
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Research supported by NS 14610 and the VA.

1399.A

Monoamine Release in Medial Medulla-Induced Muscle Tone Suppression: An in Vivo Dialysis Study

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Introduction: Activation of portions of the pontomedullary reticular formation has been shown to induce global inhibition of skeletal muscle tone. Electrical stimulation in the rostromedial medulla (RMM) induces atonia, whereas lesion to it produces REM sleep without atonia. Motoneuron pools receive input fibers from RMM as well as from noradrenergic and serotonergic cell groups in the brainstem. In the present study, we demonstrate that norepinephrine release in the hypoglossal (XII) nucleus and spinal ventral horn is decreased during RMM stimulation-induced atonia in the decerebrate cat.

Methods: Experiments were performed on 4 male and 5 female adult cats. Cats were decerebrated at the pre-collicular-post-mammillary level under halothane anesthesia. Electromyograms (EMGs) were recorded from the neck (occipitoscapularis and splenius), palatoglossal, genioglossus, diaphragm and gastrocnemius muscles with bipolar electrodes. Microdialysis probes were inserted into the XII nucleus (Type A-1-02, EICOM, Kyoto) and the spinal ventral horn (59-7005, Harvard Apparatus, South Natick, MA) 2 hours before the sampling. Three hundred msec trains with 100 Hz, 0.2 msec and 10-40 uA rectangular cathodal pulses were delivered into the RMM through a stainless steel microelectrode (A-M Systems, 5710) once every 10 sec over a period of 5 min. Ten microliters of dialysate were collected from the XII nucleus and spinal cord during 5 minutes pre-stimulation, stimulation and post-stimulation periods. The collecting polyethlene tubing was kept at 10 C and the dialysate stored at -80 C. The monoamine (norepinephrine; NE and serotonin; 5HT) levels in the perfusate were determined by a high-performance liquid chromatography (HPLC) with electrochemical detection (450 mV) system (DTA-300, EICOM). The detection limit of our analysis system was 0.5 fmol per 20 ul injection.

Results: Electrical stimulation of the RMM suppressed activity in all muscles recorded. The same stimulation elicited a significant decrease in NE (XII nucleus: $p<0.05$, df = 36, t-test; spinal cord: $p<0.01$, df = 52, t-test), but not in 5HT (XII nucleus: $p>0.3$, df = 30, t-test; spinal cord: $p>0.2$, df = 44, t-test) release in both XII nucleus and spinal cord.

Conclusions: Prior studies have demonstrated that stimulation of RMM produces active inhibition of motoneurons. Our present study found that NE, but not 5HT, release in the hypoglossal nucleus and spinal cord was significantly decreased during RMM stimulation-induced muscle tone suppression. We suggest that RMM-induced muscle tone suppression may be partially mediated through inhibition of noradrenergic neuronal activity and consequent disfacilitation of motoneurons. Thus, RMM induced muscle tone suppression appears to be linked to a combination of inhibition and disfacilitation.

This work supported by HL41370 and HL 60296.

1699.K3

Electrophysiological Analysis of the Sleep Onset Period (SOP): A Comparison Between Subjects with Long Term Insomnia Complaints Associated with Mild Traumatic Brain Injury and Matched Controls

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Introduction: While many believe that symptoms of post concussion syndrome (PCS) following mild traumatic brain injury (MTBI) resolve within 6 to 12 months, survey studies have been successful in determining that persistent insomnia complaints remain present in the MTBI population for much longer periods. As no study had previously done so, the purpose of the current undertaking was to study the electrophysiological properties of sleep and sleep onset within the population of MTBI with persistent sleep onset insomnia complaints. Analyses of standard polysomnographic (PSG) sleep parameters were conducted in order to determine any differences between normal controls and the MTBI group in terms of sleep architecture. Furthermore, Power spectral analyses were conducted over the SOP in order to determine whether the sleep difficulties associated with MTBI could be best characterised by an altered electrophysiological sleep onset signature, or by increases in variability of the power spectral data.

Methods: Data were collected from 9 individuals who had sustained a MTBI 8 months to 5 years earlier and reported sleep difficulties that had arisen within the month subsequent to injury and persisted to the present. The control group consisted of 9 individuals who had experienced neither sleep difficulties, nor MTBI. Previous to spending 3 consecutive uninterrupted nights in the sleep lab, subjects completed a two week sleep log as well as questionnaires regarding sleep difficulties, adaptive functioning, and personality.

Results: The questionnaire data confirmed the presence of a constellation of PCS symptoms including changes in adaptive functioning, psychiatric complaints, and disordered sleep, specifically related to sleep onset latency and sleep quality. The objective PSG data also confirmed the presence of sleep difficulties within the MTBI group. Sleep onset latency was significantly longer ($t(16)= 2.25$, $p=.039$) and sleep efficiency was significantly lower ($t(16)= 2.61$, $p=.019$) in the MTBI group as compared to the controls. The only group difference that was found for mean power over the SOP was within the beta frequency ($F(1,16)=5.59$, $p=.031$, $\eta 2=.26$) (MTBI group associated with lower cortical arousal than controls). However, consistent and strong group differences were found in the variability of power over the SOP and across all sites (C4, F4, and O2) within the delta ($F(1, 16)=9.22$, $p=.008$,

η2=.37), theta (F(1, 16)=6.84, p=.019, η2=.30), sigma (F(1, 16)=10.54, p=.005, η2=.40), and beta (at site O2 only) (F(1.96, 31.29)=7.82, p=.002, η2=.33) frequency bands such that the MTBI group demonstrated greater variability than controls.

Conclusions: Reports of persistent insomnia-like sleep difficulty subsequent to MTBI was confirmed for the first time by objective physiological measures. This phenomenon is characterized electrophysiologically, by oscillations in arousal level that are greater than normal. As variability in power reflects the magnitude of oscillations in arousal, the results provide a potential mechanism for understanding the sleep pathology found in MTBI. That is, greater variability of power over the SOP may result in conditions that are incompatible with rapid sleep onset.

This work was supported financially by a grant from The Ontario Neurotrauma Foundation and The Government of Ontario that was co-ordinated by The Rick Hansen Institute. It was also supported by a NSERC operating grant to R.D. Ogilvie.

1065.K3

Impaired Cognitive Function in Insomniacs vs. Normals

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Introduction: Performance deficits in chronic insomniacs have been difficult to document, although there is some evidence that, compared to normals, insomniacs perform worse on tests of semantic memory, digit span, reaction time, and body sway.[1,2] This study compares cognitive function of 35 matched pairs of insomniacs and normals.

Methods: Insomniacs were selected from 161 chronic insomniacs participating in an hypnotic study.[3] Matched normals were taken from 50 individuals recruited for the purpose of this study. 35 pairs were matched for age and education level. The final groups consisted of 25 female and 10 male insomniacs (mean age 43.6y), and 27 female and 8 male normals (mean age 43.5y). For the insomniacs, only baseline data were used for comparison with normals. Subjects were screened clinically for medical, psychiatric, and sleep disorders. Insomniacs met criteria for DSM-IV primary insomnia. After confirmation of disturbed sleep (insomniacs) or normal sleep (normals) by one week of home sleep diaries, subjects completed the following test battery selected to span a number of cognitive abilities (see Table): Porteus Mazes (PM), Optimal Telegram (OT), Wechsler Memory Scale III subtests: Letter Number Sequencing (LNS), Spatial Span (SS), Digit Span (DS), Verbal Paired Associates (VPA), and Logical Memory (LM). Group differences were evaluated by three sets of MANOVAs: one for PM and OT data, one for VPA data, and one for LNS, SS, and DS data. Variables within each of these sets which did not meet parametric assumptions (OT score, VPA retention) were analyzed separately by Kruskal-Wallis tests. LM data were analyzed with repeated measures ANOVAs, except for LM retention which was analyzed by t-test.

Results: Group differences were found for all 3 MANOVAs; significance levels reported in the table refer to the univariate F tests for each variable in the models. Insomniacs differed from normals in all tests except for VPA retention,VPA slope, LM recall, and the less complex working memory tests (SS forward, DS). Exploratory MANOVAs in a larger sample of insomniacs (N=141) revealed that neither subjective total sleep time ($F(5,134) = 1.873$, $p = .103$) nor sleep quality ($F(5,135) = 1.979$, $p = .086$) were predictive of cognitive performance.

Conclusions: Insomniacs performed worse than normals on overall learning (VPA recall), complex working memory (LNS, SS backward), and planning and problem solving (PM, OT score). They were equivalent to normals in less-complex aspects of working memory and learning rate as well as most measures of logical memory. Although insomniacs were less accurate on the OT they completed the task faster than normals, possibly suggesting some degree of impulsivity. Clearly, future research should focus on causal factors of cognitive impairment in insomniacs.

Table 1

Variable	Cognitive Ability	Insomniacs	Normals
PM test age	planning, problem solving	14.6 **	15.8
PM score	precision of execution (higher score = less precise)	56.4 **	38.5
OT time	speed of problem solving	139.1s *	163.0s
OT score	accuracy of problem solving	4.1 **	5.6
LNS	alphanumeric organization, working memory	11.3 **	13.3
SS forward	simple visuo-spatial working memory	8.6	9.2
SS backward	complex visuo-spatial working memory	6.6 **	8.5
DS forward	simple auditory working memory	10.8	11.5
DS backward	complex auditory working memory	7.4	8.3
VPA recall	immediate memory	19.8 *	24.3
VPA slope	learning rate	4.1	3.6
VPA retention	delayed recall	94.2%	98.3%
LM recall	auditory immediate recall (2 tests)	14.2, 11.9 +	15.3, 13.9 +
LM theme	thematic recall (2 tests)	5.7, 5.5	6.1, 6.1
LM retention	auditory delayed recall	83.0% *	90.1%

group difference: * p < .05; ** p < .01; time difference: + p < .01

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1047.K3

Where In The Brain Is Insomnia? A First Look With NREM sleep [18F]FDG PET/Spectral EEG Sleep Studies

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Introduction: Clinical and electrophysiologic studies suggest that patients with insomnia suffer from a dysfunctional arousal that prevents the occurrence of restorative sleep. Increased higher frequency beta EEG activity has been associated with insomnia. It remains unclear, however, if there are certain brain structures that may be responsible for the abnormal production of this higher frequency EEG activity. Basic science studies suggest that the brainstem, basal forebrain and thalamocortical networks are likely mediators of dysfunctional arousal although it is not clear if these structures are functioning abnormally in insomnia, or whether other forebrain structures that interact with these arousal centers are responsible for clinical insomniac complaints. As an initial look at this question, we correlated high frequency beta activity during NREM sleep with cerebral glucose metabolism in the same NREM period in healthy subjects who had varying subjective assessments of the quality of their sleep. If beta frequency power is a correlate of a cortical arousal process related to insomnia complaints, then this study may identify forebrain structures that may contribute to abnormal arousal in insomnia.

Methods: Nine healthy subjects underwent concurrent EEG sleep studies and [18F]2-fluoro-2-deoxy-D-glucose ([18F]FDG) PET scans during

their first NREM period of sleep. They completed sleep quality visual analog scales. A PET scan was performed during NREM sleep. PET studies used a 4-6 mCi dose of [^{18}F]FDG. The time of injection was either 5-7 minutes following the identification of the first sleep spindle (6 subjects) or after 20 minutes from sleep onset (3 subjects). Spectral analyses of the sleep EEG during the first 20 minutes of NREM sleep [^{18}F]FDG uptake was performed. For the current analysis, we examined the beta frequency range of 20-32 Hz. Statistical parametric mapping was used to identify brain structures where there was a relationship between beta power and relative regional cerebral glucose metabolism (rCMRglu) during NREM sleep.

Results: Beta power negatively correlated with the composite measure of subjective sleep quality. Correlations between beta power and relative cerebral glucose metabolism during NREM sleep were found in the ventromedial prefrontal cortex, bilaterally, and the right lateral inferior occipital cortex.

Conclusions: These functional neuroanatomic findings suggest an important role for the ventromedial prefrontal cortex in mediating the arousal that is associated with poor sleep quality. Prior functional neuroanatomic studies of human NREM sleep (Maquet et al., 1997; Hofle et al., 1997; Braun et al., 1997) have shown that the occurrence of NREM sleep was associated with reductions in ventromedial prefrontal cortex function. Anatomically, the ventromedial prefrontal cortex has widespread connections with a distributed ascending activating system including the pontine reticular formation, basal forebrain, amygdala, hippocampus, temporal pole, insula, cingulate cortex and parahippocampal gyrus, placing it in a position to integrate limbic-paralimbic afferents with those coming from more higher order association cortex and subsequently influence motivational, emotional and arousal systems in the brain. Increased function in the ventromedial prefrontal cortex has been found in other disorders that are characterized by heightened dysphoric arousal, such as depression, obsessive-compulsive disorder and post-traumatic stress disorder. Increased beta power is thought to be associated with the persistence of higher order cognitive processing in the wake/sleep transitional difficulties of insomniacs (Perlis et al 1998), a cognitive process that may reside in the ventromedial prefrontal cortex. Behaviorally and anatomically, therefore, the ventromedial prefrontal cortex may play a fundamental role in mediating the persistence of cognitive arousal that prevents the natural occurrence of restorative sleep.

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1792.K3

Fast Frequency EEG Activity in Patients with Insomnia and in Good Sleeper Controls

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Introduction: Several studies have shown that patients with insomnia exhibit elevated levels of Beta EEG activity at or around sleep onset and during NREM sleep.[e.g. 1,2] Beta activity has also been shown to vary with nonpharmacologic treatment.[3] These data suggest that Beta activity, or processes associated with it, may be directly related to the pathophysiology of insomnia. In the present study, we evaluate 1) the extent to which fast frequency EEG activity is limited to the 14-30 Hz frequency domain and/or to patients with primary insomnia and 2) whether Beta and/or Gamma activity are associated with discrepancies between subjective and PSG measures of sleep continuity.

Methods: Three groups (n=9 per group) were evaluated: Primary Insomnia, Major Depression, Good Sleeper Controls (no history of psychiatric/sleep disorders). Groups were matched for age, sex, height and weight. The sample was 66% female and the mean age was 37.5 (± 10.7). Subjects spent at least two nights in the sleep laboratory and completed sleep diaries each morning. PSGs included 2 EOGs, 6 EEGs and a submental EMG. All records were scored in 30 second epochs according to Rechtschaffen and Kales criteria. Electrophysiologic signals were acquired using AC amplifiers at a gain of 3.75 μV/mm (x 20K) for an initial bandwidth of 0.3-1000Hz. EEG signals were also passed in series to bandpass filters (48dB/octave) set at 0.25-125Hz. Digital acquisition was governed by Stellate Harmonie™ software and accomplished by a BSMI 519 AD board. The base sampling rate was 512Hz. On-line decimation was used to reduce the EEG sampling rate to 256Hz. The Digital EEG from night 1 was subjected to power spectral analyses. In the present analyses, 3 fast frequency bands were evaluated for average C3 and C4 activity for Beta-1 (14-20Hz), Beta-2 (20-35Hz) and Gamma (35-45Hz). Average profiles were created for each NREM cycle after removing waking & movement epochs and epochs containing micro- or mini-arousals. NREM cycle data were averaged. Groups were compared using one-way ANOVAs and post hoc Duncan tests. Pearson correlations for the entire sample were used to assess the association of high frequency EEG activity with subjective - objective discrepancy scores for total sleep time (difference scores between subjective report and PSG measures).

Results: Groups differed for average NREM activity for all 3 fast frequency bandwidths (Beta-1, $p < .0005$; Beta-2, $p < .0005$; Gamma, $p < .01$). Subjects with insomnia exhibited significantly more Beta-1, Beta-2 and Gamma activity than subjects with MDD or good sleeper controls. The MDD Ss and good sleepers did not differ from each other. Correlational analyses revealed that average NREM Beta-1 and Beta-2 activity were significantly correlated with subjective-objective discrepancies for total sleep time (Beta-1 & Beta-2: $r = -.46, p < .02$). Gamma activity was not significantly correlated with the discrepancy scores.

Conclusions: Our results confirm that Beta activity is increased in Primary Insomnia. Moreover, increased Beta activity during NREM sleep appears to 1) occur preferentially in patients with Primary Insomnia (vs secondary insomnia) and 2) be negatively associated with the perception of sleep.

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1868.K3

The Impact of Activity Upon Spectral EEG Parameters

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Introduction: One common finding in patients with insomnia is increase in higher frequency EEG activity. This increase was initially attributed to increased physiological activation. More recently, it has

been suggested that this EEG change may be related to increased mental content in insomniacs. However, the finding of more high frequency EEG activity in patients with insomnia may only reflect increased muscle activity contributing to the spectral data. In this study, the impact of several manipulations including physiological arousal and EMG activation upon spectral EEG measures was examined.

Figure 1

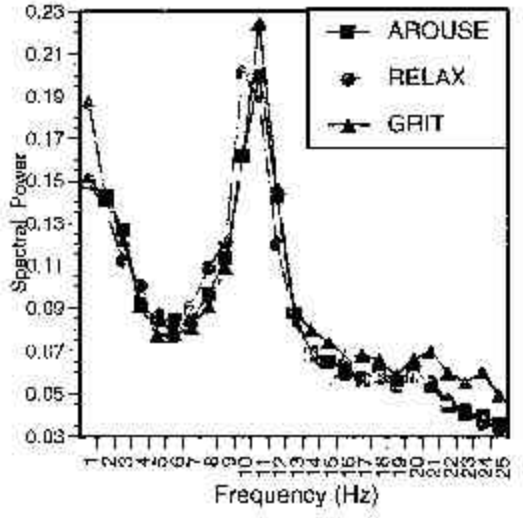
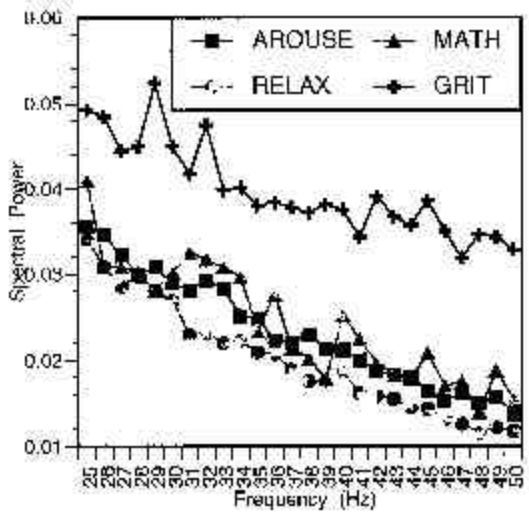


Figure 2



Methods: Thirteen normal sleeping young adults (age 25) had a normal night of laboratory sleep followed by two-hours of EEG data collection on the next evening. After standard calibrations, Ss performed eyes open and eyes closed maneuvers in the following conditions: 1) Initial (performed immediately after calibrations); 2) Following sitting up and lying down (SIT); 3) Following standing up and lying down (STAND); 4) Following a 5-min. walk around the building (WALK); 5) During a 5-min. mental subtraction task (MATH); 6) During I-min. of gritting teeth (GRIT); and 7) During a I-min. fist clench fist (CLENCH). Observations were performed during or immediately after manipulations (AROUSED) and repeated about 10 min. later (RELAXED). All EEG/EOG channels and heart rate were digitized at a sampling rate of 500 Hz and stored for later analysis. Data samples for the current study consisted of 5-sec samples from 0 1 -A2. Artifact-free samples were chosen about midway within sample windows for each condition.

Results: The major spectral analysis data are plotted in the Figures. Condition effects are most notable in Figure 2. A significant increase in power is clear in the GRIT condition in the range from 24 - 50 Hz. However, smaller but still significant increases in power were also seen in the AROUSED (Mean of Conditions 1-4) compared to RELAXED Conditions (significant at 26, 33, 36,40-42, 44, 46, and 48-49 Hz). MATH did not differ from the AROUSED data. Heart rate was significantly increased during the GRIT and CLENCH Conditions (4.6 and 5.4 bpm elevations compared to RELAXED values).

Conclusions: Consistent increases in spectral power were found during and after conditions producing arousal. The wide frequency band of changes is consistent with the previous literature which suggests increases in higher frequencies associated with increased arousal. In this study, gritting teeth produced large changes in spectral high frequency power in the same range as produced by the other manipulations. The most parsimonious explanation for such data is that the increased high frequency activity associated with various forms of arousal is not a specific cortical activity. The pattern of heart rate results is similar to that seen for the high frequency EEG spectral power analyses. This implies that while increased high frequency spectral EEG power is not necessarily a sign of increased cortical activity, it may still be a sign of increased CNS arousal, although the mechanism may be through increased muscle tension.

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1116.K1

The Use of a Nasal Cannula/Pressure Transducer System in the Detection of RERAs

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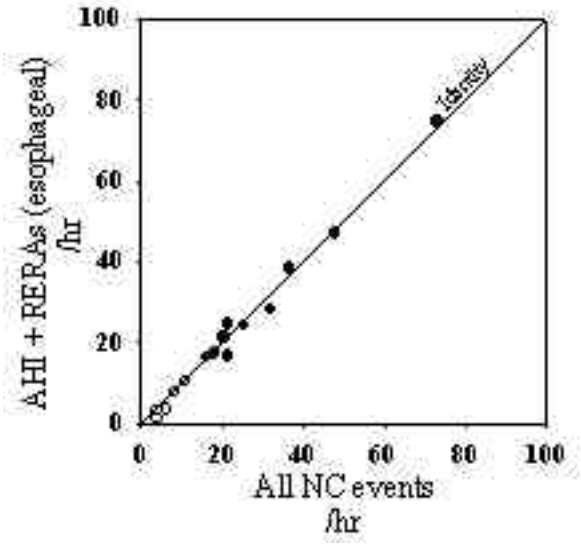
Introduction: Recently published AASM[1] guidelines approve use of a nasal cannula/pressure transducer system (NC) for detection of apneas/hypopneas, but require use of esophageal manometry to detect Respiratory Event Related Arousals (RERAs). In addition, we have shown that NC provides an inspiratory signal whose flattened shape suggests the presence of flow limitation and elevated upper airway resistance.[2] It has been our experience that esophageal manometry is poorly tolerated by many subjects (especially with mild sleep disorders); it would be desirable to use a non-invasive technique for detecting RERAs. The present study tests the hypothesis that detecting NC flow limitation events identifies the same events classified as RERAs using esophageal manometry.

Methods: 10 UARS/OSAS and 5 normal subjects underwent full NPSG. Airflow was measured using a nasal cannula/pressure transducer system; effort was measured using esophageal manometry. Events on the NC signal (esophageal pressure hidden) were identified by 2 scorers. Apneas, hypopneas (flow amplitude below 50% of baseline for >10 sec) or flow limitation events (>2 breaths with an inspiratory plateau followed by a return to normal shape/amplitude) were tabulated; differences in scoring were then reconciled. In a separate scoring pass, esophageal pressure events (NC signal hidden), defined by a crescendo pattern of negative inspiratory pressure swings lasting >10 seconds followed by a rapid decrease to baseline pressure, were identified by 2 other scorers, tabulated and reconciled. ASDA arousals were scored in a third pass. We assessed interscorer reliability and NC/esophageal agreement based on the total number of events (without and then with arousal) and based on event-by-event overlap.

Results: Agreement between scorers was high for the number of respiratory events on the NC (1962 vs. 2251 events, ICC = 0.96). Agreement between scorers was also high for #events on the esophageal signal (1717 vs 1778 events, ICC = 0.96). The total number of reconciled events scored on NC (irrespective of arousal) was slightly higher than the number on esophageal manometry (bias = 4.5/hr, 95%CI 1.0-7.9). When the analysis was restricted to number of NC flow limitation events terminated by arousal compared to number of manometry events terminated by arousal (RERAs), there was no statistically significant difference (bias 0.9/hr, 95%CI -0.3-2.0). Using esophageal manometry as a gold standard, the event-by event sensitivity of NC was 0.88 (95%CI, 0.86 to 0.89) and the selectivity was 0.77 (95%CI, 0.75 to 0.79).

Figure 1



Conclusions: The nasal cannula/pressure transducer system can be used to detect those events classified as RERAs by esophageal manometry. If one follows the recommendations proposed by the AASM taskforce, the nasal cannula (which detects apnea, hypopnea and flow limitation events) thus provides a single, non-invasive and reliable tool for detection of the full range of sleep disordered breathing events.

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1800.K1

Prediction of Esophageal Pressure Elevations by Crescendo Snoring Patterns

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Introduction: Although the symptoms of upper airway resistance syndrome (UARS) overlap those of OSAS, the polysomnographic features of UARS are distinct. UARS is characterized by decreases in the cross-sectional size of the upper airway lumen, producing an increased negative-peak end-inspiratory pressure, which accompanies an increase in inspiratory effort typically leading to arousals. Increases in esophageal pressure, as measured by an esophageal catheter or balloon, confirm the UARS diagnosis, although less-invasive methods relying on measures of inspiratory flow contour changes, phase angle, pulse transit time, systolic blood pressure profile, or forced oscillation have been used. Laboratories without these measures typically rely on crescendo snoring patterns culminating in arousals as an indication of UARS. The present study assesses the predictive value of this technique compared to measurements of esophageal pressure.

Methods: Eight polysomnograms recorded using the Sandman NT (Mallinckrodt Inc., Hazelwood, MO) System were blindly selected. The recordings each consisted of a standard polysomnographic montage in addition to measurement of esophageal pressure. Crescendo snoring and esophageal pressure patterns were each defined as successive breath-to-breath increases in magnitude culminating in an arousal. A true positive (TP) was defined whenever both patterns simultaneously occurred. A false positive (FP) was defined whenever the crescendo snoring pattern occurred independently of the crescendo esophageal pressure pattern. A false negative (FN) was defined whenever the crescendo esophageal pressure pattern occurred independently of the crescendo snoring pattern.

Results: The results per patient are depicted in the table. The total number of crescendo esophageal pressure patterns was designated as P; the total number of crescendo snoring patterns was designated as S. The overall sensitivity (TP/P = 155/240) was 64.6%, and the predictive value of a positive test (TP/S = 155/211) was 73.4%.

Table 1

	TP	S	P	FP	FN
1	8	12	19	4	11
2	77	103	90	26	13
3	17	24	25	7	8
4	6	9	9	3	6
5	14	17	29	3	15
6	13	24	28	11	15
7	6	7	15	1	9
8	14	15	25	1	11
Sum	155	211	240	56	85

Conclusions: The preliminary results indicate that identification of crescendo snoring patterns is a relatively poor predictor of esophageal pressure elevations. We are in the process of verifying these results with additional data.

1140.K1

The SleepStrip®: A Disposable Sleep Apnea Screening Device

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Introduction: Previously, we reported on a novel disposable sleep apnea screener[1] which is particularly suitable for screening high risk populations. This is comprised of flow sensors (oral and nasal thermistors), a real time analysis hardware and software, and a miniature display unit. The device, which is taped above the upper lip, monitors patients' air-

flow during sleep and displays the calculated RDI after 5.0 hours of sleep. Here, we report our experience with the SleepStrip® in a large sleep clinic population.

Methods: To evaluate the reliability of the device, we compared the RDI as computed by the device, to the RDI as determined by conventional polysomnographic monitoring in the Technion sleep laboratories. One hundred and ninety eight (198) consecutive patients (170 men and 28 women, aged 35-65 yrs), referred for whole night polysomnographic monitoring because of suspected sleep apnea, were tested with the device, concomitantly with conventional polysomnographic (PSG) recording techniques.

Results: Overall, the correlation between the RDI sleepStrip® and the PSG-determined RDI was 0.71 (.0001). This increased to 0.77 if the correlation was calculated only for patients sleeping 6 h or more (N=98). The sensitivity and specificity of the SleepStrip® for identifying patients with RDI>20 was 0.74 and 0.66 respectively, for the entire population, and 0.83 and 0.69, for patients who slept at least 6 hours. The corresponding values for identifying patients with RDI>30 were: 0.81, 0.80 (entire sample) and 0.86, 0.76 (for patients sleeping at least 6 h) and for RDI>60: 0.85, 0.93 and 1.00, 0.91, respectively.

Conclusions: These results indicate that the SleepStrip® can be effective methodology to screen large populations for sleep apnea syndrome. Devices such as the SleepStrip® can be very useful in reducing the large number of as yet undiagnosed sleep apnea patients in the general population.

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1818.K1

Night-To-Night Variability in Overnight Home Oximetry

Jones CR

Introduction: Night-to-night variability in the severity of obstructive sleep apnea (OSA) has been documented in a small number of studies using repeated nights of polysomnography (PSG) (Wittig et al 1984; Meyer et al 1993). Moreover, the expense of PSG has limited these studies to a small number of subjects. The magnitude and frequency of clinically signifcant night-to-night variability in OSA is therefore not well quantified. This study utilized the low cost of overnight home recording pulse oximetry at an altitude (4200-5200 ft) where oximetry may be slightly more sensitive to estimate the nightly variability of OSA.

Methods: 225 patients seen by the author between 02/98 and 11/99 had two nights of home oximetry (in most cases less than one week apart) before their first diagnostic night of PSG. The vast majority were thought to have OSA but the patients were otherwise not selected in terms of gender, suspected severity, or the presence of cardio-pulmonary disease. Oxygen saturation values were recorded on BCI model 3303 oximeters with 4 second moving averages and disabled alarms. A desaturation index (DI) defined as the number of desaturation events per hour of recording time was calculated from the Profox (version 142 Win NT) software package. Successive saturation values differing by >10 units (presumed artifacts) are edited out by the Profox program which was also set to count a desaturation event as a drop of at least 6 saturation units for 10 to 60 seconds. Four categories of severity of DI were arbitrarily established: 1) normal = 0-8/hr, 2) mild = 9-19/hr, 3) moderate = 20-39/hr, and severe = >40/hr.

Results: Most patients did not change DI severity category but 72 (32%) did change including 5 patients (2%) who changed from either normal to moderate or from mild to severe. Large differences in total recording time were not seen to explain these discrepancies: Normal both nights = 43 pts, mild both nights = 44 pts, moderate both nights = 30 pts, severe both nights = 36 pts, normal to mild = 12 pts, normal to moderate = 3 pts, normal to severe = 0 pts, mild to moderate = 35 pts, mild to severe = 2 pts, moderate to severe = 20 pts.

Conclusions: This preliminary analysis suggests that night-to-night variability in OSA is common and sometimes of clinical significance which reinforces the importance of repeating negative or mildly abnormal polysomnograms if the clinical suspicion of significant OSA is strong. Subsequent statistical analysis of these data should include Bland-Altman plots of this and other descriptors of apnea severity (e.g. mean desaturation, lowest desaturation and percent of time below a cut-off SpO2) to better quantify the magnitude of variability in oximetry correlates of obstructive sleep apnea. Such information may also be of help in determining the magnitude of regression dilution bias (Davies et al 1996) in studies attempting to document the morbidity and mortality associated with OSA.

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1218.N

Oximeter's Acquisition Settings Influence the Profile of the Respiratory Disturbance Index

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Introduction: The aim of this study was to determine if there are discrepancies in the profiles of the respiratory disturbance index using Sp02 data from oximeters at different acquisition settings.

Methods: Thirty patients were recorded in a diagnostic mode using standard polysomnographic techniques for EEG, EOG, EMG, sonogram, airflow, and respiratory effort. In addition, each was connected simultaneously to three Ohmeda 3740 oximeters at three different acquisition settings or response times: 3, 6 and 12 seconds. Three Sp02 traces were displayed on separate channels of the polysomnographic records reflecting each oximeter's response time setting. Scoring of the studies employed standard protocols for sleep architecture and arousals. Scoring of disordered breathing was performed by counting the numbers of each of three different types of respiratory disturbance events (RDEs). RDE-0 events were those in which less than 1% oxyhemoglobin desaturation occurred following hypopneas, apneas or crescendo snoring with cortical arousal. RDE-1-2 events were those in which between 1 and less than 3% of oxyhemoglobin desaturation occurred following hypopneas or apneas with and without cortical arousal. RDE-3 events were those in which 3% or more oxyhemoglobin desaturation occurred following hypopneas or apneas with or without cortical arousal. Each event as identified by changes in flow, sonogram and EEG was then categorized according to the change in oxyhemoglobin saturation. 2,666 respiratory disturbance

events were compared simultaneously on the three channels of oximetry and labeled as RDE-0, RDE-1-2 or RDE-3. The combination of the three RDEs formed the profile of the total respiratory disturbance index or RDI for that acquisition setting. Three separate profiles of the RDI were generated by using the Sp02 traces obtained from the oximeters set at the three different response times.

Results: The mean values of the RDE types from the thirty patients obtained at the different acquisition settings or response times are displayed below. Repeated measures analysis of variance shows that significant differences for each RDE type are found at each acquisition setting ($p<.001$). Approximately 50% of the variance in event classification can be accounted for by the response time setting. [* = mean value ** = standard deviation.]

Table 1

RDE Types	RDI Profiles per Acquisition Setting Response Times		
	3 secs	6 secs	12 secs
RDE-0	1.30* (1.80)**	3.30 (4.18)	9.07 (7.75)
RDE-1-2	13.93 (12.83)	23.50 (14.60)	38.40 (25.94)
RDE-3	73.97 (67.29)	62.40 (62.33)	41.93 (47.30)

Conclusions: The different response rates available on oximeters can significantly impact the profile of respiratory disturbance events scored on polysomnography. These acquisition settings or response times should be disclosed whenever polysomnographic data is reported.

1716.A

Orexins in the Basal Forebrain Decreases REM Sleep in Freely Moving Rats: A Simultaneous Microdialysis Perfusion with Behavioral State Recording Study

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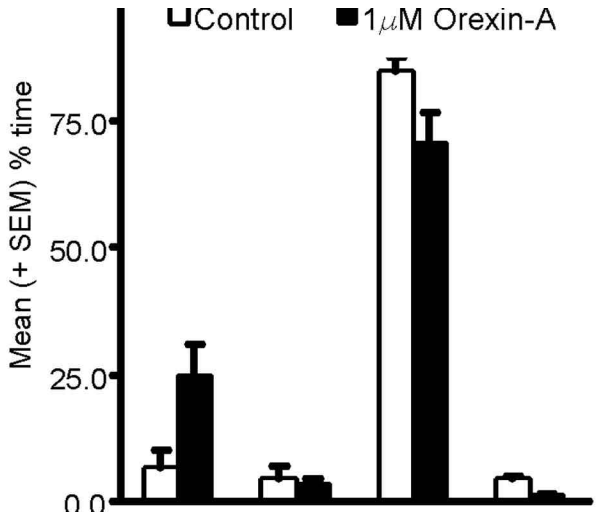
Introduction: Orexin peptides have recently been implicated in sleep control. Narcolepsy, a REM sleep disorder has been linked to the a receptor abnormality of the orexin peptide system (Lin et al 1999; Chemelli et al., 1999). Constitutive knockouts of orexin peptide have increased REM sleep and cataplexy-like episodes . Orexin peptide-containing neurons have a focused presence in the lateral posterior hypothalamus and have fibers that project throughout the central nervous system including cholinergic Basal Forebrain (BF) neurons. (David Rye, personal communication). Data indicate the cholinergic BF is involved in cortical arousal and EEG activation. BF is also known to play a modulatory role in the regulation of REM sleep (Portas et al 1997). To further understand the role of orexins and the BF in behavioral state regulation especially REM sleep, we thus decided to study the effect of behavioral states of microdialysis perfusion of orexin in the cholinergic BF.

Methods: Adult male Sprague-Dawley rats were anesthetized for implantation of standard sleep recording electrodes and two bilateral guide cannulas for microdialysis. These guide cannulas were targeted at the cholinergic horizontal diagonal band (HDB) at coordinates : AP -0.40; ML 1.8 and DV 9.0 (Paxinos and Watson rat brain atlas). After post-operative recovery and habituation to the recording chamber, the microdialysis probe (CMA- 11;1 mm length, 0.24 mm diameter) was lowered through one of the guide cannulas. After 12 hrs of recovery from probe insertion, the experiment was begun. ACSF was continuously perfused and behavioral states were simultaneously recorded for 6 h (1100 h to 1700). The EEG and EMG signals were continuously digitized with Data Wave software. The following day orexin-A was perfused for 2 h (1300 h to 1500 h). Three different concentrations (0.1, 1, and 10 µM) of orexin-A were used. Behavioral states were classified into 4 different states: active wakefulness (AW), quiet wakefulness (QW), slow wave sleep (SWS) and rapid eye movement sleep (REM). Once the experiment was completed the animals were sacrificed, and the brains removed for histological processing to verify the perfusion site. Further, off-line EEG spectral analysis was performed to study the effect on delta, theta and gamma frequencies.

Results: Our preliminary data (figure) indicate 1 µM orexin-A perfused in the cholinergic HDB significantly decreased REM sleep (n=3; $p<0.03$). There was an increase in AW and a decrease in SWS although not statistically significant with the current n=3. Spectral analysis of the cortical EEG showed a concomitant decrease in delta and theta power and an increase in gamma power. Data for 0.1 and 10 µM have not yet been analysed.

Figure 1



Conclusions: Our data suggests that orexin-A in the BF may play a role in the regulation of behavioral state control. We suspect that the AW increase and SWS decrease will become statistically significant with a larger N, and may represent a direct excitatory effect on BF neurons while the REM decrease may be an indirect effect of suppression of brainstem activity. We note that perfusion of an inhibitory agent, adenosine, into the basal forebrain produced exactly the reverse state change pattern, with a decrease in AW and an increase in SWS and REM (Portas et al 1997).

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1451.A

Sleep-Waking Discharge Patterns of Neurons in the Perifornical Area of the Rat Lateral Hypothalamus

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Introduction: Neurons containing the peptides hypocretin/orexin (hyp/orx) A and B are localized to the perifornical area of the lateral hypothalamus.[1] Hyp/orx peptides have been implicated in sleep-wake regulation. A mutation of the hyp/orx-2 receptor has been identified in canine narcolepsy/cataplexy.[2] Hyp/orx peptide knockout mice display a narcolepsy/cataplexy phenotype.[3] These findings suggest that the hyp/orx system may normally function to inhibit muscle atonia and other components of REM sleep. Therefore, hyp/orx neurons could be hypothesized to display suppression of neuronal discharge during naturally occurring REM sleep (i.e., REM-off discharge pattern). We examined extracellular neuronal activity in the perifornical region of the rat lateral hypothalamus during natural wakefulness and sleep to determine the presence or absence of neurons with REM-off discharge patterns.

Methods: Under general anesthesia, adult male Sprague-Dawley rats were chronically implanted with electrodes to record neocortical EEG and dorsal neck muscle EMG. Bundles of microwires (19 microns in diameter) were mounted in a movable microdrive and stereotaxically placed in the perifornical area. Recordings of single or multiple unit activity were achieved by progressively advancing the microwire bundle in small increments. Individual spikes were sorted from multiple unit recordings on the basis of waveform amplitude and shape. Spontaneous neuronal activity was recorded across 2-4 complete sleep-waking cycles. For each isolated cell, mean discharge rate was determined during active waking (waking accompanied by head and/or limb movements), quiet waking (fully desynchronized cortical EEG in the absence of head and/or limb movements), nonREM sleep and REM sleep.

Results: A total of 55 cells have been recorded to date. Thirteen of 55 cells (24%) were classified as REM-off neurons. These cells had a mean (+S.E.M.) discharge rate during active waking of 4.95+.95 spikes/sec (s/s) and a mean discharge rate in REM sleep of 0.44+.16 s/s. The average decrease in discharge rate from active waking to REM sleep was 90.1+2.5%. During wakefulness, discharge of these REM-off neurons was strongly related to the presence of movement. Discharge rates during quiet waking averaged only 0.79+.26 s/s. Discharge rates during nonREM sleep averaged 0.32+1.14 s/s. The other major cell type recorded (n=26) exhibited similar discharge rates during active waking (11.07+2.21 s/s) and REM sleep (9.25+1.54), with reductions in rate during quiet waking (8.18+/1.72 s/s) and nonREM sleep (6.73+1.49 s/s). The remaining 16 cells exhibited low discharge rate (<1s/s) in all sleep-waking states.

Conclusions: Within the perifornical area of the rat lateral hypothalamus, a significant number of neurons with a REM-off discharge pattern can be recorded. Previously, neurons with REM-off discharge pattern have been described in brain regions containing monoaminergic neurons. Monoaminergic REM-off neurons exhibit slow, regular discharge throughout the waking state, and have been implicated in tonic EEG activation during wakefulness. In contrast, discharge of REM-off neurons in the rat perifornical area is phasically related to movement, and not to tonic EEG desynchronization. This suggests a role for these neurons in the control of movement and/or muscle tone, rather than in cortical activation/arousal.

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1394.A

Hypocretin-1 Modulates REM Sleep Through Activation of Locus Coeruleus Neurons

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Introduction: The hypocretins (1 and 2) also known as orexins, are two neuropeptides recently identified as being localized exclusively in cell bodies in a subregion of the tuberal part of the hypothalamus (de Lecea et al., 1998). Hypocretin-containing cells project throughout the brain, with the densest projections reaching the locus coeruleus, dorsal raphe and spinal cord (Peyron et al., 1998). Recently, it was demonstrated that the absence of hypocretin in knock-out mice causes alterations in sleep architecture, particularly on the amount of REM sleep during the dark period (Chemelli et al., 1999), and these mutant mice display narcoleptic-like attacks. The purpose of our study was to determine whether the locus coeruleus is a functional target for hypocretin neuropharmacology in the regulation of the sleep/wake cycle.

Methods: Adult rats were anesthetized with 1.0 % halothane and implanted for chronic sleep recordings. In addition, two stainless steel cannulas were stereotaxically implanted bilaterally in the locus coeruleus (P -0.8 mm, L+1.3 mm, H +2.3 mm, using a posterior angle of 20 degrees from vertical). One week after surgery, rats were habituated to the recording conditions for at least 24 hours. Once the habituation period was completed, recordings were performed following microinjection of saline (0.2 ul), hypocretin 1 (2.5 and 25 pmol), hypocretin 2 (25 p mol), antibodies to hypocretin 1 (10 ug/ml) and hypocretin 1 (25 pmol) preincubated with antiserum for 1 hour. During the experiment rats were housed individually, with ad libitum access to food and water and maintained on a normal 12-hr light cycle (on 06:00 hr, off 18:00 hr). Rats were perfused under anesthesia to perform c-fos immunocytochemistry and to verify histologically the microinjection sites. Statistical analysis was carried out using an ANOVA and then a post-hoc Scheffe test.

Results: Administration of hypocretin 1, but not hypocretin 2, in the locus coeruleus suppressed REM sleep. This effect was blocked with an antibody that neutralizes hypocretin binding to hypocretin receptors. Likewise, injection of hypocretin 1 induced the expression of c-fos in the locus coeruleus.

Conclusions: Our results strongly support a modulatory role of hypocretin 1 on REM sleep.

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1214.A

Hypocretin Microinjections in the Vicinity of Locus Coeruleus and Pontine Inhibitory Area Change Muscle Tone in Decerebrate Rats

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Introduction: A mutation in the hypocretin receptor 2 (Hcrtr2) gene was observed in canine narcolepsy (Lin et al., Cell 6: 365-376, 1999), which is characterized by sleep abnormalities and sudden losses of muscle tone (cataplexy). High levels of Hcrtr1 mRNA were observed in locus coeruleus (LC) compared to Hcrtr2 mRNA (Trivedi et al., FEBS Letters 438: 71-75, 1998). The LC participates in motor and muscle tone regulation. The pontine inhibitory area (PIA), located ventral to LC participates in the suppression of muscle tone in REM sleep. In the current study we examined the role of each hypocretin in muscle tone regulation using microinjections in the vicinity of LC and PIA.

Methods: Hcrt1and Hcrt2 (Phoenix Pharmaceuticals, Inc.) were injected in the vicinity of LC and PIA in precollicular-postmammillary decerebrate rats (Wistar, 250-300g, n= 34). Muscle tone was recorded bilaterally in two hindlimb muscles (gastrocnemius and tibialis anterior) and neck muscle (splenius). The LC was identified using TH immunostaining.

Results: Hcrt1 microinjections (4 µM-1mM, 0.2 µl) into the LC resulted in two types of responses: 1) muscle tone increase and 2) locomotion (if the hypothalamus was partially spared). The latency and duration of muscle tone increase had a dose-dependent time course and changed from 78±42 s (n=3, 4µM) to 68±32 s (n=5, 1mM) and 683±183 s (n=3, 4µM) to 1058±383 s (n=5, 1mM) respectively. The latency and duration of locomotion were changed similarly. Microinjections of Hcrt1 (4 µM-1mM, 0.2µl) into the PIA produced a muscle tone decrease with a latency between 108±42 s (n=4, 4 µM) and 86±37 s (n=5, 1mM). The duration of muscle tone suppression ranged from 642±312 s (n=3, 4µM) to 918±222 s (n=7, 1mM). Microinjections of Hcrt1 (200 nM, 3 µl) into the 4th ventricle evoked locomotion with a latency of 147±38 s (n=3) and duration of 452±241 s (n=3). High doses of Hcrt2 (1mM, 0.2 µl) in the LC resulted in response types similar to Hcrt1: muscle tone increase with latency of 108±25 s (n=4) and duration of 466±129 s (n=4) and locomotion with a latency of 138±49 s (n=5) and duration of 1104±474 s (n=5). Muscle tone decrease was observed with high dose microinjections into the PIA with a latency of 66±14 s (n=5) and duration of 241±65 s (n=4). Hcrt2 doses of less 100 µM did not produce a muscle tone increase and locomotion after microinjections into the LC but induced a muscle tone decrease after PIA microinjections in 2 cases.

Conclusions: 1) Hcrt1 produced muscle tone excitation and locomotion when injected into LC and muscle tone inhibition after injection into PIA. 2) Hcrt1 produced locomotion when injected into 4th ventricle. 3) Much higher doses of Hcrt2 than of Hcrt1 are required in both LC and PIA to obtain a response, suggesting that Hcrtr's in the LC and PIA are predominantly of the Hcrtr1 type. 4) The involvement of the hypocretins in both muscle tone inhibition and facilitation may explain the link between narcolepsy and both cataplexy and the REM sleep behavior disorder (Schenck and Mahowald, Ann. Neurol. 32: 3-10, 1992).

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1904.A

Hypocretin-1 Reduces Cataplexy and Normalizes Sleep and Waking Durations in Narcoleptic Dogs

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Introduction: A mutation in the hypocretin-2 (Hcrt-2, orexin B) receptor gene is the cause of canine narcolepsy (Lin et al., 1999). A null mutation of the gene encoding the two known hypocretin (Hcrt) peptides produces aspects of the narcolepsy syndrome in mice (Chemelli, et al., 1999). These reports suggest that administration of Hcrt might reverse symptoms of narcolepsy by compensating for either inefficient receptor transduction or diminished levels of the agonist. However, some studies have concluded that Hcrt's administered systemically do not cross the blood-brain barrier at sufficient levels to affect physiological function. In the current study, we tested the effect of intravenous administration of Hcrt-1 on narcolepsy / cataplexy in canine narcoleptics.

Methods: One to 4 µg/kg of Hcrt-1 (orexin-A, Phoenix Pharmaceuticals, CA) dissolved in normal saline (100 mg in 2 ml) or saline alone was administered intravenously to six narcoleptic Doberman pinschers (5 males, 1 female). On control days, saline was administered in the same manner. We analyzed the effect of Hcrt-1 on cataplexy, using a modified food elicited cataplexy test (FECT) starting 4 minutes after the drug adminsteration. To study sleep-wake pattern, electrodes for the assessment of sleep-wake parameters (EEG, EMG, EOG and hippocampal theta) were chronically implanted in two of the dogs. The effects of Hcrt-1 on sleep-wake periods were also monitored continuously for 24 hrs/day with collar mounted actigraphs (Mini Mitter Inc., OR).

Results: Hcrt-1 administration had a significant effect on cataplexy in a dose dependent manner (cataplexy attacks, $p<0.001$; FECT time, $p<0.001$; ANOVA). The 1 and 2 mg/kg doses of Hcrt-1 did not produce any change in cataplexy. The 3 µg/kg dose produced a reduction in cataplexy ($p<0.002$, t-test) and a reduction in the FECT time ($p< 0.001$, t-test). The 4 µg/kg dose of Hcrt-1, however, increased the severity of cataplexy compared to saline control ($p< 0.01$; t-test) and increased the FECT time ($p<0.05$; t-test). Two of the 3 dogs treated with repeated doses of Hcrt-1 went for 3 or more days without any cataplexy after the administration of 3-5 doses of Hcrt-1. Polygraphic recording of sleep-wake parameters showed that the same doses of Hcrt-1 that induced a reduction in cataplexy produced a significant reduction ($p<0.05$; t-test) in REM sleep (from 18.8% ± 2.9 to 12.3% ± 3.6) and no change in nonREM sleep during the 4 hr post-injection period. Actigraph measurements calibrated by concurrent polygraphic recording ($r= 0.84$, $p< 0.001$), were used to calculate the duration of sleep and waking states before and after treatment. A single dose of Hcrt-1 increased the mean duration of both sleep periods (from 5.66 ± 0.26 to 8.84 ± 0.93 min) and

wake periods (from 1.96 ± 0.1 to 2.56 ± 0.12 min). These effects lasted for more than 24 hrs ($p<0.01$ and $p<0.002$; ANOVA, for sleep and wake periods respectively). The frequency of sleep and wake bouts was reduced ($p<0.05$ and $p<0.05$; ANOVA). During the periods of total cataplexy suppression following repeated Hcrt-1 doses, sleep was consolidated (increased sleep bout length) relative to baseline conditions ($p< 0.05$; t-test), as it was after Hcrt-1 administration. Hcrt-1 produced increased motor activity in the 60 minutes after injection.

Conclusions: In the current study we demonstrate that systemically administered Hcrt-1 produces a significant short term increase in activity level, a decrease in REM sleep without change in nonREM sleep, reduced sleep fragmentation and dose dependent reduction in cataplexy in canine narcoleptics. We hypothesize that low doses of Hcrt-1 administered systemically activate monoaminergic brainstem systems and other muscle tone facilitatory systems, whereas high doses activate both facilitatory and inhibitory systems. We find that unlike most current pharmacological therapies, Hcrt-1 administration produces dramatic and correlated improvements in cataplexy, waking duration and sleep continuity. Hcrt-1 administration has the potential for being an effective treatment for the underlying abnormality in narcolepsy and may also prove useful in the treatment of other sleep disorders and disorders of arousal characterized by daytime sleepiness and interrupted nighttime sleep.

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1787.K4

Mastery Strategies Used by Sexual Assault Survivors During Imagery Rehearsal for Nightmare Alleviation

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Introduction: Abreaction, exposure, and increased sense of mastery[1] are thought to be major contributing psychological therapeutic components of nightmare alleviation. Two studies,[2,3] however, have shown that techniques involving minimal exposure and abreaction remain effective. The present study investigated which mastery strategies patients use when rehearsing new dream imagery in the context of an imagery rehearsal (IR) nightmare treatment approach.

Methods: Sixty-seven adult women (aged 36.7 + 10.6 years) who reported past unwanted sexual experiences participated in a study on the treatment of nightmares (NM). All reported having weekly NM for > 3 months, presented complaints of disrupted sleep, and showed symptoms of posttraumatic stress disorder. Reports of NM and rehearsed dreams (RD) were collected during a nightmare treatment program. Patients were asked to select and write a NM, to "change it in any way they wanted," and to write a new dream. A period of 5-8 minutes was then allotted to allow participants to mentally rehearse the new dream. Dream reports were then transcribed and rated by two judges. Instances of mastery strategies were identified using a pluridimensional mastery scale to assess the presence of Social (using favorable social resources), Behavioral (performing actions), Emotional (changing emotional valence), Environmental (altering the dream environment), Mystical (using supernatural powers or figures) mastery, and Avoidance (waking up) in NM and RD. The overall inter-rater reliability was computed as # agreements /(# agreements + # disagreements), and was = 0.84. Paired t-tests were conducted to uncover differences between NM and RD imagery.

Results: Table 1 shows that RD were characterized by more categories of mastery strategies ($p < 0.01$) and more total number of instances of mastery strategies ($p < 0.01$) than were NM. This was mostly explained by a considerable and significant increase in the number of instances of Social ($p< 0.01$) and Emotional ($p = 0.01$) mastery strategies in RD compared to nightmares. RD also contained more instances of Environmental mastery strategies ($p < 0.01$) than did NM.

Table 1. Differences in numbers of instances of mastery strategies by type in nightmares (NM) and rehearsed dreams (RD).

Mastery Type	NM		RD		Paired t-test (df = 66)
	M	SD	M	SD	
Total # of categories	1.09	1.60	1.39	0.55	t = 8.88[a]
Total # of references	1.06	1.67	1.81	1.16	t = 3.15[a]
Behavioural	0.90	1.51	0.47	1.04	t = 1.99[b]
Social	0.06	0.24	0.67	0.82	t = 6.14[a]
Emotional	0.00	0.00	0.09	0.29	t = 2.55[c]
Environmental	0.00	0.00	0.43	0.58	t = 6.08[a]
Mystical	0.00	0.00	0.03	0.17	t = 1.43[d]
Avoidance	0.30	0.46	0.04	0.21	t = 4.74[a]

[a] $p < 0.01$
[b] $p = 0.05$
[c] $p = 0.01$
[d] $p = 0.20$

Conclusions: Increased utilization of various mastery strategies is indeed an observable component of dream scenarios elaborated during an IR technique for nightmare alleviation, when compared to pre-treatment NM. As IR minimizes the potential contributions of abreaction and exposure in nightmare alleviation, this study is the first to empirically support the suggestion that an increased sense of mastery in dream imagery is the most important component in alleviation of nightmares using IR.

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Hallucinations, REM Sleep and Parkinson's Disease

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Introduction: Psychosis manifested by visual hallucinations is a disabling complication of the treatment of patients with Parkinson's disease (PD). Sleep disorders, including vivid dreams (Nausedia et al 1982), rapid eye movement (REM) sleep with motor behaviours (RBD)

(Comella et al 1998) and daytime sleepiness (Frucht et al 1999), are frequent in these patients. In two PD patients with psychosis, we incidentally noticed that hallucinations were contemporaneous with sudden sleep onset in REM periods (SOREMp).

Methods: The association of hallucinations and REM sleep both at night and during the day was examined in 10 consecutive non-demented patients with long-standing levodopa-responsive PD and hallucinations. Seven patients felt personally in danger, believed that they were followed or threatened, and that their spouse was an impostor or unfaithful. Overnight sleep recording was followed by a standard multiple daytime sleep latency test. The results were compared to PD patients who did not experience hallucinations.

Results: RBD were detected in all 10 patients with hallucinations and in 6 without. Although night sleep parameters were similar in both groups, hallucinators tended to be more sleepy during the daytime. Daytime mean sleep latency was 8 ± 1 min in hallucinators and 11 ± 1 min in non-hallucinatirs (p=0.11). Delusions following a night REM period and daytime SOREMp were observed in 3 and 8 of the hallucinators, and 0 and 2 of the others. In hallucinators, SOREMPs occured during 4 tests (n=2), 3 tests (n=2), 2 tests (n=1) and 1 test (n=3). Daytime hallucinations, synchronous with REM sleep intrusions into awake patients, were reported only by hallucinators. Narcolepsy was ruled out by the absence of the usual HLA markers. Post-mortem brain examination in one patient showed numerous Lewy bodies in non-pigmented neurones of the subcoeruleus nucleus, a region that is involved in executive REM sleep mechanisms.

Conclusions: The visual hallucinations that coincide with daytime episodes of REM sleep in patients who also experience post-REM delusions at night may be dream imagery. Neuropathological lesions in neurones implicated in the regulation of REM sleep support this hypothesis. Psychosis in PD patients may therefore result from a narcoleptic-like REM sleep disorder.

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1465.K4

HLA Class II Association in Sleepwalking

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Introduction: Parasomnias (PSs) are usually classified into 3 groups: Partial Arousal Parasomnias (Sleepwalking, Confusional Arousals, Sleep Terrors); REM Sleep Parasomnias (Nightmares, Sleep Paralysis, Impaired or Painful Erections, REM Sleep Behavior Disorder); and Sleep-Wake Transition Parasomnias (Rhythmic Movement Disorder and Sleep Talking). The pathophysiology of PSs is considered to be closely related and children have the highest prevalance of PSs that seem to decrease or disappear at adulthood. Familial PSs have been well documented but the mode of transmission is unknown. Twin studies demonstrated a high degree of concordance for sleepwalking (47-55% in monozygotic vs. 6-35% in dizygotic twins). However, since even in monozygotic twins the concordance is far below 100%, other non-genetic factors have to be considered. Among PSs, sleepwalking has probably the highest familial incidence and up to 25% of parents of sleepwalkers have been sleepwalkers themselves during their childhood (versus 3-4% in the general population). Other studies indicate that different PSs are usually observed in a single individual suggesting an important overlap in the genetic control of their underlying mechanisms. Most PSs are movement-related and the differential diagnosis includes sleep-related seizures, especially the autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). As a genetic marker, only a significant association with the HLA-DQw1 was evidenced in a REM sleep behavior disorder population. Since sleepwalking is a common parasomnia with high genetic load that may be misdiagnosed as ADNFLE, we have initiated a collaborative project on its genetic basis.

Methods: To date, twenty-six sleepwalking subjects entered the study, including 19 sporadic (7 females and 12 males) and 7 familial cases (1 female and 6 male probands). In all cases, both parents (when available) and if familial, other family members were ascertained. As a first step in this project, two main candidate systems were investigated. Thus, the HLA-DQB1 and the neuronal nicotinic acetylcholine receptor subunit alpha4 (CHRNA4) genes were analyzed in all patients and their relatives. The 2 candidate genes have been implicated in REM sleep behavior disorder and ADNFLE (for HLA-DQB1 and CHRNA4, respectively). Reference allele frequencies were derived from 39 ethnically matched controls for HLA and 75 French normal controls for CHRNA4. DQB1 typing was performed by combination of group-specific amplification and restriction fragment length polymorphism. The CHRNA4 silent polymorphism is generated by a C to T substitution at codon 226 that can be resolved by the restriction enzyme CfoI (allele C and T).

Results: HLA-DQB1: Due to the small sample size, DQB1 alleles were grouped in 02, 03, 04, 05, and 06 specificities for comparison between groups. Overall, 15 out of 26 sleepwalkers were DQB1*05 positive against 11 out of 39 control subjects (57.7 vs. 28.2 %; Fisher's exact test, uncorrected p = 0.02). Subjects positive for DQB1*05 were 3.5 times more at risk for sleepwalking than subjects without (95% CI = 1.2 - 9.9). There was no difference between male and female subjects. Although the sample size remains small, familial sleepwalking seems to be more closely associated with DQB1*05 (5 out of 7 families or 71.4 % vs. 28.2 % in controls, Odds ratio = 8.9, 95% CI = 1.5 - 52.1). Also, 9 out of 12 (75 %) DQB*05 heterozygous parents transmitted this allele to their affected child.CHRNA4 : Although non significant, the frequency of allele T was decreased in sleepwalking subjects (5.8 % vs. 7.3 % in controls).

Conclusions: These preliminary data suggest that DQB1*05 may confer susceptibility to sleepwalking especially in the familial form, while CHRNA4 does not seem to be associated. However, the latter result does not exclude the possibility of ADNFLE misdiagnosis. Since DQw1 (DQB1*05 + DQB1*06) has been associated with REM sleep behavior disorder and these subjects as well as narcoleptic subjects are more frequently affected by several parasomnias, our finding might suggest a common HLA Class II susceptibility factor in movement-related parasomnias.

1429.K4

Sleep Deprivation Increases the Frequency and Complexity of Behavioral Manifestation in Adult Sleepwalkers

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Introduction: It is well known that adult sleepwalkers can injure themselves as well as others. Over the past few years, there has been an increased interest in this disorder due in part to the forensic implications of a clear diagnosis of somnambulism in cases of homicidal sleepwalking. Few studies have attempted to develop a reliable method for inducing sleepwalking episodes in the laboratory. The aim of the present study was to evaluate the effects of sleep deprivation on various characteristics of behavioral manifestations in sleepwalking.

Methods: Eight subjects (6 females, 2 males, mean age = 24.75, SD = 4.40) and 6 age and sex-matched normal controls (5 females, 1 male, mean age 24.50, SD = 2.43) were evaluated. All subjects underwent one screening night in the sleep laboratory prior to the study. Participants subsequently had one baseline night of recording followed one week later by a 36-40 hour period of sleep deprivation. Subjects carried a portable device (Handysleep, Glonner company) for EEG, EMG, and EOG recording and remained under observation during the entire period of sleep deprivation. The baseline and sleep deprivation sequence was reversed in half of the subjects to control for any habituation effects. Subjects also refrained from taking naps for one week prior to each recording. The complexity of somnambulistic episodes was scored using the following criteria: 1= patient remains lying in the bed, 2 = change of position in bed, including resting on one's hands, 3 = sitting up in the bed, 4 = behavior more complex than sitting, i.e. resting on one's knees or trying to get out of the bed, 5 = jumping out of the bed. Statistical analyses were based on Wilcoxon Matched Pairs tests.

Results: The control group did not show any behavioral episodes. Among sleepwalkers, there was a significant increase in the number of somnambulistic episodes during the recovery night ($p = 0.018$). Similarly, the complexity index was significantly higher for the recovery night than for the baseline night ($p = 0.028$). However, the difference in the duration (in seconds) of the episodes observed on the two nights did not reach significant levels.

Table 1-Sleepwalking episodes characteristics during baseline and recovery nights.

	Baseline night	Recovery night
# subject with at least one episode	6/8	7/8
Mean (SD) frequency of episodes	1.375 (1.06)	5 (4.40)
Mean (SD) length of episodes	30.35 (11.83)	32.93 (11.86)
Complexity of episodes	1.61 (0.49)	2.11 (.0.42)

Conclusions: To our knowledge, this is the first classification of behavioral events in sleepwalking. Sleep deprivation resulted in a significant increase in the frequency of sleepwalking episodes as well as in the episodes' complexity. This effect that was not observed among controls. The results suggest that sleep deprivation could be used as a diagnostic tool for somnambulism. These behavioral manifestations will be correlated with neurophysiological measures to further increase the sensitivity of polygraphic recording in the diagnosis of sleepwalking.

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1846.K1

Minimal Model of Circulatory Control in Obstructive Sleep Apnea

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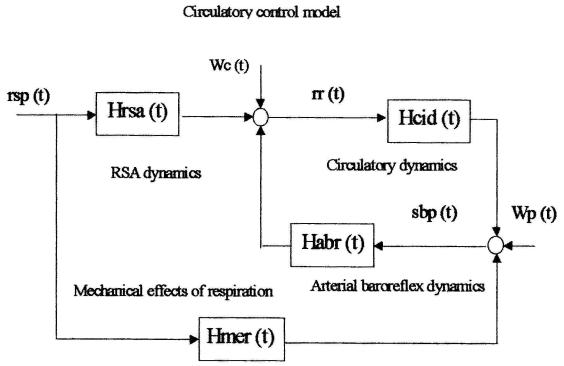
Introduction: Recent studies suggest that obstructive sleep apnea syndrome (OSAS) leads to impaired cardiovascular regulation. Traditional means for noninvasive assessment of circulatory control include autonomic function tests (eg. Valsalva response), spectral analysis of HRV, and techniques for quantifying baroreflex sensitivity. Although informative and clinically useful, the above mentioned methods provide only static characterizations of autonomic control. To circumvent this limitation, we developed a minimal model of circulatory control based on noninvasively recorded signals - respiration, RR intervals (RRI) and arterial blood pressure (ABP). Application of system analysis permitted reliable identification of the model components in terms of impulse response (IR) curves. These IR curves enabled us to compare the dynamics of circulatory control between control subjects and OSAS patients. The minimal model offers a more comprehensive representation since cardiorespiratory regulation is inherently complex and dynamic as a result of the interplay among multiple neural and mechanical factors.

Methods: **1.Experimental protocols**Thirteen OSAS patients and eleven healthy volunteers participated in the study after giving their written consent. The experiments consisted of spontaneous breathing as well as breathing on cue for 5 min. where subjects were asked to follow a target breathing pattern presented to them on a computer monitor. The target wave was randomized and preserved the average ventilation from subject's spontaneous respiration. Tests were conducted in both supine and upright positions. Respiration was recorded by calibrated respiratory inductive plethysmography (Respitrace, Ambulatory Monitoring Inc.). ECG (BMA-831, CWE Inc.) and continuous ABP (Finapres-2350, Ohmeda) were also acquired. The data sets were pre-processed off-line to deduce RRI, diastolic blood pressure and systolic blood pressure (SBP) on a beat-to-beat basis. All the signals were resampled at 2 Hz for further analysis. **2.Model formulation**The model employed in our analysis was similar to that of Baselli et al.[1] This approach allowed a separation of the major pathways contributing to the beat-to-beat regulation in the system. The model assumed that respiration led to fluctuations in heart rate through 2 channels: a centrally-mediated. component ("RSA dynamics", characterized by the IR, $H_{rsa}(t)$, and indirectly via the baroreflexes (characterized by $H_{abr}(t)$) as a result of respiratory-induced fluctuations in SBP. Fluctuations in SBP were assumed to result from the mechanical effects of respiration ($H_{mer}(t)$) and through changes in cardiac output ($H_{cid}(t)$). The unknown model component IRs were estimated by applying a Laguerre expansion technique to the measurements of respiration, RRI and SBP. Since the measurements were made under closed-loop operating conditions, delays were incorporated into the model structure so that causality constraints could be imposed. A schematic diagram of the model is shown in Fig. 1. The signals Wc(t) and Wp(t) represent the dynamics not accounted for by the model.

Results: Estimates of the baroreflex IF, $H_{abr}(t)$, exhibited a sharp positive peak between 1 and 2 seconds following an initial latency of ~1 s. The peak values of $H_{abr}(t)$ were significantly correlated ($r = 0.70$, $P<0.0005$) with baroreflex sensitivity assessed via the more commonly used "alpha index" (which is basically the ratio of change in RRI to change in SBP), thus providing some validation for the modeling approach. Changing posture from supine to standing led to the development of a longer positive tail in $H_{abr}(t)$, suggesting an increased sympathetic contribution with standing. Peak values of $H_{abr}(t)$ were significantly lower in OSAS versus normals (0.8 ± 0.2 SE vs 1.4 ± 0.2 ms

mmHg^{-1}; P <0.015), consistent with former reports of depressed baroreflex sensitivity in OSAS. The magnitude of $H_{rsa}(t)$ was also significantly lower in OSAS relative to the normal subjects (-13.4 ± 3.8 vs -39.7 ± 4.1 ms L^{-1}, P < 0.001). The IRs of the other model components were similar between the two subject groups.

Figure 1



Conclusions: The minimal modeling approach provided a multivariate and dynamic characterization of cardiorespiratory interactions. The results obtained with this model demonstrated significant impairment of RSA and baroreflex dynamics in OSAS.

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1167.K1

Hypoxia Inducible Vascular Endothelial Growth Factor (VEGF) - Possible Role in Cardiovascular Adaptive Mechanism in Sleep Apnea Syndrome

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Introduction: In spite of accumulated evidence supporting the profound impact of sleep apnea syndrome on the cardiovascular system, it is not clear yet if the syndrome is actually associated with increased cardiovascular mortality. Two independent studies[1,2] reported that the risk of mortality in sleep apnea patients peaks at the relatively young age of 30-50 years and decreases thereafter. Furthermore, the odds ratio for mortality in sleep apnea patients older than 70 was reported to be 0.2. Vascular endothelial growth factor (VEGF) is an hypoxia-inducible cytokine which plays a critical role in angiogenesis - the growth and development of new blood vessels. Recently, it was shown that interindividual heterogeneity in the hypoxic induction of VEGF may explain the individual differences in the presence of coronary artery collaterals, visualized during angiography.[3] Cardiovascular patients who had higher levels of hypoxia-induced VEGF mRNA in monocytes, considered "responders," had also more angiographically visualized coronary artery collaterals, as compared to "non-responders". We hypothesize that nocturnal hypoxia-induced VEGF may play a role in the long-term adaptation to sleep apnea syndrome.

Methods: To test our hypothesis, we measured plasma levels of VEGF in 99 male sleep apnea patients (age: 49.2±12.5, BMI: 28.7±4.2, RDI: 21.4±19.6) immediately after waking up in the sleep laboratory. Morning VEGF levels were correlated with nocturnal degrees of hypoxia. Correlation analysis (Spearman rank order) as well as stepwise multiple regression were used to investigate this relationship. VEGF was determined by a quantitative sandwich enzyme immunoassay technique (Quantikine R&D Systems, Minneapolis MN).

Results: There was a very large variability in the morning plasma levels of VEGF as indicated by the large standard deviation (77.6±58.5 pg/ml). VEGF was significantly correlated (Spearman rank order) with the percent time below 95% (.23, p<.02) and below 85% (.27, p<.01) oxygen saturation. There was a borderline statistically significant correlation with percent time below 90% saturation (.18, p<.07) and with BMI (.19, p<.06). Stepwise multiple regression analysis using Age, BMI, RDI, percent times below 95%, 90% and 85% saturation, smoking, and co-morbidity, as potential predictors, revealed that Age and Percent time below 95% saturation were significant predictors. VEGF decreased with increasing age and increased with increasing times below 95% saturation.

Conclusions: Our findings provide evidence that morning levels of VEGF are related to the percent of time sleep apnea patients spent in hypoxic state during sleep. This may indicate that hypoxia-inducible VEGF may play a role in the long-term adaptation of sleep apnea patients. Given the interindividual heterogeneity in the hypoxic induction of VEGF, it can be assumed that like in the general population, sleep apnea patients can be also divided into "responders" and "non-responders". Thus, only sleep apnea responders who respond to hypoxia by elevated levels of VEGF, adapt to the syndrome by developing coronary artery collaterals. This may protect them from cardiovascular mortality.

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1891.K1

Pulmonary Hypertension in Obese Patients with Obstructive Sleep Apnea Syndrome

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Introduction: Acute increases in pulmonary artery pressure (PAP) coinciding with sleep-induced apneas and hypoxemia have been observed in patients with Obstructive Sleep Apnea Syndrome (OSAS).[1] A significant proportion of OSAS patients also has elevated daytime pulmonary artery pressure. Although transient increases in PAP during apneas are well-recognized, the role of sleep apnea in producing sustained waking pulmonary hypertension (PH) has been more controversial. It has been suggested that PH develops in patients with OSAS only in the presence of daytime hypoxemia secondary either to clinically significant chronic obstructive pulmonary disease or obesity.[2] The aim of the present study was to determine the frequency of PH in obese patients with confirmed severe sleep apnea.

Methods: **Patients.** Endocrinologists from the Obesity Clinic of National Institute of Nutrition "Salvador Zubiran" referred patients to the Sleep Clinic on the basis of obesity and symptoms of sleep apnea (snoring and daytime sleepiness). Fifty-two consecutive patients comprised the sample of the study and included twenty-two women and thirty men with a mean age of 46.5±14.6 years and mean Body Mass Index (BMI) of 45.9±10.1 kg/m^2. Main concomitant medical conditions were hypertension (n=27), diabetes mellitus (n=15), and hypothyroidism (n=8). Seventeen patients had multiple diagnoses, and eleven patients had no other medical condition. **Procedure.** The evaluation consisted of two nights of polysomnographic recording using standard techniques. Patients were included on the basis of BMI≥30 and Apnea lndex≥5 in which more than 80% of apneic events were of the obstructive type. Doppler echocardiography was used to estimate systolic PAP using tricuspid regurgitation gradient plus 10 mmHg if the gradient was <60 mmHg and 15 mmHg if >60 mmHg. Pulmonary hypertension was diagnosed if patient had systolic PAP >40 mmHg and when data from M-mode and two-dimensional echo indicated its presence. Arterial blood gases were measured using an automatic gas analyzer (AVL-Omni Model 5). Spirometric measurements were performed according to the American Thoracic Society recommendations using a Spirometrics USA-Spirometer-CMD/PC-Flow Model 3350. Patients were divided into two groups according to the results of echocardiographic measurements: Patients with PH (Group-PH, n=37) and without PH (Group-NPH, n= 15).

Results: The data showed that 71.2% of the obese patients with OSAS had permanent daytime PH (Group-PH=55.7±14.4, Group-NPH=36.0±2.0 mmHg). There were no statistically significant differences between the groups as respects age (Group-PH=43.9±14.6, Group-NPH=47.5±14.6 years old), BMI (Group-PH=42.9±8.9, Group-NPH=47.1±10.4 Kg/m^2), %FVC predicted (Group-PH=64.9±19.5, Group-NPH=75.0±13.1), %FEVI/FVC predicted (Group-PH=105.6±6.6, Group-NPH=102.8±8.8) or Respiratory Disturbance Index (RDI) (Group-PH=46.5±31.9, Group-NPH=54.5±31.8). Obese patients with PH differed from those without PH in that they had higher $PaC0_2$ (Group-PH=38.1±4.5, Group-NPH=33.5±3.4, $p<0.003$), and lower mean waking and sleeping $\%Sa0_2$ (Group-PH=85.3±8.0, 75.5±11.8; Group-NPH=91.6±2.5, 82.6±9.6; $p<0.001$ and $p<0.05$ respectively).

Conclusions: There is a high prevalence (71%) of pulmonary hypertension among obese patients with OSAS.The increase in PaC02 in the hypertensive group suggests that hypoventilation may be a contributing factor for pulmonary hypertension in obese patients.

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1122.K1

Breathing Patterns Following Exposure to Carbon Dioxide in Congenital Central Hypoventilation Syndrome (CCHS) and Controls

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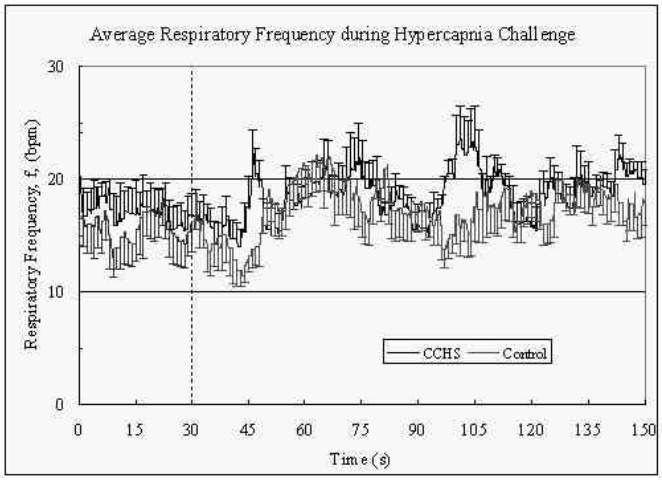
Introduction: Congenital Central Hypoventilation Syndrome (CCHS) is a rare disease of unknown etiology. The physiologic abnormalities include reduced respiratory drive during sleep and absent ventilatory responses to hypercapnia and hypoxia. Hypercapnic challenges administered to CCHS and controls during the course of brain imaging studies revealed differences in breathing patterns. These patterns may provide insights into mechanisms of chemoreceptor action operative in this syndrome.

Methods: Nine CCHS patients without Hirschsprung's Disease, ventilator-dependent only during sleep, and nine age- and gender- matched control subjects were used (Mean age = 11 ± 2 years, 6 female pairs). For 30 seconds (s), all subjects breathed room air through a mouthpiece; the gas mixture was then switched to 95% O_2 and 5% CO_2 for 120s. Breathing, assessed as end-tidal CO_2, was recorded over the scan period at 167 Hz. Peak-to-peak detection was used to calculate respiratory frequencies (f), interpolated to a curve at 100 ms intervals. Both parametric and non-parametric tests were used to assess averaged f values for each group.

Table 1. Average *f* during hypercapnia challenge (onset shown by vertical line) for CCHS and control subjects.



Results: The averaged f curves for both the control and CCHS groups are shown in Figure 1. The average f during baseline were higher for CCHS cases than controls (17.0 ± 6.3 breaths per minute (bpm) compared with 15.7 ± 7.0 bpm, respectively, $p < 0.0005$). Application of the hyperoxic/hypercapnic challenge resulted in an early f decline for CCHS and controls, with a larger decline for controls. This decline was followed by increases in f, which, remarkably, occurred earlier in CCHS, with an average time of 18.9 ± 7.5 s after challenge onset, compared with 26.6 ± 9.9 s for controls ($p < 0.02$). The early f rise of the CCHS patients was not sustained. In contrast, the control group exhibited a sustained f increase, 25.3 - 42.0 s, after challenge onset, with a peak of 22.1 bpm. Respiratory frequency fell, and then rebounded to 19.8 bpm between

48.5 - 49.5 s after challenge onset. Late in the challenge (71.0 s), CCHS cases exhibited a second transient rise (to 23.5 bpm), not observed in controls ($p < 0.02$).

Conclusions: The initial decline in breathing rate in both groups most likely relates to the hyperoxic component of the challenge; although CCHS cases respond less to this aspect, the finding suggests retention of peripheral chemoreception elements in response to oxygen changes. Similarly, the early onset of the *f* increase in the CCHS group could represent the retention and even accentuation of peripheral chemoreception in response to CO_2 transients in CCHS (Gozal, et al., 1993). However, the afferent input from peripheral chemoreceptors appears to be insufficient to maintain *f* elevation with ongoing hypercapnia, as observed in control subjects with intact central and peripheral chemoreception. The nature of the late onset transient rise in breathing rate in CCHS remains unclear. The findings support the hypothesis that elements of peripheral chemoreception are retained in CCHS, and suggest that a heightened response to transient CO_2 challenges may be operative in this group, as indicated by the early respiratory rate increase. The mechanisms underlying this enhanced sensitivity are unknown. Examination of the effects of sleep state on transient CO_2 responses may represent a useful approach for elucidating elements operative in the substantial reductions of respiratory drive in CCHS.

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1617.J

Effect of Sleep Deprivation on the Transcription Factor NF-kB and Adenosine A1R mRNA Levels in the Basal Forebrain/ Preoptic Area of Rat Brain

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Introduction: Recently, we showed that the extracellular concentration of adenosine increased following prolonged wakefulness in the basal forebrain (BF) area in rats and cats (Basheer et al., 1999; Porkka-Heiskanen et al 1997). Furthermore, increasing the BF extracellular levels of adenosine either by perfusion or by microdialysis perfusion of the adenosine transporter blocker, NBTI, into the BF increased sleepiness in rats and cats. In contrast, perfusion of the A1 selective antagonist, cyclopentyl-1,3-dimethylxanthine (CPT), increased wakefulness and decreased sleep (Strecker et al., 1999).The A1 receptor mediates its effects via Gi/Go-proteins. A common feature of the G-protein coupled receptors is its rapid attenuation in response to the agonist, the most common response being receptor downregulation, and also modulation of second messengers and transcription. The Nuclear Factor-kB (NF-kB) has been shown to be an important transcription factor involved in the regulation of several genes including that for the CNS A1 receptor, with NF-kB binding to the upstream regulatory region of A1 promoter. It is also known that signal cascades that activate protein kinase C can phosphorylate I-kB,leading to its own degradation and the release and subsequent translocation of NF-kB to the nucleus (other data indicate that A1agonists can produce phopholipase C- mediated activation of protein kinase C). Thus, to investigate the consequences of A1 receptor activation, we have examined the effects of sleep deprivation on the nuclear translocation of NF-kB protein and the fate of its cytoplasmic I-kB,whose association retains NF-kB dimers in inactive form in the cytoplasm,in the BF/preoptic area by western blot analysis. We have also determined the changes in the DNA binding activity of NF-kB following sleep deprivation, as well as changes in BF levels of A1 receptor mRNA measured by RT-PCR.

Methods: Male Long Evans rats (weight 350-450g) were housed in a room with controlled temperature (23 °C) and a 12:12 hr light :dark cycle (lights on 0700hr). Food and water were provided ad libitum. Rats were kept awake by gentle handling for three hours (from 0700hr to 1000 hr) or six hours (0700hr to 1300hr). At the end of the deprivation period the rats were killed by decapitation and the basal forebrain/ preoptic area and cingulate cortex were dissected carefully and flash frozen. Undisturbed sleeping animals killed at the same circadian time served as controls. For western blot analysis nuclear and cytoplasmic proteins were isolated. NF-kB p65 in the nucleus was detected using rabbit antibody SC 109 and I-kB in the cytoplasm using C-21 (both from Santa Cruz Biotech) and chemiluminiscent detection system (Amersham). DNA binding activity determined by gel shift assay was performed using ^{32}P gamma ATP labeled NF-kB consensus oligonucleotide (sc 2505) in a 5% native polyacrylamide gel. To determine the levels of A1R mRNA the tissue from 6 animals from each group (sleep deprived and sleeping controls) was homogenized total RNA was extracted using TRIzol reagent (Life Technologies, GibcoBRL). 100 ng of total RNA was reverse transcribed for A1R and cyclophylin mRNA as normalizer using Superscript II (Life Technologies, GibcoBRL). 5 µl of reverse transcribed cDNA was used for PCR amplicfications using ^{35}S-dATP. Samples were electrophoresed in 6% nondenaturing polyacrylmide gels. The gels were dried and exposed and analysed using Molecular phosphorimager(BioRad). The ratio of the optical density of A1/cyclophylin mRNA for each sample was calculated.

Results: **Nuclear translocation of NF-kB, degradation of I-kB in the cytoplasm and increased NF-kB DNA binding activity following sleep deprivation:** NF-kB (p65) increased (determined by western blots) in the nucleus of the rat's BFB/preoptic area following three hours of sleep deprivation while I-kB protein levels decreased in the cytoplasm, compatible with the degradation of I-kB by phosphorylation. NF-kB DNA binding activity increased by 63.3 % ($N=4;t=2.8,df=6,p<0.03$) with sleep deprivation.

Increased levels of A1 R mRNA after sleep deprivation: The levels of A1 receptor mRNA showed a significant increase (+78%; Mean ± SEM; sleep deprived 0.679 ±0.095; control 0.380 ±0.0629) in the basal forebrain following 6 h of sleep deprivation whereas in cortex no significant change was observed (sleep deprived 0.903 ±0.079; control 0.734 ±0.085).

Conclusions: Our results show that following three hours of sleep deprivation NF-kB translocates to the nucleus and its DNA binding activity is increased. We also observed that A1 mRNA levels increase following sleep deprivation. We speculate that adenosine induced activation of NF-kB may play a role in mediating the long term effects of sleep deprivation by enhancing the expression of A1 receptor. This enhancement might produce a hyper-responsiveness to adenosine, which in turn, might lead to the vigilance and performance decrements seen in "sleep debt", even at adenosine levels not normally impacting alertness and performance.

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1731.J

Sleep Deprivation Increases Translocation of Nuclear Factor Kappa B in Specific Brain Regions in Kappa B-LacZ Transgenic Mice

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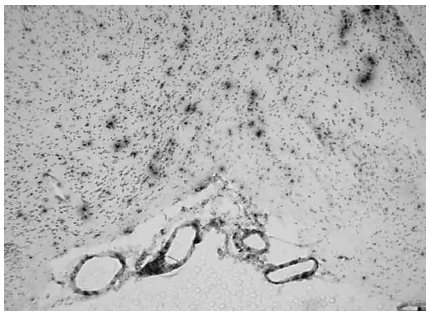
Introduction: Sleep deprivation increases sleep propensity as well as the production of a number of sleep-promoting factors within specific regions of the brain. An important transcription factor that is involved in gene activation induced by various sleep-promoting growth factors is nuclear factor kappa B (NFkB). NFkB translocates into the nucleus of cells and promotes gene transcription.

Figure 1–Nfkb-activated beta galactosidase in the diagonal band and OVLT after 6 hrs of sleep deprivation.

Control

Sleep-Deprived



NFkB-activated beta galactosidase activity in the diagonal band and OVLT after 6 hrs of sleep deprivation.

Methods: By utilizing a strain of mice with the NFkB promoter-lacZ transgene, the anatomical localizaiton of cells that translocate NFkB to the nucleus in response to sleep deprivation can be identified by analyzing the distribution of beta-galactosidase activity.

Results: Throughout the brain, NFkB-activated beta-galactosidase increases after 6 hrs of sleep deprivation. Most notably, sleep deprivation increases beta-galactosidase in the ependymal cells surrounding the anteroventral walls of the third ventricle as well as in the circumventricular organs. Sleep deprivation also increases NFkB-activated beta galactosidase in cells localized within the anterior hypothalamus, thalamus, medial septum/diagonal band, dentate gyrus, specific regions of the cerebral cortex, pons, reticular formation, cerebellum and the dorsal brainstem.

Conclusions: The fact that these increases in NFkB-activation are enhanced in specific neuroanatomical areas with increasing sleep propensity suggests that these specific local neuronal networks are involved in global sleep regulation.

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1821.J

REM Sleep Deprivation Delays Spatial Memory Task Acquisition in F344 Rats

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Introduction: REM sleep is important in learning spatial memory tasks, as demonstrated in the effects of REM sleep deprivation and enhancement and in correlations of REM sleep time with task acquisition . Most non-human behavioral sleep and memory data are collected from Sprague Dawley rats. Fischer 344 rats have been used to record hippocampal place cell activity during spatial navigation on a novel track and during subsequent REM sleep over a period of days when the track is assumed to become familiar. Tests of familiarity, such as spatial memory performance in the track environment and the importance of REM sleep in the F344 strain have not been measured. To determine whether REM sleep is important to spatial learning under experimental conditions used to test hippocampal spatial activity and whether REM deprivation impacts spatial learning in the F344 rat, we designed a track place-memory task and trained/tested over 6 days under 3 REM sleep conditions. Male F344 rats were either deprived of REM sleep (REMD) in the first 4 hours (0-4 h) after track learning, REMD 4-8 h after the track, or not deprived (controls) to test for a critical REM sleep window within 8 hours of training influencing spatial memory.

Methods: 18 of 21 three month old rats (250-300 gm) passed a visual acuity test and were randomly assigned to one of 3 groups. All rats ran on the track 1-3 h after lights on in a 12:12 light dark cycle. The track was a 89x46 cm rectangle, 8 cm wide, with either 6 (n=6 rats) or 8 (n=12 rats) evenly-spaced boxes around the perimeter which could be pushed opened to obtain mash. Food was available only during the 30 min training while the rat maintained at least 80% original free-feeding weight, corrected for growth. The same 3 box positions were baited with mash each time the rat revisited the box on a subsequent, clockwise lap. An error was counted whenever the rat investigated an unbaited box or missed a baited box. To make the task dependent on spatial, rather than procedural or odor cues, all boxes contained inaccessible food behind a screen to mask odor cues, rats were removed from the maze for 2 min every 5 laps and placed on the track again at a random start point, and every 10 laps the symmetric maze was rotated 180 degrees and boxes were again baited according to room position. From the first day on the track rats in the first group were allowed to sleep in their individual home cages (n=4, Controls). Animals in the 2nd and 3rd groups were sleep-deprived on a 6 cm diameter inverted flower pot base over 2 cm deep, room temperature water. 0-4 REMD animals were put on the pot for the 1st 4 h following training (n=8). Members of the 4-8 REMD group were allowed to sleep in home cages for 4 h after testing, then were REM deprived in the 2nd 4 h window (n=6). Rats in both REMD groups were then returned to their home cages until the track run the next day. After correction for a group mean performance difference on the

first day of 6 vs. 8 box experiments, a 2-way ANOVA with repeated measures (NCSS) was conducted to test the effect of sleep manipulations and training day on performance.

Results: F344 rats deprived of REM sleep after training required additional days to achieve the same spatial memory performance as controls ($p < 0.05$). By the 5th day of training, however, all 3 groups were performing significantly better than the first 2 days of training ($p< 0.001$). Affects of REM deprivation in the first vs. second 4 h window are less clear, since no day by group interaction emerged. However, results from both experiments showed the mean performance in the 0-4 REMD group lower than controls for one additional day as compared to the 4-8 h REMD group, and the 4-8 h REMD group required one additional day compared to non sleep-deprived controls to acquire the task.

Conclusions: Four hours of REM sleep deprivation in the first 8 h after learning impedes the rate of spatial memory acquisition in F 344 rats. REM deprivation in the first 4 h after spatial memory training may impair the animal more than REMD in the second 4 h window, however, all rats eventually learned the task when trained day after day, despite continued REM sleep deprivation. The time course of task acquisition parallels that of other spatial memory task such as the Morris Water tank and closely resembles the pattern of phase-reversed firing in the hippocampus of once novel place field cells during REM sleep. Combining the spatial memory track tasks with electrophysiological recordings should reveal whether REM deprivation induced delays in spatial memory also parallel delays in experience-dependent neural firing patterns during REM sleep.

1422.J

Unihemispheric Enhancement of Frontal Delta Power After Sleep Deprivation

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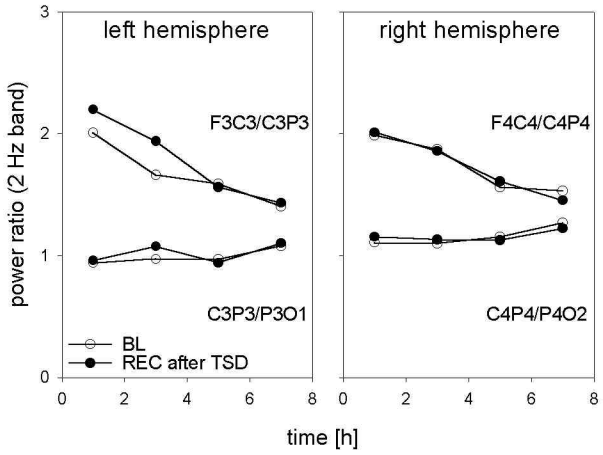
Introduction: The analysis of regional changes in EEG power spectra demonstrated that the antero-posterior gradients are not homogenous but exhibit site-specific and state-related changes in different frequency bands (Werth et al 1997). In the first NREM sleep episode, power in the 2-Hz bin was highest in the anterior derivation; over the subsequent episodes, the anterior preponderance of power declined and eventually vanished. During recovery from partial NREM sleep deprivation the increase of delta power was significantly higher in the anterior derivation than in the middle derivation (Werth et al 1998). These results support the notion of a specific involvement of the frontal cortex in the sleep process. In the present study we investigated how EEG topography is affected by total sleep deprivation (TSD).

Methods: Eight right-handed, healthy male volunteers (mean age 23 y ± 0.46 SEM, range 21-25 y) participated in the study. After a baseline night (23:00 to 7:00 h), preceded by an adaptation night, subjects were kept awake for 40 h. Subsequent recovery sleep started at 23:00 h. Subjects were allowed to sleep till 11:00 h. The EEG was recorded with a montage of 27 scalp electrodes (extended International 10-20 System). Sleep stages were visually scored for 20-s epochs according to conventional criteria. Power spectra of consecutive 20-s epochs were computed for three bipolar derivations over the left (F3C3, C3P3, P3O1) and right hemisphere (F4C4, C4P4, P4O2). Mean spectra of NREM sleep (stages 2, 3 and 4) were analyzed for 8 h and consecutive 2-h intervals.

Results: In all derivations, TSD induced a significant increase of power in the range of 0.75 - 10.0 Hz and a reduction in the spindle frequency (14.0 - 14.5 Hz) and beta range (20 - 30 Hz; not over the entire range in all derivations). Low delta activity was dominant in the anterior derivations (FC) over both hemispheres and under both conditions (baseline and recovery after TSD). The power ratios of adjacent derivations FC/CP and CP/PO of consecutive 2-h intervals for low delta activity (2 Hz) are illustrated. The FC/CP ratio reflects the frontal predominance of low delta activity, an effect that was largest in the beginning of the night and declined over consecutive 2-h intervals. TSD enhanced the frontal predominance of low delta activity in the left hemisphere ($p<0.0025$; ANOVA for repeated measures). The CP/PO ratios were close to 1 during both conditions and throughout the night, indicating no difference between the 2 derivations.

Figure 1



Conclusions: TSD effects on NREM sleep power are present in all derivations. TSD enhanced the anterior predominance of low delta activity in the left hemisphere but not in the right hemisphere. This effect may reflect a functional asymmetry between the dominant and non-dominant hemisphere.

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1066.K1

Effects of Sleep Deprivation Versus Sleep Fragmentation on Morning Reduction in Cerebral Blood Flow Velocity

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Introduction: A morning reduction in cerebral blood flow velocity (CBFV) in the middle cerebral artery has been reported in both normal human subjects and in patients with sleep apnea.[1] Non-experimental data suggest that the morning reduction is adversely affected by sleep fragmentation in sleep apnea patients[2] and is independent of preceding REM vs. NREM sleep.[3] It remains unclear whether the observed decreases represent sleep-dependent or circadian phenomena and the extent to which more profound sleep loss (sleep deprivation) would impact upon this presumably normal physiologic function. In this study, we examined the morning reduction of CBFV in normal subjects under three conditions: Baseline, Post-Sleep Fragmentation, and Post-Sleep Deprivation.

Methods: Subjects were 13 healthy male subjects without sleep disor-

ders (X age = 25.1, SD= 2.6) who spent three nights in the sleep laboratory. Transcranial Doppler (TCD) ultrasonography of the right middle cerebral artery using a transtemporal approach (2 MHz probe, 50-55 mm depth) was performed in the supine position immediately before lights out and immediately after morning lights on for each lab night. During the baseline (BASE) night, subjects were allowed to sleep uninterruptedly. On two additional nights the subjects underwent either total sleep deprivation (DEP) (with concurrent polysomnographic verification) or a sleep fragmentation protocol (FRAG) during which subjects were interrupted with novel audio stimulation presented over an intercom whenever 10 minutes of sleep accrued and then allowed to return to sleep. Order of fragmentation and deprivation nights varied across subjects. Polysomnographic data were scored by an individual blind to the TCD results.

Results: Comparison of sleep architecture across the three nights confirmed virtually no polysomnographically defined sleep on DEP (X= 1.4 mins, SD= 0.3) relative to the BASE (X= 340.8 mins, SD = 90.3) or FRAG (X =299.2 mins, SD= 79.6). Sleep efficiencies for DEP and FRAG were 90.3 (SD= 8.8) and 79.6 (SD=22.5), respectively. Differences between DEP and FRAG for TST and SE were statistically significant at $p < .001$ level, indicating considerable sleep disruption introduced by the fragmentation procedure. Mean [SD] stage 3/4 % and REM % were also significantly decreased under FRAG relative to BASE (10.8, [8.2] vs 4.4 [3.9], $t = 2.55$, $p < .03$ for stg 3/4; 18.6 [5.6] vs 12.2 [8.0], $t = 2.35$, $p < .03$, for REM).

Mean (SD) diastolic CBFV's (cm/sec) for the 3 nights, evening and morning are shown below:

Study Night	Evening	Morning
BASE	50.1 (7.2)	46.4 (6.8)
DEP	51.8 (8.1)	42.8 (7.0)
FRAG	50.2 (7.5)	52.7 (8.3)

Repeated measures ANOVAs indicated a time-by-night interaction ($F=11.5$, $p<.0001$, df 2,60) with morning values significantly lower than evening values for the BASE night ($p<.02$) and DEP night ($p<.001$) relative to the FRAG night ($p=.19$). Contrasts also indicated morning CBFV to be significantly higher for the FRAG night relative to the BASE and DEP nights (both $p<.005$). BASE and DEP nights were only marginally different ($p<.07$).

Conclusions: These results suggest a complex regulation of the post-sleep reduction in CBFV. A circadian interpretation, i.e., CBFV is decreased in the morning relative to the evening, appears possible, though this is complicated by the fact that under the FRAG condition no post-sleep morning decreases were noted. Alternatively, if the post-sleep decrease noted in earlier studies reflected a putative cerebral autoregulatory function of sleep, this function might be expected to be at least partially preempted by both a complete (DEP) and partial (FRAG) loss of sleep, a situation which also did not occur. If the morning reduction in CBFV represents a protective downregulation of the cerebral circulation afforded by sleep, these data imply that total sleep loss and sleep fragmentation have divergent outcomes for this physiologic function. These data may have clinical relevance for understanding mechanisms underlying adverse cerebrovascular events related to periodic arousals, long suspected as key pathophysiologic events accompanying repetitive episodes of sleep apnea, a disorder characterized by sleep fragmentation, rather than total sleep deprivation.

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1805.J

Neurobehavioral Effects of 66 hr of Sustained Low-Dose Caffeine During 88 hr of Total Sleep Deprivation

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Introduction: The search for safe and effective wake-promoting therapeutics for maintenance of performance capability during continuous operations has escalated in recent years. Many experiments have demonstrated the alertness-promoting effects of bolus dosages of caffeine in moderately sleepy subjects, but there have been no systematic controlled trials of the neurobehavioral effects of sustained low-dose caffeine use through a prolonged period of total sleep deprivation (TSD). To investigate this issue, we conducted a double-blind, placebo-controlled, randomized trial in which neurobehavioral functions were systematically monitored before, during and after 88 hr of total sleep deprivation.

Methods: A total of n=28 healthy adult males (age M=29 yr) who regularly used caffeine (< 500mg/daily) participated in a 10-day laboratory study in which they were randomized to either sustained low-dose caffeine (0.3mg/kg/hr for 66hr) or placebo/hr for 66 hr. N=15 subjects were randomized to caffeine for 66 hr, and n=13 to placebo for 66 hr. Following a 2-wk period in which they refrained from caffeine use and maintained a stable sleep-wake cycle, subjects entered the laboratory for the 10-day protocol. After one adaptation night, subjects had two baseline days with bedtimes from 23:30 until 07:30. They then underwent 88 hr of total sleep deprivation, during which time they were constantly monitored and kept awake with mild social stimulation. During the entire 10-day period in the laboratory subjects were tested on a 30-min computerized neurobehavioral assessment battery every 2hr. The neurobehavioral test battery included a 10min psychomotor vigilance task (PVT-192), an addition-subtraction task, the digit symbol substitution task, a critical tracking task, frontal lobe tests, the Karolinska Sleepiness Scale, the Stanford Sleepiness Scale, the POMS and many other measures of neurobehavioral functions. Physiological measures included continuous EEG, the Karolinska Drowsiness Test, heart rate, blood pressure, core body temperature, and IV lines for neuroendocrine, neuroimmune, and plasma caffeine levels. Caffeine or placebo administration began after at 0530 hr on the second day of sustained wakefulness (i.e., 22 hr into the 88 hr TSD). Thereafter, subjects took a pill every hour for the remaining 66 hr of TSD. Subjects were informed the pill could be either caffeine or placebo at any given hour, but in fact the pill was always the same, depending on the condition to which the subject was randomized. Subjects were asked to rate each hour what type of pill they received the hour before. Data were analyzed using mixed model ANOVAs with correction for sphericity.

Results: The 88 hr TSD served to effectively deteriorate virtually every aspect of performance and alertness. Analyses are still underway, but those completed on PVT lapses indicate that sustained low-dose caffeine reduced the frequency of lapses for up to 22 hr of administration (i.e., through the entire second day of TSD or up to 44 hr of TSD) relative to the placebo control condition ($F(61,1525)=1.80$, $p=0.02$). Caffeine also tended to reduce fastest RTs ($F(1,26)=3.88$, $p=0.06$). However, it had no effect on digit symbol substitution performance, which occurred in the latter portion of each test bout. Most remarkable was the complete absence of a main effect or interaction over time from caffeine on any of the subjective scales used to measure sleepiness (KSS, SSS), fatigue (POMS), alertness (VAS), or effort required to remain awake. All of these subjective dimensions only showed significant main effects (dete-

rioration) over the 88 hr TSD period (F ratios > 7, p < 0.00001). Similarly, subjects were completed unable to reliably detect whether they were receiving caffeine or placebo. Plasma levels of caffeine showed a reliable rise to a steady state around 24 hr after initial administration. No subject had to be withdrawn from the protocol due to adverse reaction to drug administration.

Conclusions: In the face of an ever-escalating homeostatic drive for sleep, sustained low-dose caffeine administration (0.3mg/kg/hr for 66hr) appeared to improve psychomotor vigilance performance capability for nearly 24 hr from approximately 22 hr of waking until 44 hr of waking. This was apparently not due to demand characteristics or unblinding, since subjects could not reliably determine what they were receiving, and their subjective ratings showed no benefits of caffeine intake. Although no subject experienced an adverse effect of caffeine that resulted in withdrawal or removal from the study, other abstracts our group have submitted at this meeting document that caffeine had physiological effects on neuroendocrine functions (Rogers et al.). Although additional variables are undergoing analyses, the results thus far suggest that a more potent wake-promoting therapeutic will be required to enhance a broader range of performance for an even longer duration during sustained TSD.

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1807.J

Cumulative Neurobehavioral Performance Deficits on a 24-hr Day with 8-hr of Scheduled Sleep

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Introduction: Chronic partial sleep loss has been reported to result in cumulative impairment of neurobehavioral functioning. Scheduled sleep episodes from four to six hr per 24-hr for one to two weeks in duration result in a level of performance equal to that observed after 24 to 48 hours of total sleep deprivation.[1] The amount of sleep required to prevent cumulative decrements in performance across weeks of sustained work-rest schedules without a day off is unknown. In the present study, we examined whether an 8-hr scheduled sleep opportunity across a sustained 32-day work-rest schedule was sufficient to maintain high levels of performance.

Methods: Seven healthy subjects, six men and one woman, participated in a 55-day laboratory protocol on circadian entrainment.[2] After three weeks of maintaining a consistent sleep-wake schedule at home, six laboratory baseline days and nights, a 40-hr constant routine (CR) and an 8-hr recovery sleep episode, subjects were scheduled to a 25-day work-rest sleep-wake schedule. Performance was assessed every 2-hr during wakefulness beginning 2-hr after awakening. Subjects were allowed leisure time, such as watching movies and reading between test batteries, but they were not allowed to sleep outside the scheduled opportunity. Repeated measures ANOVAs were used to analyze changes in performance across these 25 days. Deviation from the 25-day mean for subjective alertness, motivation and vigilance performance on a modified version of the Psychomotor Vigilance Test were analyzed. For comparison, scores for these same measures at baseline (hours two though sixteen of the CR) and after 24-hr of sleep deprivation (hr twenty-six though forty) are provided.

Results: Figure 1 shows that median reaction time slowed and the number of performance lapses increased significantly across the 25 day schedule (P<.0001). Near the end of the 25 days, the level of performance impairment approached that observed after 24-hr of total sleep deprivation. These performance changes did not appear to be mediated by changes in motivation or alertness, which remained relatively constant throughout the protocol (Figure 2).

Figure 1

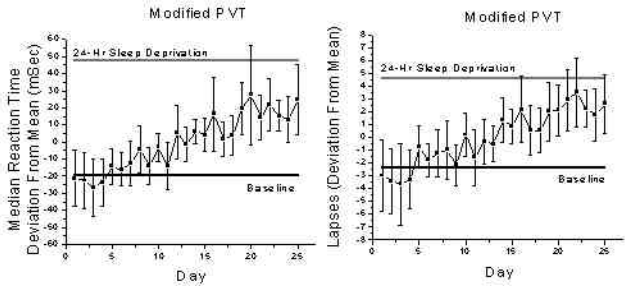
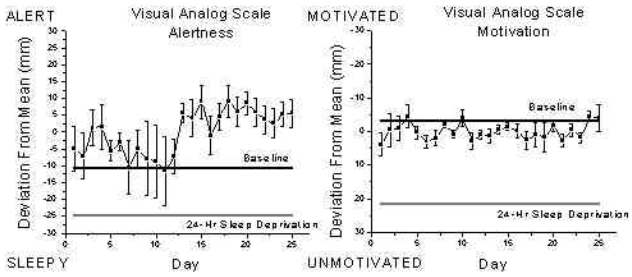


Figure 2



Conclusions: These preliminary results suggest that an 8-hr scheduled sleep opportunity may not be sufficient to maintain performance levels for work-rest schedules that do not include days off or time for extra sleep, although other explanations related to repetitive performance of the task itself have yet to be excluded. These results are consistent with those from others showing a trend for worse performance near the end of a two-week period of 8-hr scheduled sleep.[1] Taken together, these findings suggest that scheduling sleep to 8-hr per day in the laboratory may result in cumulative sleep restriction and that a longer scheduled sleep episode or days off may be necessary to prevent cumulative sleep restriction.[3]

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1885.J

Sleep Deprivation Does not Affect the Frequency or Timing of Seizures in Patients with Partial Epilepsy

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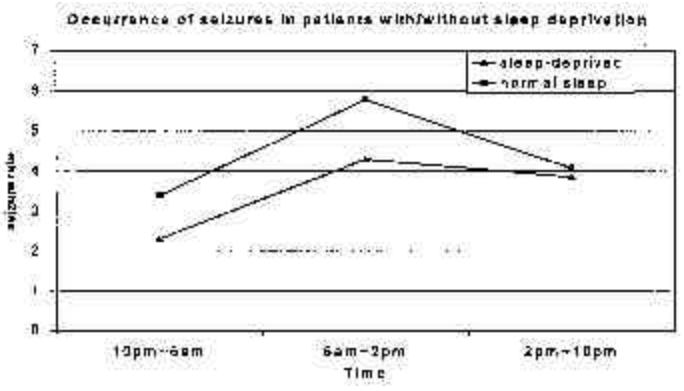
Introduction: Epileptic seizures are known to be influenced by the human circadian rhythm (Milton, et al 1987; Quigg, et al 1998). Acute sleep deprivation is frequently used in epilepsy monitoring units to facilitate seizure recordings as a part of the presurgical evaluation. Whether acute sleep deprivation changes the frequency and timing of seizures in patients with epilepsy is unknown and of clinical importance.

Methods: Thirty-nine partial epilepsy subjects, aged 18-57 years, were selected consecutively from all those undergoing inpatient continuous video-EEG monitoring at our institution. Nineteen subjects were sleep-deprived (11 men, 8 women), and 20 subjects had normal sleep (15 men, 5 women). Sleep deprivation was defined as staying up every other night (40 continuous hours from 6 am to 10 pm the following day). Subjects slept from 10 pm to 6 am, with the sleep-deprived subjects sleeping every other night and the normal sleep subjects sleeping every night. Both videotape and EEG recordings were reviewed to document that recorded events were seizures and to confirm the timing of seizures. A multivariate analog of logistic regression, based on the generalized estimation equations (GEEs) (Diggle, et al 1994), was used to determine: (i) the frequency and timing of seizures in all the subjects in relationship to the circadian rhythm; and (ii) the effect of sleep deprivation on the frequency and timing of seizures.

Figure 1



Results: Seizures were most frequent between 6 am and 2 pm, and least frequent between 10 pm and 6 am ($p<0.002$) (Figure). Seizure rate was defined as the proportion of seizures per subject-hour within each time interval. Age- and sex-adjusted GEE models showed comparable results. There were no statistically significant differences in the timing or frequency of seizures between sleep-deprived and normal sleep groups ($p>0.10$).

Conclusions: Subjects showed a circadian pattern of seizures with seizures occurring more frequently during the day than during the night. This finding is congruent with a recent report (Quigg, et al 1998). We observed this pattern regardless of whether subjects were sleep-deprived or not, suggesting that sleep deprivation did not change the timing of seizures. Our results suggest that circadian rhythms exert a stronger influence on seizure occurrence than the sleep-wake cycle in partial epilepsy patients. In addition, acute sleep deprivation did not significantly increase the frequency of seizures in subjects with partial epilepsy. Therefore, the rationale for universally sleep-depriving all partial epilepsy patients undergoing presurgical monitoring may be questioned.

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1314.E

A Phase Response Curve to Single Pulses of Bright Light in Humans

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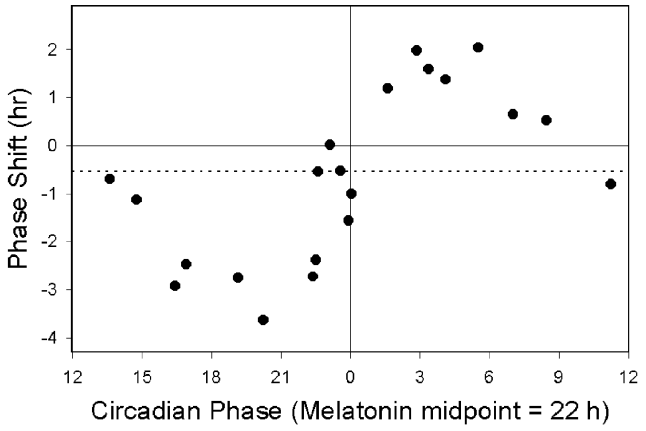
Introduction: It is now well established that light can have profound effects on the human circadian pacemaker. Low light levels typical of artificial indoor illumination are capable of generating phase shifts, and 3-cycle bright light pulses can yield a strong Type 0 phase response curve (PRC). Although PRC's to single light pulses in humans have been reported, relatively small sample sizes were used (Honma & Honma 1984; Minors et al 1991; Jewett et al 1994). In this study we present a comprehensive PRC to single bright light pulses.

Methods: Healthy, entrained male and female volunteers (N=21) completed a 9-10 day in-laboratory study. The protocol began with 3 baseline days (~80-150 lux in the angle of gaze) and nights (~0 lux) on the subjects' habitual sleep/wake schedule. Subsequently, all subjects underwent a constant routine (CR) in dim light (~3-7 lux in the angle of gaze) with enforced wakefulness in a semi-recumbent posture for 27-49 hrs. The timing of the end of the CR and the subsequent 24-hr light-treatment day varied across subjects in order to systematically span the entire circadian cycle. Following an 8-hr sleep episode subjects were awake for 16 hrs in dim light, except for a bright light treatment centered in the middle of this waking episode. The 6.7-hr bright light treatment consisted of 6-min episodes of fixed gaze at a light intensity of ~10,000 lux alternating with 6-min episodes of free gaze (~ 4,000-7,000 lux in the typical angle of gaze). Another 8-hr sleep episode was followed by a post-stimulus CR of 30-65 hr. Plasma melatonin concentration was evaluated at 0.5 hr intervals and phase shifts were calculated as the difference between the phases of the midpoint of the mean crossings of the melatonin peaks on the pre- and post-stimulus CR's.

Results: The PRC (see Figure) revealed robust phase shifts ranging in magnitude from -3.6 hr (delay) to +2.0 hr (advance). The horizontal axis is plotted relative to the midpoint of the pre-stimulus melatonin peak which is assigned a phase of 22 hrs, so that the core body temperature minimum, which occurs approximately 2 hrs later, is assigned to 0 hrs. The horizontal dotted line represents the anticipated 0.54 hr delay drift in phase due to the endogenous free-running period of the human circadian pacemaker (24.18 hrs on average) during the 3 days between the pre-stimulus and post-stimulus phase estimates. Phase delays occurred for light pulses applied prior to the core body temperature minimum, phase advances occurred for light pulses applied after this phase, and a transition from phase delays to phase advances appears at the phase of the core body temperature minimum.

Figure 1



Conclusions: Single bright light pulses of 6.7-hr duration induce both phase delay shifts and phase advance shifts, generating a PRC with a characteristic shape similar to Type 1 light PRC's in other organisms. Consistent with a previous report from our laboratory for light-induced phase shifts to 3 pulses of bright light during the subjective day, there is no discernable "dead zone" in which phase shift magnitudes are low for a prolonged segment of the circadian cycle.

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1691.E

The Circadian Phase-Shifting Effects of Light are Modulated by Recent Prior Light History

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Introduction: Timed exposure to bright light can alleviate age-related insomnia and other sleep disturbances associated with a misalignment between the circadian clock and preferred sleep time. Previous research has suggested that managing prior light history may help to optimize the effectiveness of bright light as a phase-shifting stimulus. Therefore, our aim was to examine the effects of a recent prior history (RPH) of bright or dim light on a subsequent phase-shifting pulse of bright light to the eyes. We hypothesized that an RPH of dim light would sensitize the circadian clock to a bright light pulse.

Methods: Sixteen healthy volunteers (9m,7f; aged 19-72 yrs) completed 3 separate, counter-balanced conditions, each consisting of a baseline night, a light administration night and 1-2 post-administration nights (and intervening days). Continuous core temperature measurements were used to determine circadian phase on baseline and post-administration nights. Light was administered during the expected phase delay portion of the human PRC and timed to minimize variation in phase angle between conditions. For a 10-h RPH period preceding the light administration, each subject received either Bright Light (BL, 1000 lux), Dim Light (DL, 20 lux) or Control (CL, 1000 lux). The intensity of the subsequent 3-hr light pulse for each condition was then 5000 lux (BL, DL) or 20 lux (CL). The CL condition was intended to control for any phase-shifting effects due solely to the 10 hours of 1000 lux in the BL condition (i.e. net effect of 3-h of 5000 lux = BL minus CL). Wakefulness during light administration was monitored polygraphically. Except during light administration, subjects slept each night in darkness from 2400 h, and after waking were kept in bed until 1200 h in <20 lux ambient light. Between 1200-2400 h, room lighting was kept <100 lux.

Results: Comparison of the net phase-shifting effect of the 3-h 5000 lux stimulus (BL minus CL) with the DL condition revealed a significant main effect of condition ($p<0.05$) and an interaction between condition and age ($p<0.05$). Mean phase shift magnitudes were 0.1 ± 0.5 h (BL minus CL) and 1.6 ± 0.4 h (DL). When split by age, younger subjects showed no differences between conditions ($p = 0.28$), with a mean phase shift due to a 3-h 5000 lux light pulse (BL minus CL) of 0.8 ± 0.6 h, compared with that in the DL condition of 1.1 ± 0.1 h. In older individuals, phase shifts were significantly greater ($p<0.01$) following DL (1.9 ± 0.6 h), than due to BL minus CL (-0.3 ± 0.6 h).

Conclusions: These results are partially consistent with the hypothesis that a dim prior light history sensitizes the circadian clock to a subsequent bright light stimulus, as it held true only in older individuals. Together the results support the suggestion that control of recent prior light history might be important for light treatments designed to improve an inappropriate phase relationship between the circadian clock and sleep timing, at least in the population most likely to benefit from such treatment - the elderly.

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1840.E

Sleep Alters Human Phase Response To Extraocular Light

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Introduction: It has been known since the 1960's that non-mammalian vertebrates are capable of extraocular circadian phototransduction. The circadian timing systems of every such species studied have been entrained, or phase-shifted, in response to presentation of an extraocular photic stimulus. The few studies that have examined the issue in mammals concluded that these species do not have the capacity for extraocular circadian phototransduction, though recent findings challenge the view.[1] We reported previously that light to the popliteal fossa of humans resets the circadian clock in a manner similar to that reported for ocular light exposure.[2] Here we report that the human phase response to extraocular light is altered, but not negated, when the stimulus is presented during sleep.

Methods: Thirteen subjects were studied in counter-balanced active and control conditions. In each condition, subjects spent 5 days and nights in the laboratory, during which body temperature was recorded continuously. During the first 24 hrs, baseline circadian phase was assessed. Subjects were exposed twice, during the next two 24-hr periods, to a 3-hr pulse of extraocular light (or to a sham condition) while sleeping. The timing of light exposure varied across subjects, but clock time of exposure was the same for each subject in control and active conditions.

Light was presented using fiber-optic pads placed on the popliteal fossa of each leg. In the control condition, pads were covered with an opaque sheath that blocked light from reaching the skin. Circadian phase was again assessed during the final 48 hours in the lab, and degree of shift was determined by comparing baseline with post light circadian phases. Temperature curves were fit by four individuals blind to subject and condition, and phase was determined by calculating the average time of the temperature minimum (tmin) of the blind fits.

Results: As would be expected based on the human phase response to light, there was a systematic variation in the degree to which extraocular light reset the biological clock, depending on the phase at which light was presented. The largest shifts occurred when light was presented close to tmin. The average absolute shift in response to active light presented within 5 hours of tmin was 100.72 minutes, compared to 30.6 minutes in the control condition ($p = .011$). In contrast to light PRCs obtained from waking subjects, this "sleep PRC" was characterized by a predominance of phase delays in response to light presented both before and after tmin. Not only was the biological clock affected by extraocular light presented during sleep, sleep architecture was influenced as well. Specifically, the proportion of sleep spent in REM sleep during the 3-hour light administration interval showed an average 47% increase in the active compared to the control condition. No other sleep stages were significantly affected by the light exposure. The increase in REM% was not due to a lengthening of REM period duration, but rather the consequence of an increase in the frequency of discrete REM periods. The result was a significant shortening in the average duration of REM/NREM cycles occurring during the 3-hour light presentation interval ($p = .02$).

Conclusions: These findings demonstrate that the human circadian clock can be reset by extraocular light exposure, even when presented to sleeping subjects. The results further suggest that arousal state can alter the manner in which the clock responds to phase shifting stimuli. The additional finding that extraocular light acutely, and significantly, increases REM sleep amounts indicates that non-ocular sensory stimuli are detected and responded to by multiple neuronal sites. Both findings may have significant clinical implications: clock resetting during sleep couls decrease substantially the burden imposed on individuals with circadian rhythm sleep disorders by traditional light treatment interventions. The associated REM sleep enhancement could prove useful as a non-drug treatment for cognitive declines associated with normal and pathological aging.

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1175.E

Clinical Trial of Bright Light Mask for Delayed Sleep Phase Syndrome

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Introduction: In Delayed Sleep Phase Syndrome (DSPS), sleep and circadian rhythms are chronically phase-delayed but otherwise normal. Morning bright light can advance phase and provide clinical benefit in DSPS; however, conventional light treatment is time-consuming and often inconvenient. We therefore tested light treatment of DSPS with an illuminated sleep mask that provides bright light through closed eyelids during sleep.

Methods: Fifty-nine men and women, ages 18 to 40 years (mean 25, SD 6), who met diagnostic criteria for DSPS (ASDA 1990) were stratified by baseline bedtime (< 2 am, n = 31, or ≥ 2 am, n = 28) and randomly assigned to receive either bright white light (2,700 lux, n = 29) or dim red light placebo (0.1 lux, n = 30). Light was administered through closed eyelids during sleep at home for 26 days. Lights-on (< 0.01 lux) began four hours before scheduled time of arising. The lights ramped up gradually for one hour to the assigned brightness level, then remained on for an additional 3 hours, or until the volunteer arose, whichever occurred first. In addition, all volunteers received behavioral treatment consisting of (1) systematically advancing bedtime and time of arising, (2) avoiding naps, and (3) avoiding exposure to daylight and bright artificial light after 5 pm. Each volunteer collected samples of all voided urine in dim light for approximately 48 hours immediately before and after the 26-day treatment period. Samples were assayed by radioimmunoassay for 6-sulphatoxymelatonin (6SMT). The acrophase of the 6SMT excretion rate was computed by fitting a 24-hour cosine to the data. Sleep times were estimated from wrist activity measured by an Actillume monitor worn for 7 days immediately prior to treatment and for 7 days at the end of treatment (including the last 5 days of treatment plus the 2 post-treatment urine sampling days).

Results: The light mask was well-tolerated and produced little sleep disturbance. Fifty-four (28 bright, 26 dim) subjects satisfactorily completed treatment, including two who chose to reduce their light level to 300 lux. Analyzable 6SMT data were obtained for 45 subjects. The acrophase of 6SMT advanced significantly in the bright group, from 0616h before treatment to 0514h after ($p < .0006$ by t-test), but it did not advance significantly in the dim group (0623h to 0554h, $p > .17$). When the baseline-adjusted post-treatment acrophases in the bright and dim groups were compared directly by ANCOVA, the advantage of bright over dim treatment did not reach statistical significance ($p > .13$). However, when the analysis was restricted to those participants who had more severe DSPS at baseline (6SMT acrophase later than the median of 0600h, n = 12 bright, 11 dim), bright treatment was clearly superior (ANCOVA $p = .03$, bright shift from 0732 to 0554, $p < .0009$, dim shift from 0746h to 0717h, $p > .39$). Preliminary analysis of raw sleep data (without correction for naps or environmentally induced awakenings) showed that the main sleep period advanced significantly in both the bright and dim groups when all 54 participants were considered together (sleep onset shift: bright group 0226h to 0130h, $p < .0001$, dim group 0215 to 0130h, $p < .03$; wake-up shift: bright group 1009h to 0902h, $p < .0001$, dim group 1004h to 0902h, $p < .0005$). However, when only those 23 participants with later-than-median baseline 6SMT acrophase were considered, sleep onset advanced significantly only in the bright group, not in the dim group (sleep onset shift: bright 0306h to 0145h, $p < .0002$, dim 0229h to 0211h, $p > .50$, ANCOVA $p < .05$). The corresponding results for wake-up time shift were: bright 1050h to 0909h, $p < .0006$, dim 1025h to 0932h, $p < .07$, ANCOVA $p > .27$. Considering all 54 participants, despite equal expectations at baseline when they previewed the light they would receive, those who completed bright light treatment rated it as more effective than those who completed dim light treatment ($p < .04$).

Conclusions: Bright light mask treatment through closed eyelids during sleep combined with behavioral treatment significantly advanced circadian phase and sleep in DSPS volunteers, while dim light placebo plus behavioral treatment did not advance phase and had inconsistent effects on sleep. The bright light mask showed its clearest advantage over placebo in more severely delayed DSPS volunteers. The bright light mask was

well-tolerated, and volunteers perceived it to be more effective than placebo.

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Research supported by NS34222-03. Light masks were provided by Lumitex, Inc., Strongsville, OH. Dr. Cole holds patents on the light mask and has a commercial interest in it.

1056.E

Treatment of Daytime Sleep after Night Shift Work with Exogenous Melatonin

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Introduction: When night shift workers are required to sleep during the day, they experience disturbed sleep as a result of sleeping during the "wrong" phase of the circadian cycle. Exogenous melatonin improves subjective ratings of daytime sleep and has also been shown to improve daytime sleep in polysomnographic (PSG) studies.[e.g.,1-2] The few studies that have used PSG to assess melatonin's effects on daytime sleep, however, have utilized an ultrashort sleep-wake cycle paradigm or short (4 hr) sleep opportunities. In addition, these daytime naps followed a full night of sleep or a night of partial sleep deprivation. None of the studies recorded daytime sleep after a night of work and wakefulness — the situation of a real night worker. Our ongoing study uses a placebo-controlled, double-blind, cross-over design to investigate whether melatonin improves PSG sleep compared to placebo in subjects who sleep during the day after staying awake during simulated night shifts.

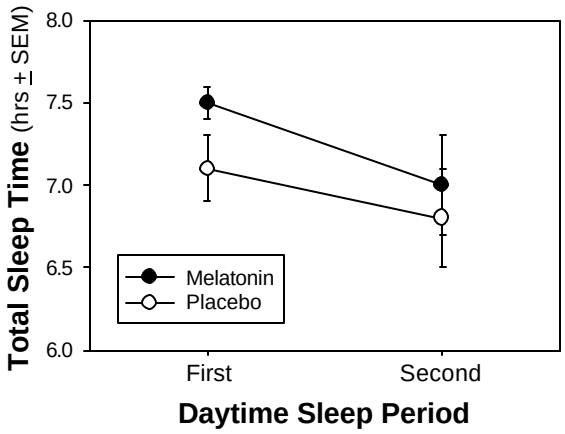
Table 1

Variable	**First**	**Second**
Mean (SD)	**Melatonin Day**	**Melatonin Day**
Stage 1 %	7 (6)	9 (5)
Stage 2 %	56 (9)	54 (9)
Slow Wave Sleep %	19 (10)	17 (10)
REM %	19 (3)	20 (5)
Sleep Efficiency (%)	94 (5)	87 (12)
Variable	**First**	**Second**
Mean (SD)	**Placebo Day**	**Placebo Day**
Stage 1 %	6 (4)	7 (4)
Stage 2 %	54 (10)	54 (11)
Slow Wave Sleep %	21 (11)	17 (10)
REM %	19 (5)	23 (6)
Sleep Efficiency (%)	89 (12)	85 (14)

Methods: So far, 14 healthy young adults who were not shift workers and did not have sleep disorders (6 female, 8 male, mean age 27.4+4.2 years) have participated. After 3 nights of adaptation and baseline PSG scheduled to match their typical routines, subjects underwent an acute 9-hr shift of the sleep-wake cycle by staying awake for 2 consecutive simulated night shifts and postponing their usual nighttime sleep until the morning. Subjects were required to stay in bed for the scheduled 8 hrs during all sleep periods. Subjects took 1.8 mg sustained-release melatonin or placebo ½ hr before bedtime on the two daytime sleep days. Sleep was scored in 30-second epochs using Rechtschaffen/Kales standard criteria. Data were analyzed using a 2 x 2 repeated measures ANOVA with within-subject factors Treatment (melatonin, placebo) and Day (first, second).

Results: In this preliminary sample, there were no significant main effects of treatment or day; thus none of the sleep variables differed as a function of melatonin administration or day of daytime sleep (Table). There was a trend (p=.15) for melatonin administration to produce more sleep than placebo (See Fig.). Interestingly, more than half the subjects (57%) had high sleep efficiencies (> 85%) during all 4 day sleep episodes.

Figure 1



Conclusions: These data suggest that a low dose of sustained-release melatonin administered before long daytime sleep episodes after night work produces minimal effects on sleep architecture. Sleep efficiency and TST, however, may be improved slightly by melatonin. In our study, the ideal, dark, quiet sleep environment and the sleep deprivation imposed by the night work schedule may have contributed to the high sleep quality we observed in many of our participants. Melatonin might produce larger differences than placebo in individuals who experience difficulty sleeping during the day or in older subjects. Larger doses of melatonin administered before long daytime sleep episodes should also be investigated.

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1267.E

Does Morning Melatonin Administration Phase Delay Human Circadian Rhythms?

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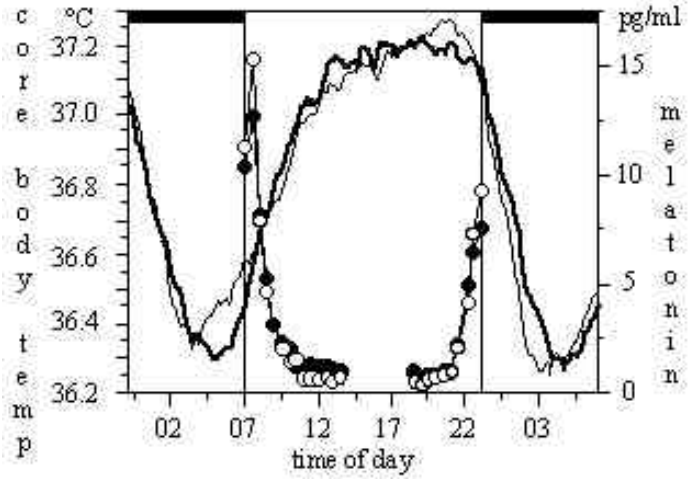
Introduction: There is good consensus that melatonin administration (MEL) in the early evening is able to phase advance circadian rhythms

in humans. In contrast, the evidence for a phase delay after MEL administration in the morning is sparse (e.g. Deacon et al. 1997, Lewy et al. 1997).

Methods: We carried out a double-blind randomized-order placebo-controlled study administering MEL at the time of putative phase delay, under the identical constant routine (CR) conditions where we had previously been able to measure a phase advance. Nine healthy young men [age: 24±1y(sem), BMI: 23.5±0.7] entered the laboratory at 20h and remained supine in bed for the next 58 hours. Sleep was scheduled between 23-07h (lights off). A CR protocol (<8 lux) was carried out during the wake period. Thermometry (rectal and skin temperatures) and heart rate were continuously recorded. Saliva was collected half-hourly for MEL assay (Dim Light Melatonin Onset or Offset threshold: 3pg/ml), together with a self-rating and performance battery. Both waking- and sleep-EEG was registered. MEL (5mg p.o.) or placebo was administered directly at 07h on the first morning. Phase shifts were measured 24 hours later.

Results: Neither the timing of morning DLMOffset (placebo: 09:23±22' vs. MEL: 09:13±16') or evening DLMOnset (22:37±19' vs. 22:33±18'), nor heart rate and skin temperature rhythms were phase shifted after melatonin compared with placebo. The mid-range crossing time of the core body temperature (CBT) rise occured earlier (placebo: 09:28±36' vs. MEL: 08:54±33', $p<0.1$) and the decline later (00:36±10' vs. 01:02±15', $p<0.01$) leading to a significant increased duration of higher-than-mid-range crossing temperature values after MEL administration (placebo: 15.14±0.53h vs. MEL: 16.13±0.44h; $p<0.05$). This complex pattern resulted from alterations in the shape of the CBT rhythm (different rate of change) and could not be interpreted as a straightforward phase shift (see figure, MEL = dark lines).

Figure 1



Conclusions: These negative results contrast with the clear phase-advancing effects obtained under the same experimental conditions after administering MEL in the early evening (Kräuchi et al. 1997). Whether there is a significant phase delay portion of the PRC to melatonin administration in humans still needs to be established.

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1369.E

Circadian and Sleep Stage Influences on Cardiac Autonomic Tone

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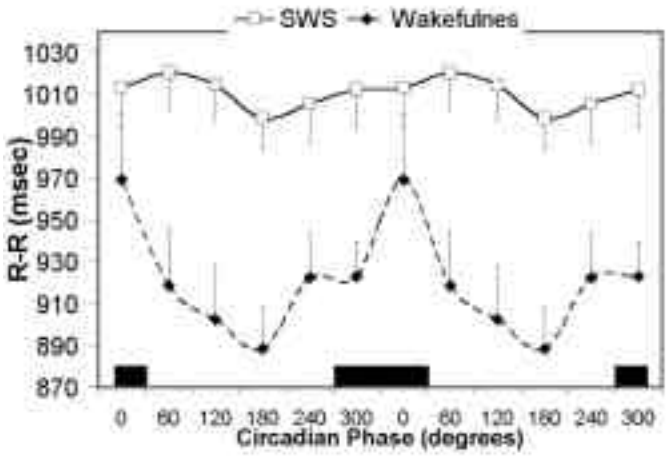
Introduction: There are prominent diurnal rhythms in the occurrence of both myocardial infarction and asthmatic episodes, and these events are possibly linked to a diurnal rhythm within the autonomic nervous system (ANS). However, the degree to which the diurnal rhythm in ANS tone is caused by an underlying endogenous circadian influence, or the effect of changes in behavior (including sleep) has not been established. A 'forced desynchrony' (FD) protocol enables the determination of the independent effects of sleep and circadian rhythms by scheduling sleep across all phases of the circadian cycle. By using a FD protocol, in conjunction with measurements of heart rate variability (HRV), we have determined (1) the degree of intrinsic circadian variability in sympathetic and vagal tone and (2) the contribution of sleep stage to ANS balance (controlling for circadian cycle).

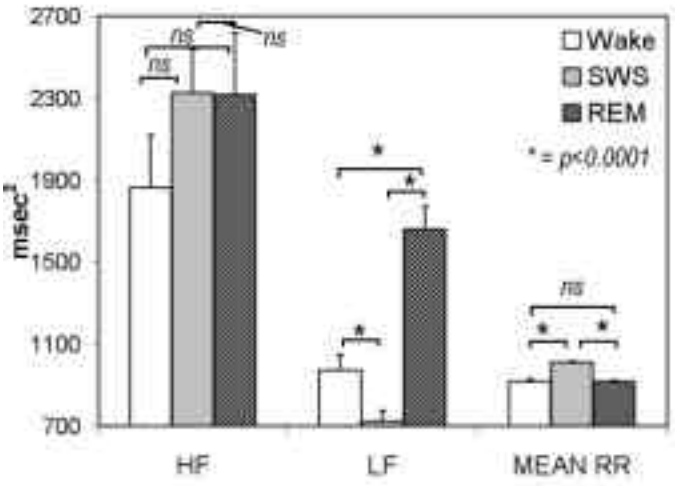
Figure 1. Circadian variability of R-R intervals



Methods: Subjects were participants in a FD protocol designed to examine the effects of exogenous melatonin administration on sleep and cognitive performance. Twelve healthy subjects (aged 20-29 years; body mass index of 18-26 kgm-2; 6 males) completed a 27 day, 20 hour FD protocol in a time isolation facility. This consisted of three baseline 24 hour days followed by 24 cycles, with each cycle consisting of 13.3 hours scheduled wakefulness and 6.7 hours scheduled sleep opportunity. To allow the circadian pacemaker to 'free run' at its intrinsic period (?24.2 hours) lighting levels were < 15 lux during scheduled wakefulness and < 0.1 lux during the sleep opportunity. Sleep stages were defined according to Rechtschaffen & Kales criteria, and categorized in to wakefulness (W), slow wave sleep (SWS), and REM sleep. Cardiac efferent vagal tone, sympathetic tone and sympatho-vagal balance were assessed from HRV measures of high frequency power (HF), low frequency power (LF) and mean R-R interval, respectively. HRV data were assigned a circadian phase relative to the core body temperature minimum (representing 0 degrees). Data were then segregated into six separate 60 degree circadian bins. The significance of circadian rhythms in HRV were tested using repeated measures ANOVAs for each behavioral state. The effects of sleep stage on HRV (independent of circadian influences), were tested using paired t-tests on data averaged across sleep stage.

Results: There were significant circadian rhythms in R-R interval during both wakefulness and REM sleep ($p < 0.05$), with R-R interval lengthening (i.e., heart rate slowing) across the 'circadian night' (dark bar in Figure 1). In contrast, there was no significant circadian rhythm in R-R interval during SWS. Figure 2 illustrates that, averaged across all circadian phases: (1) heart rate was significantly slower during SWS when compared to wakefulness and REM; (2) vagal tone (HF) was not significantly different between wakefulness, SWS and REM sleep; and (3) sympathetic tone (LF) decreased during SWS and increased during REM sleep.

Figure 2. Comparison of sleep stage HRV results



Conclusions: Waking and REM R-R interval data indicate a significant circadian rhythm in ANS sympatho-vagal balance. This finding may be important in the chronopharmacology in diseases affected by ANS function. The shift in sympatho-vagal balance toward vagal predominance over the circadian night may be a mechanism for nocturnal bronchoconstriction. When circadian variations are accounted for, vagal tone is not significantly affected by either SWS or REM. This contrasts markedly with previous reports that, as sleep 'deepens', there is a progressive increase in vagal activity. Thus, alterations in sympatho-vagal balance from wakefulness to SWS and REM appear to be principally governed by changes in sympathetic tone.

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1797.E

The Endogenous Circadian Rhythm of Pulmonary Function in Humans

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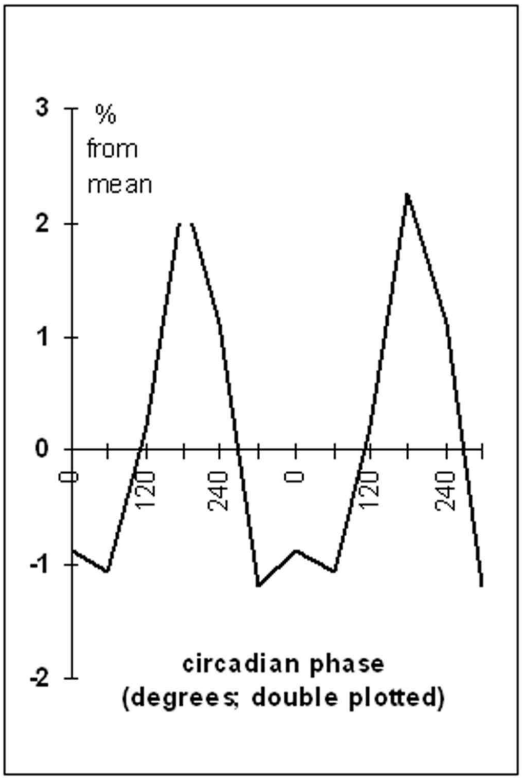
Introduction: Numerous studies have demonstrated diurnal rhythms in indices of pulmonary function in both healthy and asthmatic subjects, with minima occurring during the night.[e.g.,1-3] To determine whether such diurnal changes are caused by an endogenous circadian rhythm or by diurnal alterations in behavior (such as sleep), we measured indices of pulmonary function throughout a 'forced desynchrony' (FD) protocol designed to separate the independent effects of circadian rhythms and diurnal behaviors by scheduling sleep across all phases of the circadian cycle

Methods: Subjects were participants in a FD protocol designed to examine the effects of exogenous melatonin administration on sleep and cognitive performance. 25 healthy subjects (aged 20-29 years; 14 male) completed a 27 day, 20 hour FD protocol in a time isolation facility. This consisted of three baseline 24 hour days followed by 24 cycles, with each cycle incorporating 13.3 hours of scheduled wakefulness and 6.7 hours of scheduled sleep opportunity. To allow the circadian pacemaker to 'free run' at its intrinsic period (approximately 24.2 hours), lighting levels were < 15 lux throughout the study. Measurements of peak expiratory flow (PEF), forced vital capacity (FVC) and forced expired volume in one second (FEV1) were made once per wake period at the same time (7 hours) after scheduled wake-time. Core body temperature was measured to estimate circadian phase. Pulmonary function data were then segregated into six separate 60 degree circadian 'bins'. The significance of circadian rhythms was tested using repeated measures ANOVAs.

Results: A significant group mean circadian variation occurred in FEV1 ($p < 0.006$) and PEF ($p< 0.03$), but not in FVC ($P>0.05$). The group mean circadian minima of spirometric variables occurred within the usual sleep period (although subjects were awake for the measurements during this FD protocol), corresponding to approximately 2 AM. Expressed as a percentage of the group mean throughout the FD protocol, the amplitudes of the group mean circadian variations were small: 1.4 % for FEV1 and 3.5% for PEF (Fig. 1). Due to differences in phase among subjects, the peak to trough circadian changes within individuals were larger than the group average changes (ranges among subjects: 1.8 - 18.9% [mean = 6.1%] for FEV1; and 2.5 - 28.1% [mean = 10.1%] for PEF [Fig. 2]).

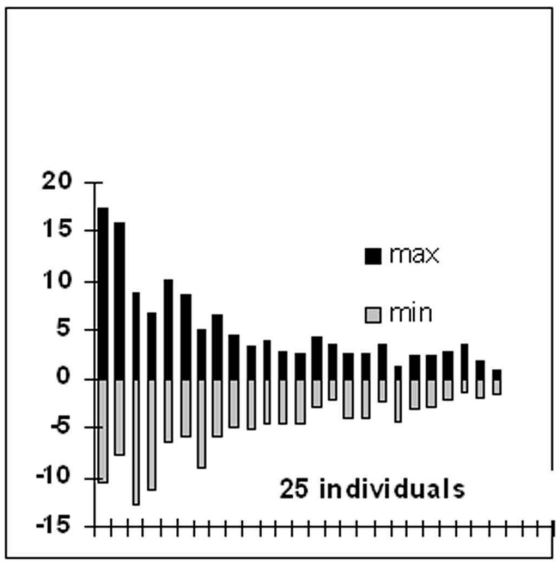
Figure 1. Group mean circadian variation in PEF



Conclusions: This study has used an established circadian technique to determine the degree to which the endogenous circadian pacemaker contributes to the previously reported diurnal changes in pulmonary function.[e.g.,1-3] Our data indicate that healthy adults have a small but significant group mean circadian variation in FEV1 and PEF, with larger rhythms within subjects (and some differences in phase among subjects).

The group mean circadian minima of spirometric variables occurred within the usual sleep period. These data are consistent with the findings of previous diurnal studies, suggesting that the diurnal effects are largely attributable to effects of the endogenous circadian pacemaker rather than posture, sleep, other changes in behavior or the environment.

Figure 2. Individual ranges of variation in PEF across circadian cycle (as % from mean)



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1623.G

Prolonged Sleep Restriction in 11- and 12-year-old Children: Effects on Behavior, Sleepiness, and Mood

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Introduction: Excessive sleepiness in children–whether induced by sleep disruption or sleep restriction–may be a significant risk factor for behavior problems. Nevertheless, behavioral manifestations of sleepiness in children have not been studied extensively. We present repeated-measures comparison of behavior in children following a week of optimized sleep and a week of sleep restriction. We hypothesized that prolonged sleep restriction would be associated with behavioral difficulties at home, at school, and during in-lab assessment.

Methods: 16 boys and 11 girls (ages 10.9 to 12.9 yr) screened for medical and psychological health participated in the three-week study. Participants slept on a self-selected schedule at home during week one and followed assigned sleep schedules for 6 consecutive nights during weeks two and three: Optimized (10 hours per night) and Restricted (6.5 hours per night), assigned in counterbalanced order. Sleep at home was confirmed with actigraphy and self-reports. At the end of each week, participants were observed at school and attended an overnight lab visit, maintaining assigned bedtime schedule during the lab visit and undergoing introspective, physiological, behavioral, and performance testing the next day. We present results of weekly behavior rating questionnaires completed by parents (Home Situations Questionnaire–Revised (HSQ–R; Barkley, 1990), Parent Questionnaire (PQ)), teachers (School Situations Questionnaire–Revised (SSQ-R; Barkley, 1990), Teacher Questionnaire (TQ)), and in-lab staff (Child Attention Profile (CAP; Barkley, 1990)). The HSQ-R, SSQ-R, and CAP rated child attention problems, the PQ rated irritable and oppositional behavior as more (+) or less (-) than usual, and the TQ rated academic performance and classroom behavior. Introspective reports of sleepiness and mood (100 mm analog scales), and the Multiple Sleep Latency Test (MSLT) were obtained during the in-lab protocol.

Results: Effects of condition (Optimized vs. Restricted sleep) were assessed with repeated-measures analysis of variance (MANOVA). Restricted sleep was associated with higher total problem scores on HSQ-R ($F(1,26) = 16.41$, $p < .001$) and PQ ($F(1,26) = 17.26$, $p < .001$), and higher Inattentive score on in-lab CAP ratings ($F(1,23) = 10.91$, $p < .01$). SSQ–R Total Problem scores revealed no significant differences, but the Restricted condition was associated with deficits on academic performance questions from the TQ ($F(1,23) = 4.70$, $p < .05$). The Restricted condition was also associated with subjective reports of increased sleepiness ($F(1,26) = 15.34$, $p < .01$), decreased happiness ($F(1,26) = 9.47$, $p < .01$), and decreased sleep latency on MSLT ($F(1,26) = 160.60$, $p < .001$).

Table 1

VARIABLE	RESTRICTED Mean	(SD)	OPTIMIZED Mean	(SD)
HSQR Total Problems***	3.0	(3.3)	0.7	(1.6)
PQ Total Problems***	4.3	(3.3)	-1.8	(4.5)
SSQR Total Problems	1.9	(2.1)	1.5	(2.1)
TQ Academic Perf.*	11.6	(2.2)	12.9	(2.2)
Analog Sleepiness**	27.1	(19.6)	18.7	(15.7)
Analog Happiness**	85.3	(19.8)	89.2	(16.9)
MSLT sleep latency***	8.5	(4.2)	17.8	(2.5)

*$p < .05$, ** $p < .01$, *** $p < .001$.

Conclusions: As expected, restricting sleep each night to 6.5 hours for one week was associated with greater daytime sleepiness, as evidenced by MSLT and subjective sleepiness ratings during in-lab assessment. Restricted sleep was also associated with inattentiveness, irritability, non-compliance, and academic problems. These findings indicate that prolonged sleep restriction has a pervasive impact on behavior at this age, and these effects are especially striking given our screening of behavioral and academic problems.

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1042.G

Long-Term Impact of Snoring During Early Childhood on Academic Performance in Middle School

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Introduction: Obstructive sleep apnea in young children is associated with adverse outcomes as they relate to learning during 1st grade. Indeed, among 297 poorly performing 1st graders in public schools, there was an estimated 6-8 fold increase in the number of children who had symptoms and nighttime-associated gas exchange abnormalities compatible with obstructive sleep apnea syndrome (OSAS; 1). In those who had OSAS, treatment led to amelioration of school performance.[1] However, after the 2-6 year old peak in the frequency of adenotonsillar enlargement, there appears to be a regression in sleep-related breathing symptoms, as well as a reduction in the prevalence of snoring and possibly OSAS. However, the long-term impact of snoring and OSAS remains unknown. We hypothesized that lower school performances would be more likely to occur among children who had a history of snoring during their early years of life.

Methods: Questionnaires were mailed to 2,000 7th and 8th graders attending public middle schools who were ranked in their class either in the top 25% (n=1,003; HP) or bottom 25% of their class (n=998; LP). The questionnaire specifically inquired about snoring frequency and severity at ages 2-6, as well as whether surgical removal of tonsils and adenoids had occurred at any time due to snoring or to recurrent throat infections. In addition, the cumulative average school grades were also requested.

Results: Of the 2,001 questionnaires, 114 were returned due to wrong address; 679 parents responded to the questionnaire and correctly filled out all the pertinent questions (36% return rate). An additional 122 responded with many items missing, and are currently being contacted by telephone to improve response rates. Of the responders, 336 were in the LP group and 343 in the HP group (p-NS). Similarly, there were 51.7% girls in LP and 50.9% girls in HP (p-NS). Frequent snoring (> 3 times/week) during early childhood was present in 38 LP children (11.3%) while it was reported in only 15 HP (4.4%) (OR [odds ratio]: 2.79; CI: 1.45-5.42; $p<0.001$). Furthermore, 10 LP and 3 HP children underwent adenotonsillectomy for their snoring (OR: 3.48; CI: 0.88-16.05; $p<0.04$).

Conclusions: Low performers in middle school were more likely to have snored and require adenotonsillectomy for snoring than high performing schoolmates. If further confirmed in a larger cohort, these findings support the concept that reversibility of OSAS-induced neurocognitive morbidity is only partial or that a "learning debt" may develop during early childhood and hamper subsequent learning performance.

References:
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Research supported by National Institutes of Health HL-65270 and American Lung Association CI-002-N

1688.G

Daytime REM Sleep in Adolescents

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Introduction: A previous study (Carskadon et al., 1998) of US high school students with school start time at 0720 showed an unexpectedly high incidence (48%) of REM sleep on daytime multiple sleep latency tests (MSLT), related to onset phase of melatonin, which was 2146 in students with daytime REM and 2036 in those without. The present study examines daytime REM sleep in a separate adolescent sample.

Methods: Participants were 13 boys, 18 girls (ages 14 to 18) selected from 133 screened with one week of actigraphy and self and parent report forms. Participants were excluded for medical or psychiatric illness, personal or family history of major sleep disorder, or use of prescribed psychoactive medications. Eligible students in upper and lower quartiles of actigraphically-estimated school-night sleep were invited for a 16-week study with actigraphy, sleep diaries, weekly structured interviews, and two laboratory visits (4-6 weeks apart), including morning and evening saliva collection, overnight sleep on school-night schedule, and MSLT at 0830, 1030, 1230, and 1430.

Results: 28 students completed the first in-lab session, 27 the second, and 24 both. Daytime REM was identified in 9 (32%) in Session 1 and 12 (44%) in Session 2. Mean daily MSLT was shorter ($p < .05$) in those with daytime REM (Session 1 = 6.6±4.0 min.; Session 2 = 6.8±3.7 min.) than those without daytime REM (Session 1 = 10.6±4.9 min.; Session 2 = 10.6±5.5 min.). REM episodes did not vary with time of day. For Session 1, salivary melatonin offset phase was significantly ($p<.05$) later in those with daytime REM than in those without daytime REM (0805±69 min. vs. 0709±26 min.); melatonin onset phase did not distinguish groups in Session 1 (2117±78 min. for REM group vs. 2039±64 for no-REM group). Neither melatonin onset (2047±60 vs. 2042±58) nor melatonin offset (0719±54 vs. 0708±45) phases distinguished groups in Session 2. Pre-screen actigraphically-estimated school-night sleep in Session 1 showed significantly ($p=.01$) lower sleep for those with daytime REM (362±47 min.) than those without REM (415±48 min.). A similar trend did not achieve statistical significance for Session 2. Mean daily MSLT and melatonin onset and offset did not differ significantly across sessions and showed strong correlations (MSLT $r = .63$, $p =.001$; melatonin onset $r = .87$, $p<.001$; melatonin offset $r = .88$, $p<.001$), indicating reliability.

Conclusions: These data support previous findings showing a high incidence of daytime REM sleep in adolescents. Morning distribution of REM sleep episodes did not replicate, nor did the association of REM with melatonin onset, although melatonin offset in Session 1 was related to REM sleep. Chronically reduced sleep in the present sample may have influenced daytime REM propensity, perhaps in association with REM deprivation. Further analyses on an expanded sample will examine these possibilities. These data indicate troublesome levels of daytime sleepiness and increased REM propensity in many adolescents.

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1299.G

Sleepiness in ADHD Children: Impact of Clinical Subtypes on MSLT Profiles

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Introduction: Polysomnographic studies conducted in ADHD children failed to show striking abnormalities in sleep architecture and continuity. Combined measurements of sleep and daytime sleepiness may provide more information and may lead to a better understanding of the syndrome. Sleepiness is an important physiological variable, rarely addressed in ADHD studies (Palm et al., 1992). The multiple sleep latency test (MSLT) is an appropriate test to measure sleepiness in normal children, seven years of age and older (Carskadon and Dement, 1982). The aim of the present study was to measure sleepiness in ADHD children and to compare MSLT profiles according to the clinical subtype.

Methods: 30 ADHD boys (DSM IV), mean age 7.8 ± 1.6 years, underwent all-night PSG followed by 4 MSLT (10 am to 4 pm) in the sleep laboratory. The clinical subtypes (DSM IV) were as follows; combined type (n=16), predominantly inattentive (n=9) and predominantly hyperactive-impulsive (n=5). All subjects were unmedicated. Subjects were also evaluated using Conners Parent Rating Scales (CPRS), Conners Teacher Rating Scale (CTRS) and Abbreviated Conners Rating Scale (ACRS).

Results: PSG findings did not differ significantly from those of a control group sex and age-matched. Mean sleep latency at MSLT was (16.7 ± 5.4 min). ADHD children who fell asleep more than three times at MSLT had predominantly inattentive subtype. Children from the predominantly hyperactive-impulsive subgroup were more opposant to the test but once in bed could fall asleep very rapidly (less than 5 minutes in 2 MSLT for 2 subjects). Most of the children belonging to the predominantly inattentive subgroup fell asleep on 3 or 4 occasions.ADHD children with moderate inattentive-passivity indice at CTRS (40-50) had sleep-onset latency values distributed around the 15 minute value where children with high indice (>50) had shorter sleep-onset latencies. Sleep-onset latencies values were more spread out (10-50 minutes) in children with moderate Conners hyperactivity-impulsivity indice (<70 at CPRS and <60 at CTRS) and were very short (<10 minutes) in children with severe indice (>80). We report a negative correlation between sleep-onset latencies and hyperactivity-impulsivity indice at CPRS ($p<0.001$) and at CTRS ($p<0.002$). A positive correlation was found between the number of sleep-onsets at MSLT and the inattentivity-passivity indice at CTRS ($p< 0.008$).

Conclusions: Children with ADHD have an abnormally strongest tendency to fall asleep during the day. In the present study, the number of daytime sleep-onsets and the rapidity of sleep-onsets measured by MSLT were pertinent physiological indices to discriminate between ADHD subtypes.

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1700.G

Sleep/Wake Patterns in One to Five Year Old Children From Activity Monitoring and Maternal Reports

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Introduction: In the Journal of Child Neurology (1998), Scher estimated that 20 percent of pediatric clinical practice issues relate to sleep, yet much of the objective data on sleep/wake patterns of pre-school children are from laboratory studies over 25 years old or small samples with polysomnography in the home. We describe behavioral sleep/wake patterns in the home for a cross-sectional sample of children ages 1 to 5 years.

Table 1

Mean (SD) for Nocturnal Actigraph Measures				
Age (mo)	SS (hh:mm)	SP (hr)	*TST (hr)	Wake (min)
12	20:28 (51)	10.5 (1.0)	8.4 (0.8)	122 (48)
18	21:00 (46)	10.3 (0.7)	8.8 (0.6)	87 (34)
24	21:16 (38)	9.9 (0.5)	9.0 (0.6)	53 (22)
30	21:08 (47)	10.0 (0.7)	8.9 (0.8)	65 (40)
36	21:11 (59)	9.9 (0.6)	8.5 (0.8)	82 (30)
48	21:22 (44)	10.0 (0.5)	8.7 (0.8)	73 (33)
60	21:05 (34)	9.9 (0.6)	8.7 (0.8)	69 (26)
* Age was significant for all variables except TST				

Table 2

Mean (SD) for Diary Measures		
Age (mo)	Nap Time (hr)	NAP#
12	2.5 (1.0)	1.4 (0.6)
18	2.0 (0.7)	1.0 (0.2)
24	1.4 (0.6)	0.8 (0.3)
30	1.4 (0.6)	0.8 (0.3)
36	1.0 (0.9)	0.5 (0.4)
48	0.4 (0.4)	0.3 (0.3)
60	0.2 (0.4)	0.2 (0.2)
Age was significant for both measures		

Methods: Children (97 male, 95 female) 12 (n=24), 18 (n=29), 24 (n=22), 30 (n=21), 36 (n=21), 48 (n=24), and 60 (n=28) months (± 1 month) of age participated. Screening excluded medical, neurological, and developmental problems, routine co-sleeping, and history of psychiatric or sleep disorders in first-degree relatives. Children wore actigraphs (AMA-32, Ambulatory Monitoring Inc., Ardsley, NY) on the left ankle (12-30 months) or left wrist (36-60 months) for one week. Mothers kept a concurrent diary of children's bedtimes, risetimes, naps, actigraph off, and external motion. Nocturnal sleep/wake measures were estimated from actigraph data delimited by diary report using a validated algorithm (Sadeh et al. 1994) and include: Sleep Start Time (SS); Sleep Period (SP) (time from Sleep Start Time to end of scored sleep); Sleep Time during

Sleep Period (TST); and Wake Minutes during Sleep Period (Wake). Diary measures include Nap Time (summed time of reported 30-minute periods of daytime sleep) and number of reported daytime naps (NAP#). For each measure, ANOVA was performed on individual weekly means, with Age and Sex as between subject factors.

Results: We found significant age effects: SS was earlier at 12 months than at other ages ($F(6,155)=3.6$, $p=.002$); SP was longer at 12 and 18 months than at later ages ($F(6,155)=2.9$, $p=.01$); Wake decreased over the first 2 years ($F(6,155)=9.5$, $p<.001$); and both Nap Time ($F(6,155)=38.3$, $p<.001$) and NAP# ($F(6,155)=40.6$, $p<.001$) declined linearly over age. Nocturnal Sleep Time did not show a significant age effect. We found no main effect of sex for any variable.

Conclusions: Contrary to conventional wisdom, our findings showed no age-related decline in nocturnal sleep time. Rather, the major developmental change occurred during daytime naps. Polysomnographic studies of children in this age group have reported sleep period times in the range of 10-11 hours, total sleep time near 10 hours, and nocturnal wake ranging from 10 to about 40 minutes (Williams et al., 1974; Louis et al., 1997). The lower nocturnal sleep and higher wake estimates in our data may reflect a scoring algorithm bias towards wake or cohort differences in child sleep patterns. Other analyses within our sample also relate sleep findings to parental sleep patterns and demographic data.

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1816.G

First Degree Relatives of ALTE Children

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Introduction: Between 1985 and the end of 1995, three hundred and forty-eight infants aged three weeks to three months were referred to the Stanford Sleep Clinic for "apparent life threatening events" (ALTE).

Methods: We conducted a systematic investigation of relatives (parents, siblings, and grandparents) of the infants, including a clinical evaluation, cranio-facial investigation, and completion of an extensive (189 question) validated sleep/wake questionnaire.

Results: 42.5% of the infants were negative for sleep-disordered breathing (Group A), whereas 57.5% of the infants were positive for sleep-disordered breathing (Group B). Forty-three percent of the relatives of Group B infants had been treated for sleep-disordered breathing (with nasal CPAP, surgical and dental appliance treatments) compared to 7.1% of Group A relatives. Clinical investigation indicated the presence of small upper airways in the families of index cases where sleep-disordered breathing was seen during early infancy. There were also about twice as many relatives who reported the presence of asthma in Group B as compared to Group A.

Table 1. Family members treated for sleep disordered breathing (SDB) (Questionnaire and verification during exam)

TREATMENT	Grp A n= 770	Grp B n= 1129	χ^2	p	B vs A O. R. (95%CI)	B vs C O. R. (95%CI)
Nasal CPAP	0	121 (10.7)	157.7	<.0001		
Surgeries				<.0001		
Tonsillectomy with/without adenoidectomy	48 (6.2)	189 (16.7)	61.8	<.0001	3.0 (2.2-4.2)	3.7 (1.9-6.8)
UPPP	0	54 (4.8)	68.8	<.0001		
Septoplasty	7 (0.9)	87 (7.7)	69.2	<.0001	9.1 (4.2-19.7)	17.5 (2.4-126.6)
Other surgeries impacting the upper airway size	0	6 (0.5)	7.5	<.05		
Dental appliances for SDB	0	41 (3.6)	51.9	<.0001		
Rx recommended for SDB but not implemented*	0	0		<.0001		
Orthodontic Rx**	18 (2.3)	48 (4.3)	6.0	n.s.	1.8 (1.1-3.2)	1.8 (.7-4.6)
Rx for nasal allergies	52 (6.8)	156 (13.8)	42.8	<.0001	2.2 (1.6-3.1)	5.5 (2.4-12.5)
Rx for asthma (including effort induced)	17 (2.2)	61 (5.4)	19.9	<.0001	2.5 (1.5-4.3)	6.0 (1.4-24.6)

Conclusions: Because a child's dolichocephaly is often masked, the presence of signs or symptoms of sleep-disordered breathing in the relatives of an infant can provide an important diagnostic clue when dealing with infants referred for an ALTE, noisy breathing during sleep, or abnormal nocturnal behavior. Certain naso-oro-maxillo-mandibular anatomic traits that may lead to small upper airways may be risk factors for abnormal breathing during sleep.

1514.G

Assessment of Hypoxemic Episodes in Extremely Low Birth Weight Infants (ELBW) by Synchronized Digital Video, EEG, and Cardiorespiratory Monitoring

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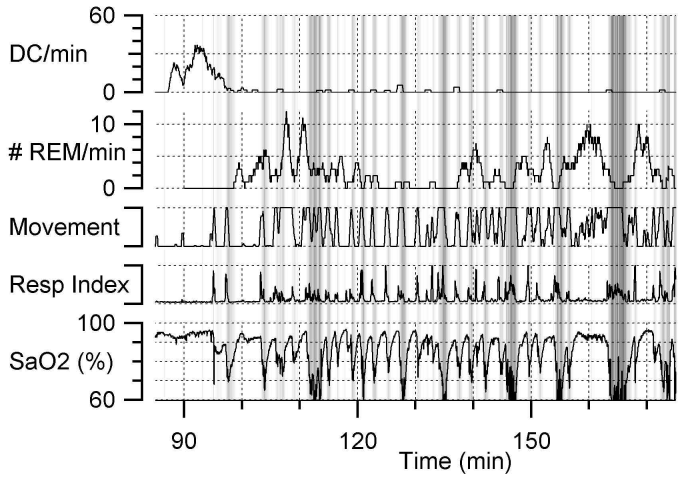
Introduction: Evaluation of rudimentary state transitions in preterm infants lack clear operational definitions. More accurate physiologic descriptions may improve the clinician's ability to assess functional brain organization for a given postconceptional age, follow functional brain maturation and detect dysfunction.[1,2] We developed a system to study the relationship between behavioral states, brain activity and cardiorespiratory output in mechanically ventilated ELBW infants for assessment of spontaneous hypoxemic episodes.

Methods: A 3-hour EEG with polysomnography and video was performed on five ELBW infants with a history of hypoxemic episodes. Eleven channels of cerebral EEG were recorded (Nicolet) and scored for discontinuity. A dual face/body video image of the baby was synchronized with the EEG. REM was scored from the face picture. Limb, body and head movements were each scored from the body images. Chest and

abdominal breathing (Respitrace) and O2 saturation (Datex-Ohmeda) were also recorded. Gestational age of the infants was 24.6 weeks (±1.1). Postnatal age was 34 days (±19). Birthweight was 684g (±149g). Weight at the time of study was 910g (±134g).

Results: We studied five infants, for a total of more than 15 hours of recording. Over that time period, three of the infants had SaO2 levels that were below 85% for 24% to 30% of the record. The other two infants had only about 4% of the record below 85%, but had numerous less significant drops in SaO2. The figure shows a 90 minute segment from one study. From the top, the traces show: seconds of EEG discontinuity per minute; REM count per minute; combined body/limb movements; a measure of respiratory irregularity; and SaO2. The vertical gray bars highlight the depth of the hypoxemic events. Our preliminary results indicate that periods of quiet sleep (see EEG discontinuity at minute 90), as well as periods of sleep with high REM count (scored visually - see minute 160), were associated with good SaO2 scores, and hypoxemic events generally occurred during a state of continuous EEG, but low REM count. Hypoxemic events were also associated with limb/body movements, and chest/abdominal movements picked up by the breathing bands.

Figure 1



Conclusions: We have demonstrated that it is possible to record video images of ELBW infant behavior with synchronized EEG and cardiorespiratory monitoring. Preliminary results indicate that hypoxemic events occur in an intermediate state between quiet and REM sleep. This technique provides an exciting new method for better understanding brain development in infants.

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1442.G

Respiratory Monitoring by Means of an Unattended Device in Children with Suspected Obstructive Sleep Apnea

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Introduction: Ambulatory monitoring of respiration is considered reliable for the diagnosis of OSA in adult population. Unattended devices using sleep, video and cardiorespiratory recordings are not yet recommended in children since clinical trials are lacking.[1] Nocturnal polysomnography (PSG) is still considered the gold standard for testing OSA and its severity in children. However, PSG is an expensive tool and the results may be affected by environmental and instrumentation effects. Aim of our study was to test an unattended device for cardiorespiratory monitoring (Polymesam, MAP)(PM) compared to nocturnal PSG in a sample of habitual snorer children and aged 3 to 6 years with suspected OSA.

Methods: Twelve children (mean age 4.0 yrs) complaining of chronic snoring (mean age of onset 18.7 months) and with suspected apnea were enrolled in the study. The mean BMI was 16.6 (with failure to thrive in 3 cases), familiarity for habitual snoring was found in 80% of the cases. Only one child underwent adenoidectomy before the study (without resolution of the symptoms). All children had diurnal symptoms (irritability, recurrent upper airway infection, and forced daytime oral respiration) but in only 50%of the sample the parents referred daytime sleepiness. The whole group underwent a full-night PSG with monitoring of EEG, EOG, and EMG of submental and intercostal muscles, oro-nasal airflow, thoracic and abdominal efforts and SaO2% detection. The night after (or the first night, in a balance manner) they were recorded in the same lab bed with an unattended device (PM), monitoring respiration (oro-nasal, thoracic and abdominal transducers), heart rate, body position and SaO2%. Data of both nights were collected and analyzed considering obstructive and mixed apneas (OA) and hypopnea (OH), central events (CA) (at least 8 sec in duration), desaturation events (> 4%) (DE), RDI, ODI, Minimal SaO2%, Mean low SaO2%. Cut-off >5 and >10 and ODI >5 and >10 were considered for establishing the diagnosis of OSA.

Table 1

	RDI >5	RDI >10	ODI >5	ODI >10
Sensitivity (%)	87.5	80	100	100
Specificity (%)	25	71	37.5	67
PV (%)	70	67	44	50
NPV (%)	50	83	100	100

Results: According to PSG criteria (mean RDI 14±12.4, mean ODI 6.2±6.2) 9 out of 12 children had an RDI>5 and 5 had an RDI>10; 4 out of 12 had an ODI>5 and 3 of them had an ODI>10. The table below shows validity indices of PM at different cut-off values from PSG.Agreement between PM and PSG indices was analyzed according to the Bland and Altman method of concordance to identify bias between the two methods of recording. As there was an association between the differences and the size of the measurements a log-transformation of raw data has been employed. No significant bias were found for OA ,OH,

total events, RDI, while significant bias were found for CA (mean difference was 3.98, CI 0.18-88.3), DE (0.34, CI 0.06-2.02), ODI (0.4, CI 0.07-2.1), Minimal SaO2% (7.7 CI -43.8-59.3) and Mean low SaO2% (2.42 CI 9.6-14.5).

Conclusions: The unattended device PM seems to have a good sensitivity but a low specificity in detecting a clearly increased apneic activity associated[2] or not with O2 desaturations. The agreement with PSG parameters seems better for respiratory indices than for SaO2 results. The disagreement and the low specificity may be due to night-to night variability of the syndrome and to the reliability of oro-nasal flow signal on the unattended device. Only adding the visual analysis of the PM raw data (semiautomatic analysis) a suspected diagnosis of OSA in 3-to-6years old children may be confirmed.

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1382.A

Working Memory and Excessive Daytime Sleepiness - A Functional Magnetic Resonance Imaging (fMRI) Study

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Introduction: The neurobiological basis of abnormal cognitive performance while sleepy is not well understood. Executive dysfunction on neuropsychological testing has been described in patients with obstructive sleep apnea. To explore the role of abnormal executive function in conditions associated with excessive daytime sleepiness, we studied working memory, using fMRI, following acute sleep deprivation and in narcolepsy with and without stimulant (methylphenidate) treatment. We hypothesized that an inability to sustain cortical activation (time-on-task decrement) in the prefrontal cortex during a sustained working memory task (visual verbal 2-back) would be demonstrable in the sleepy state.

Methods: One normal subject and one patient with narcolepsy were studied on multiple occasions. The sleep deprivation duration was 40 hours. All scanning was performed in a 3.0 Tesla scanner. The task used for working memory was a 2-back verbal working memory, 32 seconds off (fixation) and 120 seconds on (stimulus on for 500 milliseconds, 9500 milliseconds delay period, generated by MacStim). Run duration: 15 minutes. Subject were trained on the task prior to the scan, and could perform > 90% correct responses in the scanner. Reaction times were a measure of performance. Basic scanning parameters were 20 slices, 7 mm-no gap, axial images, asymmetric spin echo T2* weighted, TR: 4000 msec, TE: 30 msec, Flip angle: 30 degrees. Data analysis: All data sets were motion corrected, normalized to a mean value of 1000, and linear trends eliminated. Statistical maps for individual subjects were generated using a non-parametric test, the Kolmogorov-Smirnov (K-S) statistic, and overlaid on high-resolution anatomical scans. The statistical comparison was between fixation and the working memory task, using a standard block-design analysis. The time course of blood oxygen level dependent (BOLD) signal in areas of peak activation were plotted. Performance (mean reaction time in each test block) was correlated with BOLD % increases in activated cortical regions.

Results: Cortical regions activated were as previously described during the 2-back task, including prefrontal, posterior parietal and cingulate cortex.[1-3] A reduction in BOLD signal (% increase) was seen across the time of the task following sleep deprivation and narcolepsy-off stimulants. This pattern, a time-on-task decrement of BOLD signal, was not seen in the alert/medicated state, and was maximal in the dorsolateral prefrontal cortex. Task performance, as measured by mean reaction times, showed a negative correlation with the peak signal increase in untreated narcolepsy (r2: -0.67) and following sleep deprivation (r2: -0.66). The alert state did not show a significant correlation (r2: -0.50), as the BOLD signal and mean reaction time slopes largely paralleled each other. In treated narcolepsy, there was a positive correlation (r2: 0.69), suggesting an uncoupling between the degree of cortical activation and performance.

Conclusions: fMRI may be used to demonstrate differences in cortical activation during cognitive performance in the sleepy vs. alert state. This method holds promise in better understanding the basis of sleepiness, may provide objective markers of this state, and may demonstrate changes due to medication effects.

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1138.A

Absence of Sleep Spindles in Human Medial and Basal Temporal Lobes

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Introduction: The reticular thalamic nucleus (RE) is the generator of sleep spindles, and its activities are conducted to thalamocortical (Th-Cx) neurons and subsequently to the cortex. Since thalamic neurons project topographically to the cortex, the scalp distribution of sleep spindles will reflect the activities of nuclei within the thalamus. We had the opportunity to record subdural electrocorticographic activity (ECoG) during human natural sleep in epileptic patients and examined ECoG signals from medial temporal and basal temporal lobe areas.

Methods: Subjects were five patients (2 male and 3 female; age 28-34 years) who were candidates for neurosurgical treatments of partial epilepsy. Specially designed T-shaped sets of eight electrodes were surgically placed on the medial and basal temporal of both hemispheres to record cortical electrical activities. The ECoGs and Cz-scalp electroencephalogram (EEG) recordings were monopolor, referenced to the A1 electrode on the left mastoid. Recording started between 8:30 and 10:30 p.m., and continued for approximately ten hours. Non rapid eyes movement (NREM) periods from later sleep epochs were selected for Fast Fourier (FFT) analysis and fifty 2048 point (2.73 sec) epochs were FFT analyzed. Subsequent analyses were limited to the non-epileptogenic hemispheres.

Results: No obvious spindle bursts were observed in the medial and basal temporal lobes signals. Power spectra of scalp Cz EEG electrodes during NREM sleep showed a characteristic peak in a sigma (12-16 Hz)

band and these peaks were considered to represent mean sleep spindle frequency. However, ECoG signals from temporal lobe showed no obvious sigma peak during NREM sleep in any case. Across-night fluctuations of delta (0.3-3 Hz) and sigma (12-16 Hz) activities from Cz signal showed were typical of those we have previously reported (Uchida et al., 1991). Delta activity from temporal lobe signals appeared nearly identical to that at Cz. By contrast, little or no pattern of change in sigma activity was seen at either medial or temporal lobe.

Conclusions: From the present study we concluded that spindle activities are absent in the medial and basal temporal lobes. The posterior part of the parahippocampal gyrus receives projections from anterior thalamic nucleus, and this region lacks connection to RE (Steriade et al., 1984). We consider this anatomical feature may accounts for the lack of spindling activity in the medial temporal lobe. The anterior part of the parahippocampal gyrus receives projections from midline thalamic nuclei and the basal temporal lobe is largely innervated by thalamic pulvinar nuclei. These nuclei, however, do have connections to RE. We speculated that some mechanism may suppress the emergence of sleep spindle in basal temporal lobe and anterior part of medial temporal lobe.

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1673.A

Short Sleepers Tolerate a Higher Homeostatic Sleep Pressure than Long Sleepers: Evidence From the Waking Electroencephalogram

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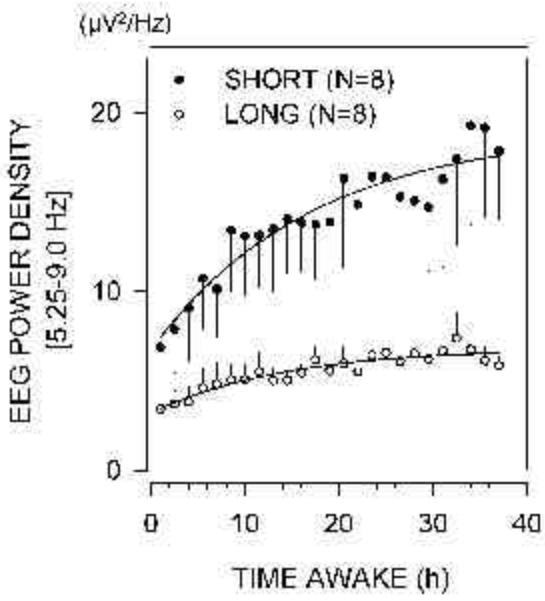
Introduction: The neurobiological basis of the variation in sleep duration among individuals is unknown. Recent evidence derived from the sleep electroencephalogram (EEG), and simulations based on the two-process model of sleep regulation (Aeschbach et al. 1996) suggest that natural short sleepers live under a higher homeostatic sleep pressure than long sleepers. Thus, the two groups appear to differ in the tolerance to this pressure, rather than in the kinetics of the wake-dependent increase of sleep pressure. Here we used theta/low frequency alpha activity (power density in the 5.25-9.0 Hz range) in the waking EEG as a marker of the homeostatic sleep pressure (Aeschbach et al. 1999, Cajochen et al. 1995). We hypothesized that theta/low frequency alpha activity in the waking EEG is higher in short sleepers than in long sleepers, whereas the kinetics of its wake-dependent increase would not differ between the two groups.

Methods: Young (21-31 years) healthy short sleepers (3 males, 5 females; sleep duration <6 h) and long sleepers (4 males, 4 females; >9 h) were recruited on the basis of 2-4 week sleep logs and wrist motor activity recordings. After two nights of sleep that were scheduled to match each individuals habitual bed time and wake-up time, subjects underwent a ~40-h constant routine protocol during which they stayed awake in bed in dim light (<10 lux), and without time cues. The EEG was recorded every 30 min for 3 min with eyes open.

Results: Within the frequency range of 0.25-20 Hz, power density in the 5.25-9.0 Hz range was higher in the short sleepers than in the long sleepers ($p<0.05$, t-tests for 1-Hz bins). In both groups, increasing time awake was associated with an increase of theta/low frequency alpha activity, which after removal of a circadian component (Aeschbach et al. 1999) was approximated by a saturating exponential function (see Fig.). Whereas the estimated time constants of the wake-dependent increase did not differ significantly between short sleepers (18.4 h) and long sleepers (14.2 h), the short sleepers showed a higher asymptote (non-overlapping asymptotic 95% confidence intervals).

Figure 1



Conclusions: Short sleepers live under a higher homeostatic sleep pressure than long sleepers. Differences in the asymptote of theta/low frequency alpha activity during wakefulness may reflect trait-specific differences in the saturation level of the homeostatic process. These differences may contribute to the ability of short sleepers to tolerate a higher sleep pressure than long sleepers.

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Research supported by the NIMH Intramural Research Program and fellowships from the Swiss National Science Foundation and Boral Foundation (to D.A.).

1236.A

Phenelzine-Induced Suppression of REM Sleep Can be Reversed by Rapid Tryptophan Depletion

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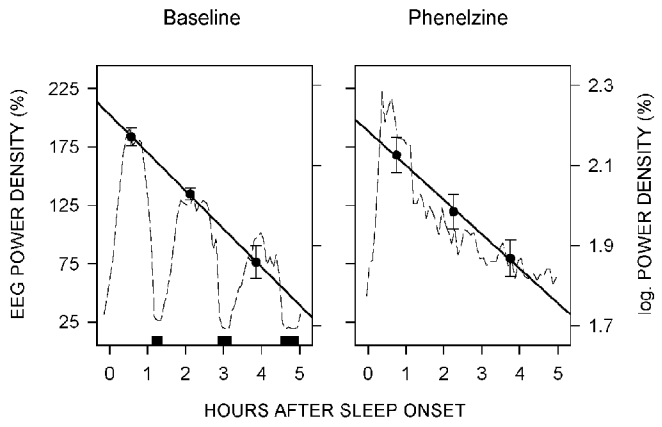
Introduction: Monoamine oxidase inhibitors (MAOI) such as

phenelzine inhibit the enzyme MAO thereby increasing the concentrations of serotonin and catecholamines including norepinephrine dopamine and phenylethylamin. It has long been known that phenelzine can virtually eliminate REM sleep in patients treated for depression (Wyatt et al. 1971). Despite the possibly important implications of this finding for theories concerning the functions of REM and nonREM sleep (Rechtschaffen et al. 1989), little research has focused on the exact nature and underlying mechanisms of MAOI-induced alterations of sleep. We investigated in the present study whether inhibition of MAO affects the homeostatic regulation of nonREM sleep. Furthermore, we studied the role of serotonin in phenelzine-induced REM sleep suppression.

Methods: A daily dose of 30-90 mg phenelzine was prescribed in open-label fashion to eleven depressed patients (six males, five females; mean age: 41±2 [SEM] years). They were physically healthy and had no sleep disturbances such as sleep apnea or nocturnal myoclonus. Sleep was studied in the sleep laboratory from ~22.30 h to ~06.30 h at baseline, i.e. prior to initiation of treatment, and in the third and fifth weeks of pharmacotherapy. Each night was preceded by an adaptation night. To investigate whether the REM sleep-suppressive effect of phenelzine is mediated by serotonin, we administered in a double-blind fashion a tryptophan-free amino-acid drink (TFD) with and without the addition of tryptophan, the biosynthetic precursor of serotonin, to four remitted patients (three females, one male; mean age: 38±3 years).Data were analyzed by one- and two-way ANOVA for repeated measures.

Figure 1



Results: Eight patients responded favorably to the treatment and remitted from depression; three patients showed no antidepressant response. The major change in sleep induced by phenelzine consisted of a gradual and almost complete suppression of REM sleep. It was eliminated in six patients and on average, only 4.9 minutes of REM sleep (1.3 % per total sleep time [TST]) were observed in week five of treatment. This effect was compensated by increased stage 2 sleep. No differences were noted for TST, sleep efficiency, sleep latency, slow wave sleep and wakefulness after sleep onset. EEG power density during nonREM sleep (stages 2, 3 and 4) was higher than in baseline in the entire beta frequency range (16.25-25 Hz). In contrast, slow-wave activity (SWA, power within 0.75-4.5 Hz) and its exponential decline were not affected (linear regression through mean logarithmic episodic values [baseline] and 90-min values [week five of phenelzine] of SWA in nonREM sleep: $p>0.1$ for slope and intercept, respectively). However, due to the absence of REM sleep (indicated in the Figure by black bars above the abscissae), SWA declined progressively throughout the phenelzine sleep episode (Figure). Following the TFD REM sleep increased from zero to 35±8 % of TST. After addition of tryptophan, however, TFD had no significant effect on REM sleep, which remained below the baseline level (5±4 % vs. 17±2 %).

Conclusions: Inhibition of MAO with phenelzine caused an almost complete suppression of REM sleep. In contrast, the drug did not affect SWA and its exponential decline in nonREM sleep. Together with the finding that TFD can reverse the REM sleep-suppressive effect of phenelzine, these data suggest that drug-induced increased serotonergic neurotransmission inhibits the structures in the brain, which promote REM sleep. Our findings may open up a new technique to address the functions of REM sleep by studying patients with and without REM sleep under double-blind experimental conditions.

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Research supported by the Swiss National Science Foundation (Grant Nr. 823A-056616), the UCSD Mental Clinical Health Research Center (MH30914), NIMH RO 1 (MH38738) and a VA Merit Grant.

1581.A

The Effects of Sleep Deprivation on the N350 During the Wake/Sleep Transition

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Introduction: Event-related potential (ERP) studies of cognitive processing during sleep onset show the gradual appearance of a negative-going vertex potential: N350.[1] This waveform may reflect an elicited form of the vertex sharp wave (VSW).[2] Although its functional significance remains uncertain, it has been suggested that N350 reflects a breakdown of sleep related inhibitory processes and that it is followed either by arousal or restoration of sleep reflected by synchronized activity such as spindles.[3] To examine this hypothesis, the current research assessed the effect of one night of sleep deprivation on N350 amplitude and related EEG phenomena. With increased sleep pressure, three outcomes were expected: 1) sleep related inhibition would increase and consequent N350s (breakdowns of inhibition) following stimulus presentation would be larger; 2) VSW and spindle frequency would increase; and 3) arousals would decrease.

Methods: Ten subjects took two 20 m naps separated by a 20 m break at their normal bedtime for baseline and again 24 hours later following total sleep deprivation. During naps, tones were presented at three intensity levels (60, 75, and 90 dB) with a 5-second interstimulus interval. ERPs, recorded from Fz, Cz, and Pz, were averaged across all trials (maximum: 20; minimum: 5) for each subject in six wake/sleep stages determined by the 10 second prestimulus EEG activity: Wake/Alpha (A), Wake/Mixed (M), Wake/Theta (T), Stage 1 (S1), Stage 2 no K-complex (N), and Stage 2 with the stimulus eliciting a K-complex (K).

Results: Mean N350 amplitude (in microvolts) across deprivation and tone intensity were examined using 2-way ANOVAs for each stage (Table 1). Postdeprivation amplitude was significantly higher for the moderate and loud tone during Alpha, the loudest tone during Mixed, and all tones during Theta. Deprivation effects approached significance for both Stage 2 NoK ($p=.059$) and Stage 2 K ($p=.060$). Wilcoxon Signed Ranks (WSR) tests were used to compare the average proportion of trials eliciting EEG phenomena between pre and postdeprivation across tones; and when significant, followed-up using WSR for each tone (see

Table 2 for findings). The decrease in spindles from pre to postdeprivation during Theta approached significance (Z=-1.63, p=0.051).

Table 1

	Pre		Post	
	Mean	**SE**	**Mean**	**SE**
A60	5.50	*1.22*	6.41	*1.24*
A75	3.99	*1.15*	6.79	*1.43*
A90	2.76	*0.87*	6.90	*1.61*
M60	4.79	*0.87*	4.77	*0.73*
M75	4.43	*1.14*	6.35	*0.95*
M90	4.08	*1.23*	8.23	*0.73*
T60	3.40	*0.91*	7.05	*1.40*
T75	6.15	*1.96*	10.81	*1.62*
T90	4.11	*1.54*	10.36	*1.07*
S160	4.26	*0.94*	6.69	*0.85*
S175	10.53	*2.88*	12.91	*2.21*
S190	11.34	*2.80*	11.65	*2.46*
N60	4.01	*0.77*	8.25	*1.41*
N75	10.91	*2.10*	16.39	*2.78*
N90	23.12	*3.95*	25.41	*3.73*
K60	*Insufficient N for Averaging*			
K75	34.02	*3.62*	41.82	*2.29*
K90	45.23	*6.06*	51.32	*6.03*

Table 2

	VSW		Spindle		Arousals	
	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**
A60	0.50	0.00	0.00	0.00		
A75	0.00	1.00	0.00	0.00		
A90	0.00	2.56	0.00	0.00		
M60	1.00	2.43	0.00	0.00		
M75 *	1.00 *	8.74	0.00	0.00		
M90	2.17	3.77	0.56	0.00		
T60	1.17	3.39	0.00	0.00		
T75 *	2.53	4.19	1.36	0.00		
T90	2.09 *	10.16	0.71	0.00		
S160	13.45	17.24	4.14	1.32	13.10 *	6.46
S175	20.74	23.18	2.02	2.03 *	19.68 *	9.32
S190	19.69	26.14	2.03	0.00	31.85	19.66
N60	11.50**	23.50	16.50 *	7.50	1.50	0.50
N75 *	23.50 *	35.50 *	22.00**	10.50	2.00	0.00
N90	31.55	38.83	14.53	13.33	3.08	1.83
K60	14.17	17.48	4.50	6.39	9.17 *	0.00
K75	6.12	23.07	14.58	19.47 *	6.22	1.00
K90	23.17	22.50	14.00	15.50	8.17	2.50

Conclusions: As predicted, following sleep deprivation, N350 amplitude increased and arousals decreased. However, a significant decrease, rather than increase, in the number of spindles was seen. If N350 reflects a breakdown in inhibition, and frequency of arousals decrease during recovery sleep; then some form of reestablishment of inhibition must follow the breakdown. If not spindle activity, perhaps some other synchronized activity not examined here. These data support the hypothesis that N350 reflects a breakdown in sleep related inhibition, but do not exclude the alternative interpretation that N350 reflects sleep related inhibition itself.

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1343.M

Selective REM Sleep Deprivation Can Relieve Depression - So Can Appropriate Awakenings From NonREM Sleep

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Introduction: In their classic study of 1975 Vogel and coworkers randomly applied two paradigms of short awakenings from sleep to 34 depressive patients over a period of several weeks.[1] A first group was selectively deprived of REM sleep, while in a second group an equal number of NonREM interventions was arranged in blocks shortly after the end of the REM periods. An antidepressive effect was demonstrated for the first procedure but not for the second. The authors claimed that the circadian REM pressure accumulating over days and weeks was responsible for the improvement of the depressive symptoms in the REM deprivation group. The heroic efforts necessary to perform the study restrained researchers for more than 20 years from repeating the experiment.

Methods: In an attempt to replicate these results we conducted a similar investigation involving 27 depressive patients. Deviating from the original study the awakenings in the control group were equally distributed during the NonREM part of the sleep cycle involving the sleep stages II, III and IV. Both treatment conditions were applied for ten consecutive nights. A neural network based software was developed to evaluate the sleep stages in real time and to automatically wake up the subjects in both conditions. Hamilton and Bech Rafaelsen ratings were evaluated after five and ten days of treatment as well as on the sixth day after the last treatment.

Results: In the own control group the distribution of sleep stages was similar to the undisturbed sleep of depressed patients.[2] In the REM deprivation group the remaining REM sleep was 55% of controls, while slow wave sleep was extended. There was a strong antidepressive impact in both groups. During the treatment period the Hamilton scores did not differ significantly. However, at the post treatment rating, the REM deprivation group was inferior to the control group. This last result was rather surprising and might be due to a REM rebound in the REM deprivation group after the end of the treatment.

Conclusions: The antidepressive effect of selective REM sleep deprivation could be confirmed. A second intervention paradigm with therapeutic impact could be identified involving appropriate NonREM awakenings. A potential antidepressive agent is suggested:Supposed there is a common factor that is responsible for the improvement of the depressive symptoms by selective REM sleep deprivation as well as in the own control condition. Then two implications derive from both investigations taken together. First, the REM deprivation itself or the circadian REM pressure can not be the critical antidepressive agent - as was proposed by Vogel and coworkers -, because in the control group of the second study there is no REM deficit or REM pressure outlasting the individual treatment nights. Second, the NonREM deprivation can not be the critical antidepressive agent - as proposed by Beersma and van den Hoofdakker[3]

-, because in the control group of the first study the depressive symptoms did not improve. The divergent results can be reconciled by the assumption that an increase of the intracyclic REM pressure is responsible for the antidepressive effects.

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1650.M

A Blinded Comparative Trial of Partial and Total Sleep Deprivation During Major Depressive Episodes

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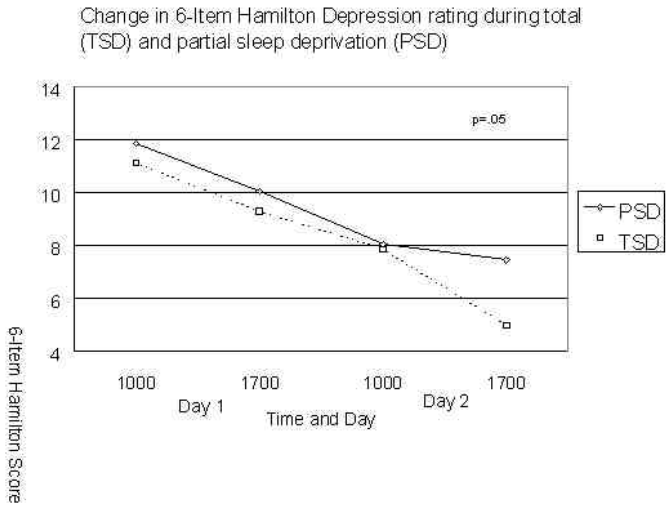
Introduction: The acute but transient antidepressant effects of sleep deprivation have been well documented.[1,2] However, the mechanism by which sleep deprivation alleviates depression has not been clearly elucidated. One theory is that a homeostatic factor associated with wakefulness produces the antidepressant effects.[3] To test this, we compared the effects of partial sleep deprivation (PSD) and total sleep deprivation (TSD) on depressed subjects.

Methods: Forty-five subjects (33 women and 12 men) with Bipolar or Unipolar depression were randomly assigned to one night of PSD (N = 22) or TSD (N = 23). PSD subjects remained awake from 07:00 to 21:00 on Day 1. On Day 2, they remained awaked from 02:00 until 21:00 (18 hours of deprivation). TSD subjects were awakened at 07:00 on Day 1 and remained awake until 21:00 on Day 2 (36 hours). Investigators, blind to sleep deprivation condition, rated subjects with the 6-Item Hamilton Depression (HAM6) and the 6-Item Young Mania Rating (YMR6) scales at 10:00 and 17:00 on both days.

Figure 1



Results: PSD and TSD subjects did not differ in age or baseline mood ratings ($p > 0.1$). Fifty-nine per cent of PSD subjects and 65% of TSD subjects were responders to sleep deprivation ($p = 0.8$). Hypomania was noted in 32% of PSD and 17% of TSD subjects during the study ($p = 0.3$). Analysis of variance (ANOVA) with repeated measures revealed that HAM6 ratings significantly improved in TSD ($p < 0.0001$) and PSD ($p = 0.0075$) conditions. The improvement on the HAM6 was not significantly different between PSD and TSD, except at 17:00 on the second day, when TSD subjects were significantly less depressed than PSD subjects ($p = 0.003$) (see figure). YMR6 ratings rose during TSD ($p = 0.03$), but not PSD, ($p = 0.3$) and by 17:00 on Day 2 TSD subjects had higher mania ratings than PSD subjects ($p = 0.05$).

Conclusions: This blinded direct comparison confirms the antidepressant effects of both PSD and TSD. These results suggest that the antidepressant effects of acute sleep deprivation are highly similar, regardless of whether sleep is completely or only partially restricted. We found no difference in the onset of antidepressant effect between PSD and TSD, which is not consistent with the theory that wakefulness alone accounts for the antidepressant effects. However, the results must be interpreted with caution since the depressive symptoms continued improving through the end of our rating period, particularly in the TSD group.

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1672.M

Total Sleep Deprivation Induces Opposite Effects on Mood States in Depressed and Control Subjects

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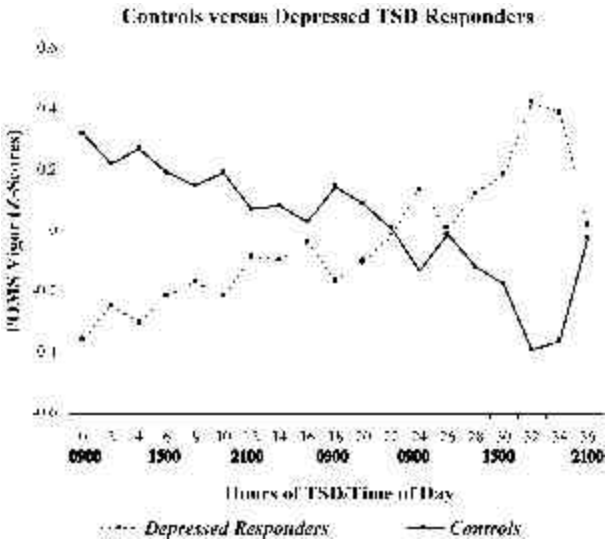
Introduction: Sleep deprivation (SD) is well established to have an antidepressant effect in a majority of depressed patients. Beyond improvements in depression ratings, however, beneficial effects from SD have been found in patients' moods as assessed by the Profile of Mood States (POMS).[1] In contrast, healthy control subjects report detrimental effects of SD on mood.[2] Studies have generally not compared mood responses to SD of depressed and control subjects as a function of the time course of escalating homeostatic drive for sleep. Therefore, an investigation was conducted comparing multiple dimensions of mood in depressed and control subjects, across 36 hr of total sleep deprivation.

Methods: Depressed subjects (n=22) underwent 38 hr of total sleep deprivation (TSD), and were categorized as responders (n=14) or non-responders (n=8) based on consensus clinical global impressions of subjects and physicians. In a separate experiment, healthy subjects (n=24) underwent a similar TSD protocol. In both experiments, subjects completed the POMS every 2hr, beginning in the morning after awakening from the baseline sleep, until 2100hr the next day (i.e., following a night

without sleep). POMS subscale scores were analyzed for the first 36 hr of TSD using a mixed model ANOVA with correction for sphericity.

Results: ANOVAs revealed significant main effects between groups throughout TSD for depression/dejection, fatigue/inertia, confusion/bewilderment, tension/anxiety and anger/hostility (all $p<0.001$). Overall, depressed responders (n=14) were more depressed, more fatigued, more tense, and more angry than controls. However, these effects varied over TSD, as evident in significant interactions between group and time in TSD. Depressed responders decreased negative mood states as TSD progressed, while controls increased negative mood scores as TSD progressed. This was evident for depression/dejection ($F=7.40$, $p=0.0001$), fatigue/inertia ($F=2.68$, $p=0.017$), confusion/bewilderment ($F=6.59$, $p=0.0001$), tension/anxiety ($F=7.34$, $p=0.0001$), anger/hostility ($F=2.71$, $p=0.008$) and vigor ($F=4.95$, $p=0.0001$). The steady progression of improving mood in depressed responders and declining mood in control subjects resulted in equivalent mood ratings between depressed and control subjects at 1900hr (34hr TSD) for confusion/bewilderment, tension/anxiety and anger/hostility. Depressed responders actually reported significantly more vigor than controls at 1700hr ($p=0.001$) and 1900hr ($p=0.003$) or 32-34hr TSD. This is clearly illustrated in the figure.

Figure 1



Conclusions: While depressed TSD responders reported more depression and more fatigue than control subjects across TSD, sleep loss eliminated differences between the two groups on confusion, tension and anger. The bulk of these effects were due to the depressed responders improving on these negative mood ratings. Noteworthy in these changes was the improvement of depressed responders' ratings of vigor, which near the end of TSD were elevated well above comparable ratings for control subjects. The fact that TSD has opposite effects in depressed and control subjects on a range of mood measures suggests that the homeostatic drive for sleep may play a role in the emotional perceptions of some depressed subjects. These results are consistent with the hypothesis that increased pressure for slow wave sleep mediates the antidepressant effects of sleep deprivation.

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1511.M

Overnight Mood Regulation: A REM Sleep Function?

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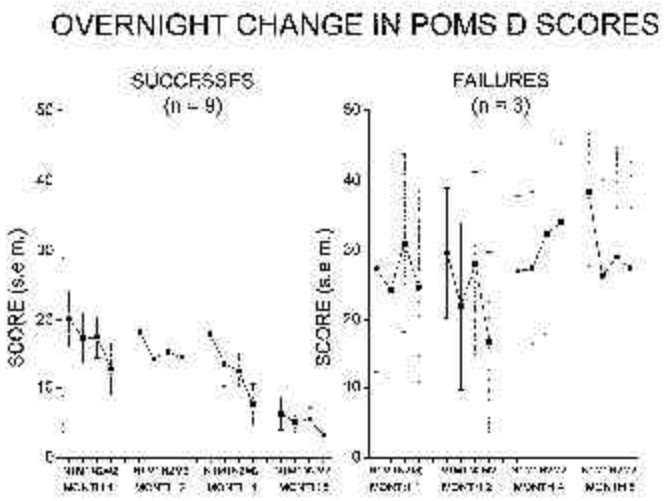
Introduction: One suggested REM sleep function is that it aids assimilation of pre-sleep affective experience. An expected effect of such a process is a reduction in the level of morning mood. Although this has been supported in healthy adults (Cartwright, Luten et al 1998) many suffering from Major Depression feel most depressed following sleep. However these patients also exhibit some REM sleep abnormalities. Nonetheless about 50% of depressed who go untreated do remit within a year. To examine changes in REM sleep and the accompanying affect during this process, the mood before and after sleep was tested in a group of 12 depressed volunteers over an eight month period.

Methods: Subjects were volunteers going through a divorce who met depression criteria on the SCID-NP, Hamilton Rating Scale =>I8 and Beck Depression Inventory (BDI)=> 14. All subjects slept for two nights on four occasions: at months 1,2,4, and 8. The first of these was a sleep-through night and the second a REM interruption night for a report of on-going mental activity. Subjects completed a BDI before each of the first nights and a POMS mood scale before and after all lab nights. On months 3,5,6 and 7 subjects were interviewed on current status, and retested on Hamilton and BDI.

Figure 1



Results: Nine subjects reached normal scores on the Hamilton and Beck by Month 5 and no longer met depression criteria on the SCID at the end of the study. Three were unchanged. The successful cases had progressively lower POMS Depression scores in the AM than on the previous night. This score reached normal levels by the 4th month. There was more change on this scale following the REM interruption nights than on the sleep- through nights. REM interruption resulted in greater REM

pressure: a higher Eye Movement Density, and greater number of REM periods in depressed than in a healthy control sample The reported affect from REM awakenings differed between the success groups: success subjects reported more positive or negative affect while the failures had more reports with neutral affect or failures to recall. The degree of overnight change on the POMS depression score was negatively correlated with the REM latency on REM Interruption night Month 1. N=12 r= -.605 p<.01, and on Month 2 r= -.618 p.<.Ol (the shorter the latency the greater the overnight reduction in depressed mood).Although total sleep time and REM time are both reduced by REM interruption, REM pressure is increased. This is more effective in those with less severe depression. Overnight mood regulation is aided by increasing REM pressure and precedes change in waking depression measures, possibly by interrupting the negative affective associations during sleep.

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Supported by MH 50471.

1521.M

Dream Reports and PSG Findings Acutely Following Traumatic Injury and PTSD

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Introduction: Nightmares that refer to, or replicate traumatic events are considered to be cardinal symptoms of PTSD. Dreams following trauma have also been postulated to potentially serve adaptive and integrative functions (Hartman, 1998). Sleep deprivation and fragmentation have been postulated to have a role in the early development of PTSD (Schlosberg & Benjamin, 1978). Systematic data relating dream content to PTSD are limited, and most of the available data from polysomnography (PSG) has come from very chronic phases of the disorder.

Methods: Fifty nine subjects admitted to a regional trauma center following life threatening incidents who were conscious on arrival and had recall of the trauma, were assessed at baseline (approximately 2 weeks following the incident) and follow up 6 weeks later. Assessments at baseline included 2 to 3 morning diaries that queried dream recall and included a rating of the similarity of the dream to the recent traumatic incident. A subset of these injured subjects (n=20) were able to be free of narcotic analgesics and received PSG assessment close to the time of the baseline evaluation. A non-injured, healthy comparison group (n=8) was also recruited for PSG.

Results: Twenty-one of the subjects (36%) recalled 24 dreams that were described on the diary forms. Eleven produced reports that were endorsed to be similar to the recent traumatic event and were threatening (trauma dreams). Nine patients recorded threatening scenarios, dissimilar to the traumatic event and 5 subjects reports were neither threatening nor trauma-related. The patients with trauma dreams at baseline had more severe PTSD at baseline and follow-up and were more likely to go on to meet PTSD criteria (86% versus 38%, x2=5.1, p<.03).
Among the subjects who had PSG, those who ended up meeting criteria for PTSD at follow up (n=10) were not distinguished from those not meeting PTSD criteria by their sleep duration or architecture. (Both injured groups had reduced sleep duration compared to the controls). There are trends in the preliminary findings suggesting an association of increased REM density with injury and divergent patterns of sleep disruption as indexed by wake intrusion within the injured subjects, with disruption of REM sleep occurring in the subjects developing PTSD.

Conclusions: The data suggest that during an early phase of a trauma response, activation of unaltered trauma memories in dreams accessible to recall, and preliminarily, frequent awakenings or micro-awakenings from REM sleep, are associated with the continuation and progression of PTSD symptoms.

References:
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(2) Shlosberg A & Benjamin M: Sleep patterns in three acute combat fatigue cases. J Clin Psychiatry 39:546-549, 1978.

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1164.K1

Airway CT and Multi-level Airway Pressure Monitoring During Obstructive Sleep Apnea Syndrome

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Introduction: Although cine airway CT during waking or sleep has been performed to detect the level of airway narrowing (LAN) in obstructive sleep apnea syndrome (OSAS), the usefulness of this method has not been confirmed. We monitored multi-level airway pressures (MAP) throughout night polysomnography and cine CT of airway during sleep apnea and normal respiration in OSAS to find the patterns of airway narrowing during OSAS and determine whether or not airway CT reflects the status of upper airway narrowing during OSAS.

Methods: Twelve patients with OSAS had night polysomnography with continuous MAP monitoring by 4 micro-sensor (nasopharynx, uvula, hypopharynx and esophagus) or 2 micro-sensor (just below uvula, esophagus) catheter. The LAN measured by MAP monitoring was defined as the following categories: 1) velopharyngeal obstruction when significant pressure fluctuation was observed with parallel at uvula, hypopharynx and esophagus, 2) oro-hypopharyngeal narrowing when pressure fluctuation was seen only at hypopharynx and esophagus, and 3) combined obstruction when the amplitude of pressure fluctuation at hypopharynx and esophagus was 1.3 times or greater than that of pressure fluctuation at uvula. All patients had cine CT scan at 5 airway levels of high retropalatal, low retropalatal, retroglossal, epiglottis and hypopharynx during waking state and sleep apnea. The cross-sectional areas of airway at 5 levels were measured. The LAN determined by airway CT scan during sleep apnea was classified as the following patterns: 1) velopharyngeal narrowing when significant airway narrowing during sleep apnea was observed only at retropalatal level, 2) oro-hypopharyngeal type when significant airway narrowing was seen at retroglossal, epiglottal or hypopharyngeal level, and 3) combined narrowing pattern when airway was significantly narrowed simultaneously at retropalatal level and below retropalatal level. In each patient, LAN by CT scan during apnea was compared with LAN by multi-level pressure monitoring.

Results: MAP monitoring revealed that only 2 patients (16.7%) had either velopharyngeal or oro-hypopharyngeal narrowing and the remaining 10 (83.3%) showed two or more LAN patterns of velopharyngeal, oro-hypopharyngeal and combined narrowing. The sites of predominant airway narrowing reflected by MAP monitoring were velopharynx in 3 patients (25%), oro-hypopharynx in 2 (16.7%) and combined levels in 7 (58.3%). CT scan during apnea showed that airway obstruction occurred at velopharynx in 5 patients (41.7%), oro-hypopharynx in 4 (33.3%) and combined in 3 (25%). The LANs by airway CT were concordant to LAN by MAP monitoring in only 3 patient (25%), partially concordant in 4

(33.3%), and discordant in 5 (41.7%).

Conclusions: Airway CT during single episode of sleep apnea does not reflect correctly the LAN in OSAS because most patients showed two or more different patterns of airway narrowing during different episodes of sleep apnea. To know the whole picture of airway narrowings in OSAS, MAP monitoring during night polysomnography is recommended.

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1674.K1

Normal Versus Apneic Upper Airway Anatomy: A Volumetric Study

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Introduction: The proposed mechanism of airway occlusion in patients with Obstructive Sleep Apnea (OSA) is dynamic collapse of the upper airway soft tissue structures (Schwab 1998). This suggests that anatomic factors may be identified within the oropharyngeal tissues that compromise the upper airway and its surrounding space. While it is known that upper airway caliber in apneics is smaller than that of normal subjects, little is known about upper airway tissue structures with respect to volumetric differences between the two groups. Furthermore, since no study has quantified differences in surrounding tissue volumes using Magnetic Resonance (MR) imaging, we hypothesized that in apneics, the volume of the upper airway tissues would be larger. In addition, we hypothesized that the volume of lateral pharyngeal walls would be greater in apneics.

Table 1

Average Volume of Upper Airway Structures (mm^3) ± SD

Tissue	Normal	Apneic	p-value
Soft Palate	5200 ± 5300	6400 ± 2600	0.17
Tongue	75700 ± 19100	84300 ± 21000	0.05
Lateral Walls	14600 ± 7100	18400 ± 6600	0.01
Fat Pad	7700 ± 7100	9900 ± 4600	0.09
Total (soft tissue)	103100 ± 31800	119000 ± 27200	0.01
Mandible	52600 ± 15200	53000 ± 15800	0.90

Table 2

Average Proportions of Soft Tissue Volume (% Total(soft tissue) Vol.) ± SD

Tissue	Normal	Apneic	p-value
Soft Palate	4.8% ± 3%	5.4% ± 1.9%	0.22
Tongue	74.4% ± 7.6%	70.8% ± 5.4%	0.01
Lateral Walls	13.9% ± 3.9%	15.3% ± 4.1%	0.11
Fat Pad	6.9% ± 3.6%	8.4% ± 3.8%	0.06

Methods: Each subject underwent one full night of polysomnography. Software was implemented to reconstruct and measure the volumes of the mandible, soft palate, tongue, lateral pharyngeal walls, and lateral pharyngeal fat pads from axial T-1 MR images during wakefulness. A total of 90 subjects were studied, 52 normals (age: 36.4 ± 12.2 yr, BMI: 28.1 ± 6.2 Kg/m2, RDI: 1.0 ± 2.2 events/hr) and 38 apneics (age: 47.7 ± 11.3 yr, BMI: 32.8 ± 6.3 Kg/m2, RDI: 45.4 ± 24.9 events/hr).

Results: The results of the volumetric measurements are shown in Tables 1 and 2. Table 1 includes all individual soft tissue volumes, their summation as a total soft tissue volume, and bony structure volume. Table 2 includes individual soft tissue proportions relative to total soft tissue volume. Mean values and standard deviations are reported for each group as are the p-values using an unpaired t-test comparing normals to apneics.

Conclusions: These data demonstrate that there are significant differences between the average total soft tissue volume of apneics compared to normals. Apneic soft tissue volumes were found to be larger than normal soft tissue volumes. The volume of lateral pharyngeal walls (p-value: 0.01) were found to contribute significantly to this difference whereas the mandibular volume was constant between groups (p-value: 0.90). The decreased tongue proportion (p-value: 0.01) found in the apneic group is due to the enlarged surrounding soft tissues. This underscores the contributions of the soft palate, lateral pharyngeal walls, and lateral pharyngeal fat pads, as they relate to the mechanics of OSA.

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(1) Schwab RJ: Upper Airway Imaging; Clinics In Chest Medicine. Volume 19, Number 1, 1998, pp 33-54.

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1287.K1

The Influence of Obesity on Upper Airway Structure and Function

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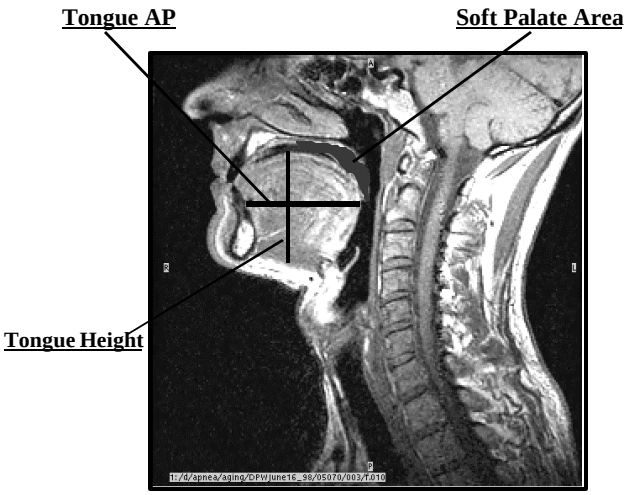
Introduction: For poorly defined reasons, obesity is a major risk factor for Obstructive Sleep Apnea (OSA). Although the pathogenesis of OSA likely involves abnormalities of both upper airway structure and function, few studies have combined anatomical assessment with physiologic measures. To date, no studies have examined the impact of obesity on both upper airway structure and function in combination.

Methods: We studied 46 subjects across a range of body mass indices (BMI, 19-39 kg/m2, n=22 lean BMI<25, n=24 obese BMI >25). Each subject underwent studies of upper airway physiology during wakefulness, which included assessment of pharyngeal mechanics as well as dilator muscle activation. This involved recordings of intramuscular genioglossus (GG) EMG plus choanal and epiglottic pressure (using Millar pressure catheters) during basal breathing, and in response to both applied pulses of negative pressure and hypercapneic stimulation. In addition, we performed magnetic resonance imaging (MRI, axial, coronal and sagittal sections, volumetric analyses) during tidal ventilation on these same subjects. (modified methods of Schwab et al). Finally, a standard in-laboratory polysomnography was performed.

Results: We observed:· The tongue dimensions are substantially larger among obese compared with lean individuals. Significant differences were seen for three tongue dimensions (two antero-posterior, one lateral, all $p<0.05$) and axial cross sectional tongue area ($p<0.05$). (see Figure 1)· Soft palate area was greater in the obese compared with lean subjects

even when normalized for body surface area (P <0.05).· Airway volume, measured from the hard palate to the top of the epiglottis, was reduced among obese compared with lean individuals, even when normalized for body surface area (p<0.001).· The responsiveness of the GG to CO2 was reduced in obese compared with lean individuals (p<0.05).

Figure 1



Conclusions: Obesity has a measurable impact on multiple upper airway dimensions (on both axial and mid-sagittal sections), even when normalized for body surface area. Diminished GG response to CO2 may reflect functional impairment in pharyngeal dilator muscles. These structural and functional changes with obesity may impact the vulnerability of the pharyngeal airway to collapse.

References:
(1) Schwab et al, Am. J. Respir. Crit. Care Med., 1995, 152: 1673- 1689.

Research supported by NCRR GCRC RR02635, NHLBI HL48531/HL60292

1309.K1

The Effects of Surgically Induced Weight Loss on Sleep-Disordered Breathing and Phayrngeal Muscle Function

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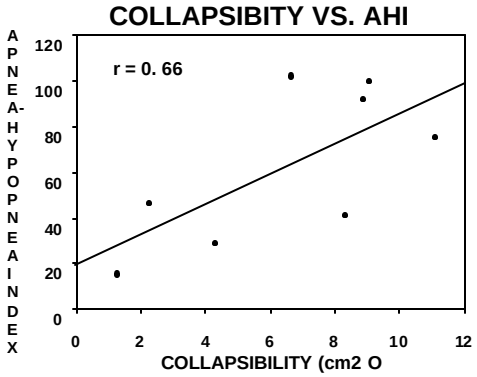
Introduction: Obesity is the most important risk factor for the development of Obstructive Sleep Apnea. While previous studies have documented improvement in sleep disordered breathing following substantial weight loss, the impact of weight loss on pharyngeal dilator muscle function and responsiveness has not been previously determined. We hypothesized that surgically induced weight loss would lead to a decrease in awake basal genioglossal muscle activation (GGEMG, less need for neuromuscular compensation) and an improvement in genioglossal muscle responsiveness to negative pressure.

Methods: We studied 8 morbidly obese subjects (BMI > 45 kg/m2) before and after (5 to date) substantial weight loss following gastroplasty. All subjects underwent standard polysomnography, measurement of pharyngeal muscle function, muscle responsiveness to pulses of negative pressure, (GGEMG) and pharyngeal mechanics (airflow resistance and airway collapsibility) during wakefulness. Collapsibility was measured as the pressure difference between the choanae and the epiglottis (with Millar catheters) during brief (<300 millisecond) pulse of negative pressure.

Figure 1



Results: Table 1 shows that associated with significant weight loss, sleep disordered breathing improved in all subjects. Evaluation of pharyngeal mechanics revealed a decrease in pharyngeal arflow resistance during basal breathing, along with a decrease in airway collapsibility during pulses of negative pressure. In addition, while basal GGEMG decreased following weight loss, genioglossal responsiveness to pulses of negative pressure increased. Finally, as can be seen in the figure above, collapsibility measured during wakefulness correlated with the severity of sleep disordered breathing pre-operatively (r = 0.66, p < 0.05).

Table 1

	PRE-OP	POST-OP	P
WEIGHT (lbs)	332 +/- 60	273 +/- 49	<.001
BMI (kg/m^2)	54.2 +/- 8.5	44.6 +/- 6.4	0.001
AHI (events/hour)	54 +/- 28	25 +/- 14	0.03
Peak Phasic GGEMG (% of maximum)	18.8 +/- 6.4	8.1 +/- 4.7	0.04
EMG Response to negative pressure (% increase)	47.3 +/- 21	81.7 +/-29	0.02
Pharyngeal Resistance (cm H2O/L/S)	5.7 +/-2.9	1.6 +/- 0.8	0.03
Pharyngeal Collapsibility (cm H20)	7.5 +/- 2.9	5.5 +/- 2.4	0.053

Conclusions: Weight loss is associated with an improvement in sleep disordered breathing as well as decreased basal genioglossal EMG, decreased pharyngeal airflow resistance, collapsibility and an increased GGEMG response to negative pressure. We speculate that weight loss led to an anatomically larger airway yielding decreased resistance, less requirement for neuromuscular compensation and increased ability of muscles to respond to negative pressure stimuli.

References:
(1) Schwartz AR, Gold AR, Schubert N, et al.: Effect of weight loss on upper airway collapsibility in obstructive sleep apnea. Am. Rev. Respir. Dis. 1991; 144: 494-498.

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1270.K1

Aging-related Changes in the Pharyngeal Structure and Function in Normal Subjects

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Introduction: Obstructive sleep apnea (OSA) is a disease characterized by deficient pharyngeal anatomy in combination with a loss of neuromuscular reflexes leading to a fall in dilator activation at the onset of sleep. Thus, OSA is a disease of both upper airway anatomy and physiology. However, to date few studies have assessed both of these variables in the same individuals. For unclear reasons, OSA becomes progressively more common with increasing age. In theory, aging could increase the propensity for OSA by impacting airway anatomy or pharyngeal dilator muscle activation.

Figure 1. Axial MRI at Minimum Lumen

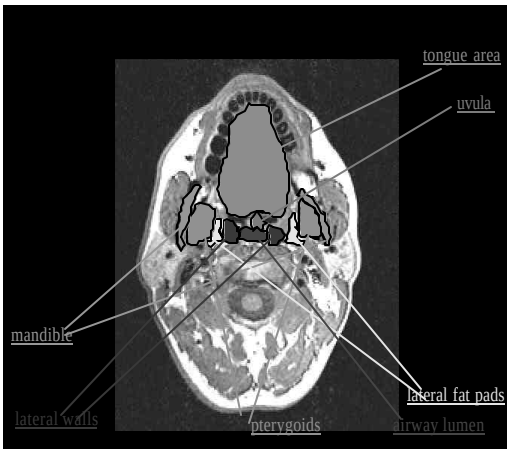
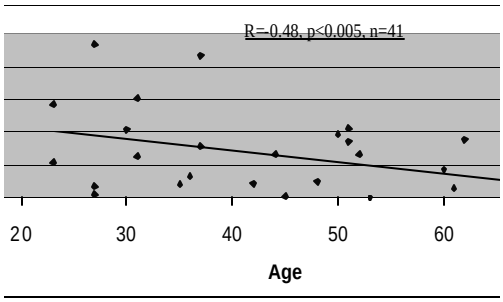


Figure 2. Decline in Negative Pressure Reflex with Age



Methods: In order to assess the influence of aging on the upper airway, we prospectively evaluated 41 normal subjects (AHI <15, male=female) across a range of ages (23-80 years) and body mass indices (19-39 kg/m2). Each subject underwent three studies a) in laboratory polysomnography (ASDA criteria plus nasal pressure, to exclude substantial apnea) b) detailed anatomic assessment using magnetic resonance imaging (MRI, axial, sagittal, and coronal sections), during tidal ventilation. Measured airway lumen, soft tissue and skeletal features (modified methods of Schwab et al) c) physiologic assessment of genioglossal EMG during basal breathing and in response to stimulation with both negative pressure and hypercapnia.

Results: We observed the following with increasing age: Increased length of the soft palate on mid-sagittal section (normalized for body height, R=0.67, p<0.001). Increased size (greater area) of the para-pharyngeal fat pads at the level of the minimum pharyngeal lumen, independent of changes in body mass index (R=0.62, p<0.001). (see Figure 1) A change in shape (AP/lateral) of the bony structures around the pharyngeal airway, with a progressive relative loss of AP dimension (R=-0.51, p<0.001). Diminished responsiveness of the genioglossus muscle to negative pressure stimulation (R=-0.48, p<0.005). (see Figure 2)

Conclusions: These observations suggest that changes in both upper airway anatomy and muscle function occur with increasing age in normal individuals. The increased vulnerability of the upper airway to collapse with increasing age may be based on both anatomical changes and loss of protective reflexes.

References:
(1) Schwab et al, Am. J. Respir. Crit. Care Med., 1995, 152: 1673-1689.

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1396.F

Behavioral Sleep in a Young Gray Whale (Eschrichtius robustus) in Captivity

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Introduction: We had the opportunity to conduct visual observations of the behavior of a gray whale which had been rescued and then was kept for 14 months at "Sea World" in San-Diego. The aim of the present study was to describe behavioral sleep in the gray whale and to try to identify behavioral signs of paradoxical sleep (REM and muscular jerks), which had been previously described in bottlenose dolphins (Mukhametov, Lyamin, 1994) and beluga whales (Lyamin et al., 1998).

Methods: The behavior of a young (about 15 months old) female gray whale (Eschrichtius robustus) was recorded continuously on a time-lapse video recorder using 2 underwater and 3 aerial TV cameras for 9 days. The animal was kept in a spacious pool approximately 6400 m3 but rested in a shallow channel. The behavior of the whale was visually scored and all behavioral events of interest were counted.

Results: On average during the first 6 recording days, active wakefulness accounted for 37.9 ± 1.7% of each day; behavioral sleep, 41.3 ± 1.7%; transitional stage, 17.5 ± 1.4%; unidentified states, 3.4 ± 1.1%. The gray whale slept lying on the bottom of the pool (13.2 ± 1.7%) or hanging on the surface (28.1 ± 1.7%). During this stage the whale was immobile most of the time moving only to perform respiratory acts. Usually, only one and rarely both eyes were closed in this stage. The pattern of respiration in the whale was dependent on the behavioral stage and prolonged respiratory pauses (up to 460 sec) were observed when the whale lay motionless on the bottom. Characteristic jerks of the head, neck, whole body and eyelids movements were observed in the whale during behavioral sleep. In total, 48 jerks were registered in the gray whale during the first 6 days. Most jerks were single and only 70% of all jerks occurred within 10 sec of a prior jerk. Eyelids movements accompanied 40% of jerks. We also documented two episodes in which head and body jerks followed each other continuously during several seconds

and were accompanied by eyelid movements. During these episodes the whale was slowly falling on its side and shortly after this woke up and started actively to swim in the pool.

Conclusions: Our study has shown that the sleep of the gray whale, like beluga whales (Lyamin et al., 1998), is accompanied by long respiratory pauses and almost full immobility. The presence of jerks during behavioral sleep in the studied gray whale and in the previously studied bottlenose dolphins (Mukhametov, Lyamin, 1994) and beluga whales (Lyamin et al., 1998) suggests that short periods of paradoxical sleep do exist in Cetaceans but in a modified form that is not accompanied by all of the classical polygraphic or behavioral signs of paradoxical sleep.

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(2) Lyamin OI, Shpak OV, Nazarenko EA, Mukhametov LM: Behavioral signs of paradoxical sleep in the beluga whale. J. Sleep Res., 1998, 7, Suppl 2:166.

Research supported by the Medical Research Service of the Veteran Administration, USPHS grant NS32819 and partly by Utrish Dolphinarium Ltd.

1124.F

State-Related Discharge of Neurons in the Ventral Cerebellum and Brainstem of the Box Turtle, Terrapene Carolina

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Introduction: In mammals, the sleep cycle is characterized by changes in the rate and pattern of discharge of neurons throughout the brain (Siegel, 1994). The state-related behavior of brainstem units of freely-moving reptiles has not been recorded. Analysis of brainstem unit discharge in reptiles would provide the first insight into the nature of sleep in reptiles at the neuronal level.

Methods: We recorded unit activity extracellularly from a total of 33 neurons of the ventral part of cerebellum (15 units), and reticular formation (18 units) of 3 freely-moving turtles of the species Terrapene carolina, using tungsten microelectrodes (5 Mα). EEG, EMG, EKG, and EOG were also recorded. Polygraphic, video and visual observations were used to define periods of active wakefulness, quiet wakefulness (QW), a transitional state (T-state), and two substages of quiescence (Q1 and Q2, based on the presence or absence of EMG). Neuronal discharge rates in each state were calculated in each state using 30 sec epochs.

Results: 32 of the 33 recorded units (97%) fired in association with active movement. The remaining unit (from cerebellum) was inhibited during movement. 11 of 20 (55%) tested units responded somatotopically to tactile stimulation, to visual stimulation, or both.During quiescence, the firing rate of all units decreased. The mean discharge rate in cerebellum (based on 11 spontaneously active units with stable firing in all stages) was 2.30±0.81 Hz (1.3-9.16 Hz) in QW; 1.19±0.56 Hz (0.07-6.53 Hz) in T-state; 1.00±0.50 Hz (0.02-5.19 Hz) in Q1 and 0.83±0.46 Hz (0.02-5.10 Hz) in Q2. The mean discharge rate of reticular formation units (based on 13 stable cells) was 0.95±0.23 Hz (0.11-2.73Hz) in QW; 0.52±0.16 Hz (0.03-1.98 Hz) in T-state; 0.56±0.24 Hz (0.01-2.80 Hz) in Q1 and 0.37±0.16 Hz (0.01-1.99 Hz) in Q2.In all units recorded from the cerebellum and reticular formation, rate and variability of discharge in Q2 were significantly lower than in QW and T-state. Mean discharge rate during Q1 and Q2 was lower than 0.02 Hz in 5 of the 15 cerebellar neurons (33%) and 5 of 13 stable neurons (38%) in the reticular formation. The longest pauses in firing were 58 minutes and 27 minutes, respectively.

Conclusions: All neurons recorded to date from the cerebellum and reticular formation of freely-moving turtles showed movement-related discharge which decreased in rate and variability as turtles moved from quiet wakefulness to total quiescence. No periods of increased activity during quiescence were seen under the conditions of our recordings. Further data may allow specific conclusions about the presence or absence of paradoxical sleep based on firing patterns in specific structures. The proportion of neurons that are silent or have very low spontaneous activity may be higher in reptiles than in mammals.

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1228.F

Unihemispheric Slow-Wave Sleep and Predator Detection in the Pigeon

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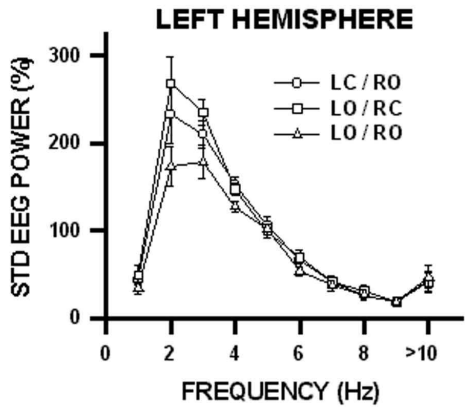
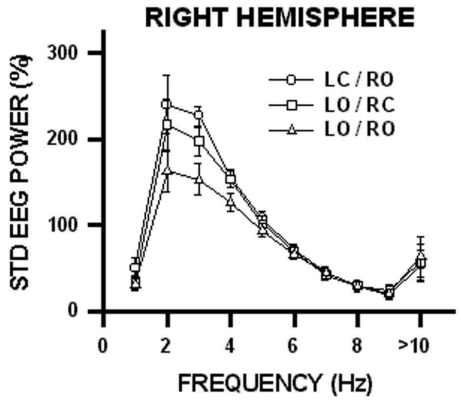
Introduction: Birds and aquatic mammals exhibit unihemispheric slow-wave sleep (USWS), a unique state during which one cerebral hemisphere sleeps while the other remains awake (Rattenborg et al. 1999a,b; Mukhametov 1984). USWS in birds is associated with unilateral eye closure (UEC); closure of one eye is associated with USWS in the contralateral hemisphere, and closure of both eyes is associated with bihemispheric SWS or REM sleep. We recently demonstrated that mallards (Anas platyrhynchos) utilize USWS to mitigate the inherent conflict between sleep and predator detection (Rattenborg et al. 1999a,b). Herein we quantify the association between UEC and USWS in the pigeon (Columba livia) using period amplitude analysis (PAA) of the EEG, and demonstrate that pigeons also utilize USWS for predator detection.

Figure 1



Methods: Bipolar EEG recordings were obtained from the left and right hemispheres (hyperstriatum accessorium) of adult pigeons (n = 9). Eye state was simultaneously video-taped via four cameras. A PAA algorithm (Sandman 2.4) was used to quantify EEG power (micro-volts squared) during 4-s epochs from each eye state; 1) left and right eye open (LO/RO), 2) both eyes closed (excluding REM sleep), and 3) UEC with the left eye closed (LC/RO) or right eye closed (LO/RC). Since several pigeons exhibited little SWS with both eyes closed, the PAA was restricted to the other eye states. For each hemisphere, EEG power was standardized as a percent of the average power observed during UEC with the contralateral eye closed. Based on our findings in mallards, during UEC we expected 2-4 Hz power to be greater when the contralateral eye was closed. Moreover, since each bird's cage was positioned against a wall, we expected pigeons to direct the open eye during UEC away from the wall, the only direction from which a threat could approach.

Figure 2



Results: For each hemisphere, when compared to UEC with the contralateral eye closed, 2-4 Hz power was lower during UEC with the contralateral eye open, indicating USWS ($t > 3.14$, $P < 0.01$ for both hemispheres; Figures). Moreover, as observed in mallards, 2-4 Hz power was lowest with both eyes open ($t > 4.80$, $P < 0.005$ for both hemispheres). During UEC, pigeons spent 88.02 ± 3.27% of the time with the open eye directed away from the wall (% away vs. 50 % indicating no orientation preference; $t = 9.56$, $P < 0.0001$).

Conclusions: The PAA confirms an interhemispheric asymmetry in 2-4 Hz power associated with UEC in pigeons, thus indicating USWS as previously observed in mallards. Although the degree of asymmetry was small, we have previously shown that mallards are responsive to threatening visual stimuli during this state. Moreover, both mallards and pigeons utilize this state in an adaptive manner by directing the open eye toward a potential threat. Since pigeons and mallards are distantly related, UEC and USWS may serve a predator detection function in birds in general.

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1748.F

Homeostatic Aspects of the Rest-Activity Cycle in Drosophila Melanogaster and Their Molecular Correlates

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The Neurosciences Institute

Introduction: In mammals, sleep is believed to be under homeostatic control and can be characterized by both behavioral and electrophysiological criteria. Because electrophysiological criteria are difficult to meet in invertebrates, the identification of sleep-like states depends primarily upon behavioral analysis.[1] The essential behavioral criteria for sleep include quiescence, increased arousal threshold, and sleep rebound following prolonged waking. Moreover, physiological variables such as respiration and heart rate that have been shown to correlate with behavioral state in mammals[1] show similar modulation across state in some invertebrates. Recently, physiological correlates of behavioral state have been extended to the level of gene expression.[2] With this in mind, the goal of the present study was to evaluate the rest-activity cycle and their molecular correlates in drosophila melanogaster.

Figure 1

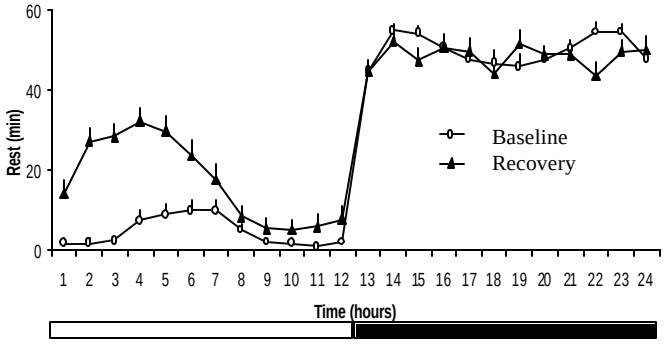
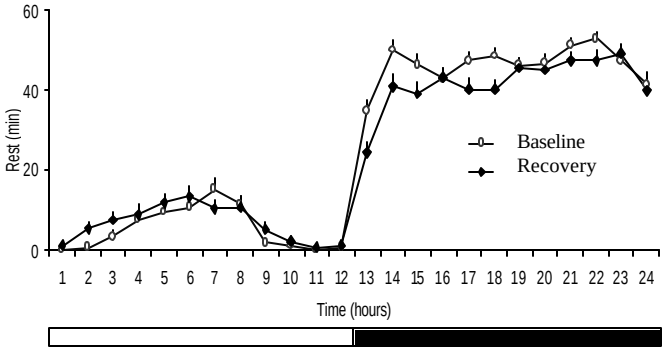


Figure 2



Methods: Wild type (Canton-S) flies were maintained on a 12:12 LD schedule. Activity patterns were monitored using infrared and ultrasound technology. The infrared system recorded activity each time a fly crossed a low-level infrared light beam. The ultrasound system permitted the continuous measurement of fly activity by detecting movement as a change in phase and amplitude of a standing sound wave. In order to determine whether periods of rest are associated with increased arousal thresholds, flies were subjected to vibratory stimuli of increasing intensity (.05g, .1g, and 6g). The effect of 12 hours of rest deprivation (RD) during the dark period was evaluated in 5-day-old virgin female

flies (n=286) in 10 independent experiments. Differential display was performed on RNA extracted from whole heads of flies that: (i) had been spontaneously resting for 3h during the dark period; (ii) had been rest deprived for 3h and were collected at the same circadian time, or (iii) had been spontaneously awake for 3h during the light period. Using this experimental paradigm, it is possible to distinguish between changes in gene expression associated with behavioral state and those associated with circadian factors or stimulation.[2]

Results: As in mammals, sustained periods of quiescence in Drosophila are characterized by increased arousal thresholds (.05g and .1g; $p<.001$, χ^2). Following 12 hours of RD during the dark period, rest was increased in the 10 replications by a mean of 301.8 ± 60.2% over baseline values during the first six hours of the following light period (Fig 1). In contrast, RD during the light period (n=36) reduced the amount of rest by 15.9 ± 4.1% during the first six hours of the following dark period (Fig 2). Changes in gene expression were evaluated using mRNA differential display and confirmed using RNase Protection Assay. Several transcripts that were modulated by the rest-activity cycle in Drosophila showed a similar expression pattern as that seen in rats during spontaneous sleep and waking.

Conclusions: These results suggest that rest periods in Drosophila are under homeostatic control and that transcripts modulated by the rest-activity cycle show similarities to molecular correlates of behavioral states in rats.

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(2) Cirelli C., and Tononi G., Mol Brain Res, 56:293, 1998

Supported by Neurosciences Research Foundation

1186.E

Low-Dose, Repeated Caffeine Administration as a Countermeasure to Neurobehavioral Deficits During a Forced Desynchrony Protocol

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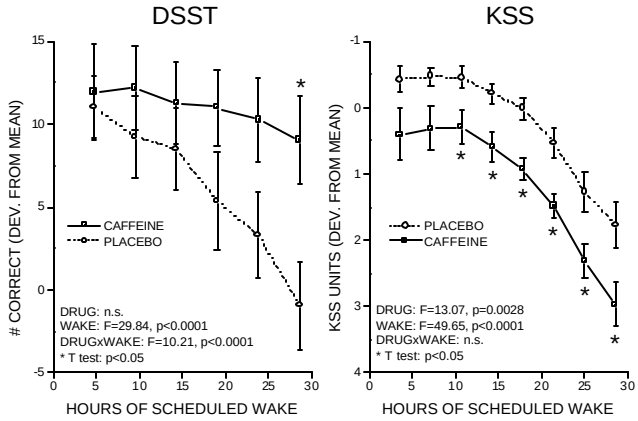
Introduction: Enforced wakefulness and/or circadian phase misalignment impairs neurobehavioral functioning. Caffeine is a promising countermeasure, but studies have failed to repeat administration over many days, used large doses associated with unstable plasma concentrations, and measured few neurobehavioral functions. We assessed the efficacy of low-dose, repeated caffeine administration under enforced wakefulness at a full range of circadian phases with the forced desynchrony protocol, to investigate whether caffeine interacts primarily with homoeostatic (sleep-wake dependent) or circadian components of neurobehavioral functioning.

Methods: Sixteen healthy males (age 18-30) lived for 29-days without obvious time information, after maintaining a regular sleep schedule (8-hr TIB) for 2-3 weeks prior to admission. Following 3, 24-hr baseline days under placebo conditions, subjects were placed on a forced desynchrony protocol with 14 repetitions of a 42.85-hr forced period (28.57-hr enforced wake, 14.28-hr scheduled sleep). Each hour during wakefulness, ending 1.57hr before bedtime, subjects were administered caffeine (8 subjects, 0.3mg/kg/hr) or identical-appearing placebo capsules (8 subjects), under double-blind conditions. Every 2hr during wakefulness, subjects took 30-min computerized neurobehavioral assessments: Probed Recall Memory Task (PRM), Psychomotor Vigilance Task (PVT), Addition Task (ADD), Digit Symbol Substitution Task (DSST), visual analog mood scales (VAS), and Karolinska Sleepiness Scale (KSS). Repeated measures ANOVAs (Huynh-Feldt correction) were used, with factors DRUG, duration of prior scheduled WAKE, and circadian PHASE.

Figure 1



Results: Caffeine attenuated decrements across the 28.54-hr wake episodes in correct responses on the DSST ([DRUG x WAKE]F=10.21, p<0.0001, see Figure) and ADD ([DRUG x WAKE]F=4.89, p=0.0097), and attenuated DSST accuracy deficits ([DRUG x WAKE]F=2.81 p=0.484). However, caffeine effects on psychomotor vigilance (PVT median RT: DRUG p = n.s.) and memory (PRM: [DRUG]p = n.s.) were not significant. Caffeine subjects reported more sleepiness on the VAS ([DRUG]F=5.28, p=0.0388) and KSS ([DRUG]F=13.07; p=0.0028, see Figure). Caffeine was associated with lower self-assessments of sleepiness during the first 28.54-hr wake episode, but this reversed for subsequent wake episodes. For all measures except the PVT, regardless of drug condition, there was an interaction of WAKE and PHASE (p<0.05), with worst neurobehavioral impairment seen toward the end of scheduled wake episodes and at or just after the body temperature trough. These interactions suggested that caffeine primarily affects declining neurobehavioral functioning associated with time awake and does not significantly modulate the contribution of circadian phase.

Conclusions: This is the first report of caffeine administration during extended wakefulness scheduled at a full range of circadian phases, and a novel caffeine administration procedure. Caffeine attenuated deficits associated with time awake (DSST and ADD), and even offset accuracy decrements (DSST). However, performance was not different from placebo on the PVT and PRM. Although it increased subjective alertness on the VAS and KSS during the first 28.54-hr wake episode, caffeine was associated with higher subjective sleepiness in subsequent wake episodes. We hypothesize the properties of caffeine administration that attenuate neurobehavioral deficits on certain measures may impair depth/duration of subsequent sleep, increasing subjective sleepiness in following wake episodes. We conclude that caffeine interacts with the homeostatic component in regulating neurobehavioral performance, presumably through interactions with adenosine receptors.

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1732.E

Circadian and Homeostatic Contributions to the Regulation of Slow Wave Activity During Sleep in Adolescents

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Introduction: Studies of adults have shown that modulation of slow wave sleep and computer-detected slow wave activity (SWA) during sleep, is related to primarily a sleep-dependent homeostatic process with a small but significant contribution of the circadian timing system (Dijk and Czeisler, 1995). The relative contributions of these systems to slow wave regulation have not been assessed in children and adolescents, who exhibit higher amplitude and more abundant slow wave sleep than adults. We used a 28h "forced desynchrony" (FD) protocol to investigate circadian and homeostatic effects on SWA in adolescents.

Figure 1

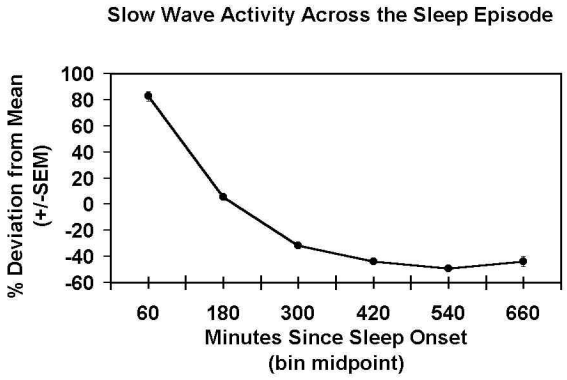
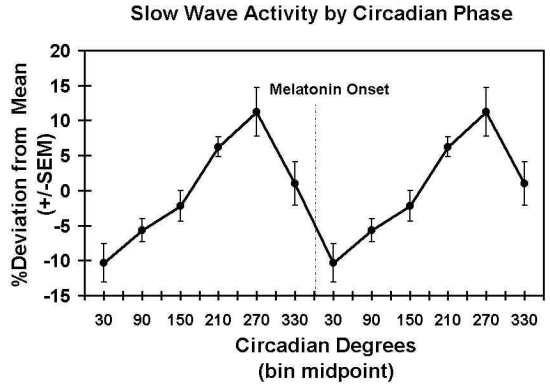


Figure 2



Methods: Sleep EEGs were analyzed from eight healthy children (ages 13-15 years; Tanner stage 3-5; 4F) who completed a 20-day 28h FD protocol. After 10 cycles of a 24h sleep-wake schedule at home, participants came to the laboratory, where lighting was held at <20 lux. After an adaptation night, participants underwent a 36h constant routine followed by a recovery night and 12 cycles of 28h FD consisting of an 11h40m sleep opportunity and 16h20m wake episode each cycle. C3-A2 EEG was recorded onto Nicolet Ultrasom workstations for all sleep episodes. Average amplitude of EEG activity in the frequency range of 0.75-4.5 Hz was determined for each 30-sec epoch scored as sleep stage 2, 3, or 4. Activity in this frequency range was estimated by squaring the amplitude of each epoch. A sleep-dependent effect was assessed by averaging data in 2h bins from sleep onset irrespective of circadian phase. An independent effect of circadian phase was assessed by averaging data in 60 degree bins using circadian phase estimates based on intrinsic period obtained from dim-light salivary melatonin (0 degrees=melatonin onset phase). We used a repeated measures ANOVA to assess sleep-dependent (Minutes Since Sleep Onset), circadian (Phase), and interaction effects.

Results: We found significant main effects for Minutes Since Sleep Onset ($F=331.74$; df (4,28); $p<0.001$) and Phase ($F=7.11$; df (5,35); $p<0.001$) but no significant interaction between the two factors. SWA exhibited maximal values at the start of each sleep episode, declining abruptly across the sleep episode. SWA exhibited a significant circadian rhythm, with the peak of activity occurring at 270 degrees and the minimum at 30 degrees.

Conclusions: Both the circadian system and the sleep-dependent homeostatic process significantly influenced the regulation of SWA in adolescents under conditions of forced desynchrony. These data also indicate the primacy of the homeostatic process relative to the circadian system similar to that observed in adult subjects. The potential importance of the circadian timing system to slow wave regulation (or related neurobiological processes) is highlighted by the consistency of our results with those from similar assessments in adults, particularly the finding that SWA manifests a peak during the circadian day and its trough during the circadian night.

References:
(1) Dijk DJ, Czeisler CA. Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. Journal of Neuroscience 1995; 15(5):3526-3538.

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1417.E

Evidence that the "Post-Lunch Dip" is Endogenous to the Circadian System

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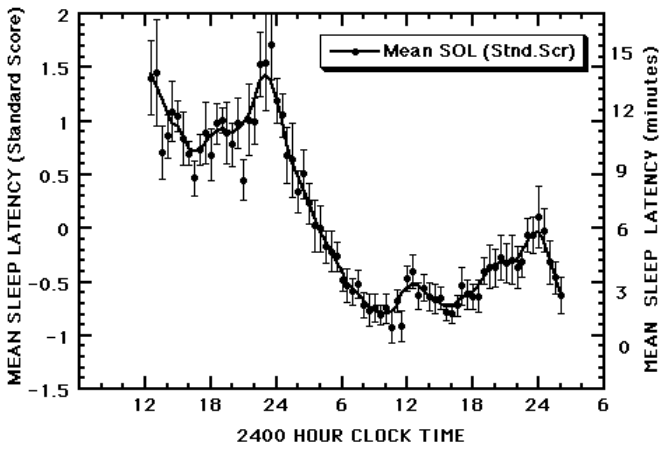
Introduction: Recently it has been suggested that the afternoon depression of sleep onset latency (SOL) or "post-lunch dip" of alertness, may not necessarily be taken as evidence in support of it being endogenous to the circadian system.[1] Instead, the afternoon decrease of SOL may result from the combination of two effects (exponentially decreasing SOL from Process S and linearly increasing SOL from a circadian effect). However, if wakefulness were extended to 40 hours, the combination effect would predict the absence of a "post-lunch dip" in the second afternoon. The combination effect would be dominated by the circadian effect, thus "unmasking" a possible afternoon sleepy period on the second day.[2]

Methods: Twelve (7f, 5m) healthy, young (mean age, 21 years) good sleepers who were non nappers participated as paid volunteers. The experimental session consisted of a 40 hour constant routine/half-hourly MSLT. It utilized the constant routine method of continuous bed rest in a time-free, physically constant environment. In addition we measured SOL half-hourly using the Multiple Sleep Latency Test awakening the subject after three consecutive 30-second epochs of sleep.

Results: The afternoon decrease of SOL was significantly (.05) evident in about the same number of subjects on both days (five on the first and seven or 58% on the second). A mean curve was calculated in order to illustrate the typical variation of SOL over the 40 hour experiment. Since

there were large differences between subjects in the range of SOL values, the raw SOL values for each subject were first converted to standard scores. The mean standard scores of SOL with standard error bars and fitted weighted smoothed curve are illustrated in the figure. The mean in minutes is also shown on the right hand Y axis. Although the magnitude of the afternoon depression of sleep latencies at about 1400hr on the first day is greater than the depression of SOL at 1300hr on the second day, this seems to be due mostly to the restriction of the range of SOL values on the second day.

Figure 1



Conclusions: These data suggest that the combination of the circadian effect and Process S contribute to the magnitude of the early afternoon decrease of sleep latency on the first day. However, the presence of a significant depression of sleep latency on the second day of this experiment is consistent with our earlier study.[3] It suggests that the early afternoon sleepiness period arises from an endogenous component of the circadian system perhaps indicative of an endogenous circasemidian (12-hour) rhythm of sleepiness.

References:

(1) Webb WB. Prediction of sleep onset. In Ogilvie RD and Harsh JR (Eds). Sleep onset: Normal and abnormal processes. Amer Psychol Assoc, 1994.

(2) Lack L, Patrick S. The 40 hour constant routine/half-hourly MSLT protocol: An attempt to unmask the "Post-lunch dip" in the circadian system. Sleep Research Online 1999:2(Supp.1):614.

(3) Lack L, Lushington K. The rhythms of human sleep propensity and core body temperature. J Sleep Res 1996;5:1-11.

Research supported by Australian Research Council

1104.E

Circadian and Homeostatic Influences on Sleep During a 90-Minute Day Paradigm

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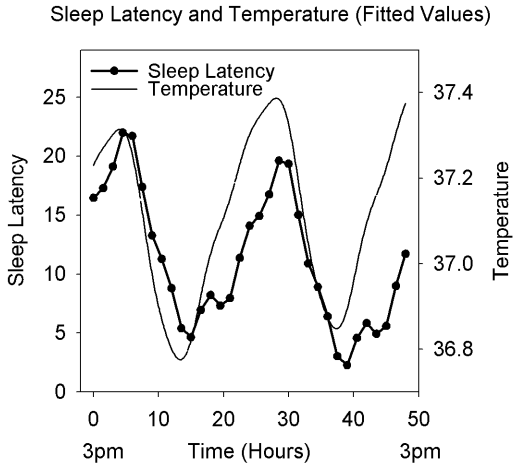
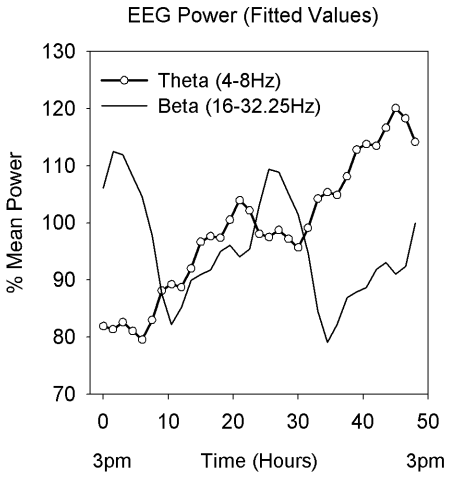
Introduction: Circadian, homeostatic, and sleep-dependent aspects of human sleep can be disentangled by imposing very short or very long sleep-wake schedules. Dijk and Czeisler[1] described circadian modulation of sleep propensity, as well as circadian and sleep-dependent modulation of EEG power in specific frequency bins, during a forced desynchrony protocol with a 28-hour day. However, this design is less sensitive to changes in homeostatic sleep drive. The aim of the current experiment was to identify circadian and homeostatic influences on EEG sleep using a 90-minute sleep-wake schedule.

Figure 1



Methods: Subjects were medication-free adults (7 men, 4 women; 22.8 ± 2.4 yrs) with no sleep, medical, or psychiatric disorders. Following a baseline day, subjects followed a 90-minute sleep-wake schedule for 60 hours. Each cycle consisted of a 30-minute sleep opportunity in bed with lights out and continuous EEG monitoring, followed by 60 minutes of wakefulness. Core body temperature was measured by rectal thermistor. EEG sleep recordings were digitized, filtered, and stored for analysis. Sleep episodes were visually scored in 20-second epochs. Sleep onset was defined as the first of three consecutive epochs of any stage sleep. Following computerized rejection of artifacts, EEG signals were analyzed with power spectral analysis. EEG power density was determined for the following frequency bins: delta (0.25 - 4 Hz), theta (4 - 8 Hz); alpha (8 - 13 Hz); sigma (13 - 16 Hz); and beta (16 - 32 Hz). Data in each bin at each time point were expressed as a percentage of each subject's mean power across all sleep episodes. Only sleep episodes with >5 minutes of continuous NREM sleep were considered. Circadian and homeostatic influences were assessed with mixed effects models, including a first-order autoregressive error structure, for each outcome variable. Each model tested for 24-hour, 12-hour, 6-hour, and linear components, using data from the middle 48 hours of the study. The linear component was interpreted to indicate increasing homeostatic sleep drive.

Figure 2



Results: Mixed-model analysis of core body temperature indicated significant 24- and 12-hour components ($p < .002$ for each). The model for sleep latency showed significant 24-hour ($p < .0001$), 12-hour ($p < .02$), 6-hour ($p < .02$), and linear ($p < .02$) components (Figure 1). EEG delta, theta, alpha, and sigma power had strong linear components ($p < .0001$); delta and theta also had weaker 24-hour components ($p < .03$). Beta power was modeled by a prominent 24-hour component ($p < .003$), but no 12-hour, 6-hour, or linear component (Figure 2).

Conclusions: Young adults following an ultradian sleep-wake cycle showed a combination of homeostatic and circadian influences on sleep. EEG power in slower frequencies showed evidence for a linear increase, consistent with increasing homeostatic sleep drive. Faster EEG frequencies showed prominent circadian modulation, and sleep latency showed a combination of homeostatic, circadian, and ultradian influences. Different aspects of the sleep EEG show different mixtures of circadian and homeostatic sleep regulatory influences during an ultradian schedule.

References:
(1) Dijk DJ, Czeisler CA:Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. J Neurosci 15:3526-3538, 1995

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1875.K3

Urban Traffic Noise in Sydney - Effects on Sleep and Performance

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Introduction: Increasing urbanisation is associated with higher levels of traffic noise exposure. Traffic noise leads to subjective reports of sleep disturbance. However, the exact relationship between traffic noise and sleep is unclear with no threshold levels for sleep disturbance reported.[1] In addition, some researchers claim that there are adaptation effects to traffic noise and this has been used by planning authorities as a counter to community concerns about road traffic. Most studies also measure ambient outdoor noise that is variable and can be attenuated by some home designs and not others. Therefore we studied the effects of a controlled traffic noise exposure on subjective and objective sleep parameters as well as subjective daytime function and objectively measured morning performance.

Methods: Ten couples were studied (aged 21-55). All subjects were screened for the presence of sleep problems, hearing disorders, normal health and lived in a locality with low levels of traffic noise. A computerised traffic noise generation system was developed and programmed to produce similar noise levels and heavy vehicle passes to a major urban road in western Sydney (15 minute average sound level 52-55 dB (A), in conjunction with the National Acoustic Laboratories, Chatswood, Sydney). Subjects slept in their own homes and were exposed in random order to traffic noise exposure (TN) or no noise (NN). Noise was measured from within the bedroom by 2 separate monitoring systems verifying the noise levels intended for generation by the computer system and also ensuring the absence of any extraneous noise. Each exposure (TN and NN). was over 4 nights. There was a 1-2 week washout period between exposures. Actimetry during TN and NN periods was performed using Actiwatch devices (Mini Mitter, USA). Subjects completed daily measures of sleep quality, Karolinska Sleepiness Scale (KSS) and underwent a morning neurobehavioural test procedure (NAB, D.Dinges and J. Powell, University of Pennsylvania). Analysis of data was by ANCOVA examining for effects of noise and day and interaction effects (SPSS).

Results: TN exposure produced subjective reductions in sleep length and quality and greater reported awakenings. KSS results showed noise impaired sleep initiation, morning awakening and sleep quality (all $p < .01$). On actimetry, TN caused increased wake time, impaired sleep efficiency and increased wake bouts during the night (all $p < .02$). On NAB testing, TN reduced a range of subjective impairments with increased agitation and fatigue and poor mood. Objective testing revealed decrements in performance with serial addition/subtraction and digit symbol substitution $p < .01$). There were no adaptation effects over 4 days of exposure.

Conclusions: Noise levels equivalent to exposure experienced by residents of Sydney living near major urban roads produces marked impairments in subjective and objectively measured sleep quality, psychosocial function and performance. Further development of such roads and increased urbanisation post-Olympics in Sydney may lead to increased levels of insomnia in the population and possibly even, loss of productivity. Further data is required to determine the noise "threshold" that will not produce sleep effects and examining effective methods of noise attenuation.

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(1) Carter N. ransportation noise, sleep and possible after-effects. Environment International 1996;22:105-116

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1473.K3

Ethanol and Caffeine Effects on the Sleep of Insomniacs

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Introduction: In a previous study, low dose ethanol [breath ethanol concentration (BrEC) <.05%] improved the sleep of insomniacs who were moderate social drinkers.[1] When given the opportunity to self-administer ethanol before sleep, the insomniacs chose ethanol more frequently than age-matched normals with similar moderate social drinking histories. A question arises as to whether insomniacs preferred ethanol because of its hypnotic effects or its other mood-altering effects. A daytime study in healthy normals has shown that caffeine 150 and 300 mg reversed the sedative effects of low dose ethanol.[2] Thus, this study evaluated the effects of low dose (0.5 g/kg) ethanol and a combination of ethanol and caffeine (150 mg) on the sleep and mood of insomniacs.

Methods: Eight insomniacs (5 females and 3 males), 21-50 yrs old, with otherwise normal physical, psychiatric and laboratory test results volunteered. No history of alcoholism and drug abuse and no current drug or alcohol use was allowed. All had chronic (>1 yr) insomnia complaints and a sleep efficiency <85% on a 8-hr screening NPSG. No subjects with apnea or periodic leg movements on the screening NPSG were admitted. On 2 consecutive nights each they received 3 treatments presented in a Latin Square design with 2-7 nights between treatments. The treatments were: ethanol 0.5 g/kg and caffeine placebo (EP), ethanol 0.5 g/kg and caffeine 150 mg (EC), and ethanol placebo and caffeine placebo (PP). The caffeine or caffeine placebos were prepared as capsules and administered at 2200 hrs. The ethanol and ethanol placebo was consumed in three divided doses from 2200-2230. Prior to the treatment and at bedtime (i.e. post treatment) the Profile of Mood States (POMS) was completed. Subjects went to bed at 2300 and remained in bed until 0700 hr

while a NPSG was collected. They completed a post sleep questionnaire at 0730 hr. Data were submitted to two factor (days and treatments) repeated measures ANOVAs with SNK post hoc comparisons.

Results: BrEC 5 min before bedtime did not differ between the EP and EC conditions and averaged .04+02% and .05+02% (EP) and .05+02% and .04+01% (EC) on nights 1 and 2, respectively. Tabled below are the sleep data presented as two-day means (sd) for the 3 treatments; there were no significant days effects or days interactions. The ethanol affected sleep and caffeine did not alter that effect as seen on the first 4 hrs of the NPSG with % REM sleep reduced similarly relative to placebo in both ethanol treatments. On the 8 hr NPSG min of wake plus stage 1 sleep was reduced by ethanol and the ethanol-caffeine combination reversed the effect disturbing sleep beyond the placebo level. On the am post sleep questionnaires ethanol increased estimated total sleep relative to placebo and the ethanol-caffeine combination reversed that effect without further disturbing sleep beyond placebo levels. Latency to persistent sleep on the NPSG was increased with the ethanol-caffeine combination relative to both placebo and ethanol. Self-rated sleep latency showed the same pattern of effects. Sleep staging was not altered over the 8 hr NPSG. While significant pre-post treatment ethanol effects were not detected on the POMS, the ethanol-caffeine combination increased POMS concentration.

Table 1

	PP	EP	EC
%REM (4hrs)	18.9 (3.6)	13.8 (1.0)	13.6 (7.1)
Min wake + 1	132.5 (64.4)	107.5 (35.8)	168.3 (56.8)
Sub TST (hrs)	5.89 (1.9)	8.62 (0.6)	6.05 (1.3)
Lat PS	26.8 (20.2)	23.8 (16.0)	57.0 (41.8)
Sub Lat (min)	33.6 (16.4)	30.4 (13.2)	55.3 (31.3)

Conclusions: Low dose ethanol improved the sleep of insomniacs, decreasing the amount of wake and light sleep and the addition of caffeine reversed those effects. The following morning insomniacs rated their sleep time as increased and detected the caffeine reversal of the ethanol effect. These data partially support the hypothesis that ethanol's hypnotic effects explain the general population reports of pre-sleep use of ethanol by insomniacs and laboratory studies showing preference for pre-sleep ethanol in insomniacs.

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1311.K3

Insomnia is Not a Mortality Risk Factor: Maybe It's Good for Your Patients!

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Introduction: In the Cancer Prevention Study I, it was found that reported usual sleep 8 hours or <7.0 hours was a highly significant mortality predictor (Kripke et al., 1979). Although this study has been inaccurately characterized as showing that insomnia was associated with increased mortality, that is hardly what was reported. For example, after controlling for age, reported hours of sleep, and reported sleeping pill use, among women, insomnia "often" predicted no significant increase in mortality. The American Cancer Society revisited this issue in a later study.

Methods: Over 1.1 million participants in the Cancer Prevention Study II who answered sleep questions in 1982 were followed up in 1988 (Kripke et al., 1998). Using SAS, Cox proportional hazards models were computed for each gender, controlling simultaneously for 31 covariates including frequency of insomnia, sleeping pill use, reported hours of sleep, age, education, body mass index, diet, exercise, cigarette use, current illness, and comorbidities such as heart disease, hypertension, diabetes, stroke, and cancer. Responses to the question, "On the average, how many times a month do you have insomnia," were compared as separate categories of 1/month, 2/month, 3/month, 4-9/month, and >9/month versus the reference response of "None."

Results: Among 480,841 men, reported insomnia 1, 2,3, 4-9, or >9 times per month was associated with risk ratios of 0.86, 0.89, 0.90, 0.94, and 0.89. All of these risk ratios were significantly less than 1.0 ($p<0.05$). Among 636,095 women, the risk ratios were 0.81, 0.87, 0.82, 0.86, and 0.87, all of which were significantly less than 1.0. As previously reported, those who reported using sleeping pills in the prior month had significantly elevated mortality, especially if they reported usage 30 times per month, whether or not they reported insomnia. However, the risk ratio for sleeping 5.5-7.5 hours was less than that for sleeping >7.5 hours, whether or not participants used sleeping pills or reported insomnia.

Conclusions: Insomnia is NOT associated with excess mortality after control for common comorbidities. The more definite absence of excess insomnia mortality in the second Cancer Prevention Study may be explained by the improved control for comorbidities which was possible with contemporary computer systems. Several much smaller epidemiologic studies have had similar results, so the findings of the two Cancer Prevention Studies have been widely replicated. Many studies which have suggested links of insomnia with reduced survival or disability have failed to control adequately for the many conditions with which insomnia is comorbid. We can reassure patients that there is little risk in insomnia or short sleep, as long as they avoid sleeping pills.

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1310.K3

Late-life Insomnia: Sleep EEG Power Spectra of Chronic Users of Benzodiazepines and Drug-Free Individuals

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Introduction: Pharmacotherapy, especially Benzodiazepines (BZD), is

the most frequent treatment for insomnia in elderly individuals. The effects of chronic BZD use on the sleep EEG remains poorly understood. Recently, Bastien and Morin (1998) reported a higher frequency of micro-arousals in chronic BZD users compared to non-users. Although BZD users perceived their sleep quality as being worse than drug-free insomniacs, there was no other objective differences between the groups. To further document the effects of chronic BZD use on the sleep microstructure, the EEG of elderly insomnia sufferers chronically using BZD, drug-free insomniacs, and good sleepers was quantified by spectral analysis.

Figure 1

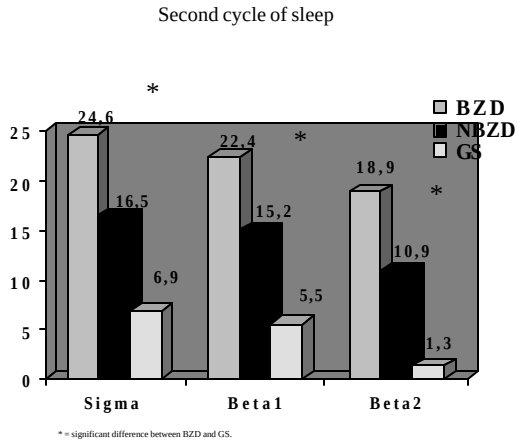
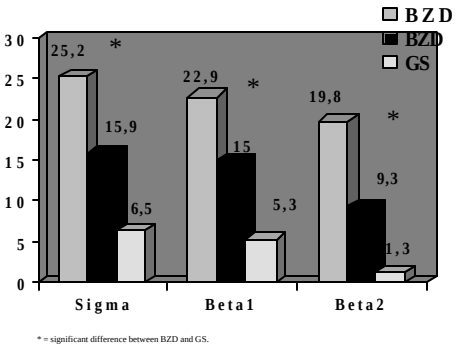


Figure 2



Methods: Participants were 45 older adults [M age: 62.6 (SD = 5.7) years old] divided equally in three groups: insomniacs using BZD chronically (BZD; 8 men, 7 women) or drug-free insomniacs (NBZD; 7 men, 8 women), and self-defined good sleepers (GS; 7 men, 8 women). Medicated patients had used BZD almost nightly for a duration of 14 years [nightly M: 2 mg (lorazepam eq.)]. Participants underwent three consecutive nights of polysomnographic (PSG) recordings digitized at 200 Hz. Sleep was scored according to standard criteria using a 30 seconds resolution. Fast Fourrier Transformations (FFTs) were carried out on the C3 lead. Power spectra were computed for consecutive 2.56 seconds epochs with a 25% overlap and a 0.39 Hz resolution. The record length was set at 33.28 seconds. The spectra were then divided into six frequency bands: delta (0.39-3.90 Hz), theta (3.90-7.02), alpha (7.02-11.70), sigma (11.70-14.04), beta1 (14.04-19.89) and beta2 (19.89-30.03). Two spectra ratios were also computed (alpha+beta)/(theta+delta) and, (theta)/(alpha). The first wake episode, stages 1, 2, 3-4, and REM of the first four NREM-REM cycles of the second night were retained for spectral analysis.

Results: Spectra frequencies were expressed in log power. ANOVAs showed no significant differences among groups for any frequency bands in wake or any sleep stages in the first and fourth NREM-REM cycles. However, significant differences ($p < .01$) were found in the second and third cycles for sigma, beta1 and beta2 in stage 2 (see figures 1 & 2). BZD spectra values were greater than those of GS. Furthermore, ratio1 values were significantly increased in BZD than NBZD and GS in stage 2 of the second cycle ($p < .002$). On the other hand, the values of ratio2 were significantly greater in GS compared to BZD in stage 2 of the second cycle ($p < .01$).

Conclusions: Our results corroborate earlier findings reporting increased activity in the sigma frequency range with prolonged benzodiazepines use. Although the EEG power spectra was not significantly different, between medicated and unmedicated insomniacs, greater activity in fast frequency bands was observed (as expressed by ratio1 values) in BZD users relative to drug-free and good sleepers. In addition, frequencies in the beta range (14.04-30.03) were significantly increased in chronic BZD users when compared to good sleepers. These results suggest that chronic BZD use may alter the sleep EEG towards lighter sleep and decreased sleep quality.

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1520.A

Descending Targets of the Pedunculopontine Region in the Rat

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Introduction: The pedunculopontine region of the dorsolateral mesopontine tegmentum remains an area of considerable interest in elucidation of its role in effecting daytime function and its modulation of behavioral state control. Delineation of the descending targets of this region, however, has been limited by the lack of specificity of the methodology employed or has not addressed the chemo- and cytoarchitectural heterogeneity of this area in their analysis. The current experiments analyzed the pattern of descending projections from this region with specific attention to small tracer placements in the cholinergic pedunculopontine nucleus (PPN) versus the adjacent glutamatergic midbrain extrapyramidal area (MEA), and surround.

Methods: Small stereotaxic injections (< 900 sq. μm) of 10% biotinylated dextran amine (BD; 10 000 MW) were placed in male Sprague Dawley rats (250-350 g) at the location of either the PPN, MEA or surrounding control sites. Tracer was injected using iontophoresis with a positive current of 3-4 μA at a 6.5 seconds on/6.5 seconds off cycle for 10-15 minutes. Following 8-12 days survival the rats were transcardially perfused with normal saline followed by a fixative of 4% paraformaldehyde and 0.05-0.1% glutaraldehyde. Tissue was processed for BD alone (using the ABC method with DAB, Ni-DAB or tungstate-TMB) or in combination with counterstains for Nissl substance, choline-acetyltransferase, or tyrosine hydroxylase.

Results: Injection sites were defined on the basis of cytoarchitecture, chemoarchitecture and the topography and pattern of afferent/efferent connectivity with forebrain nuclei. The pedunculopontine region injec-

tions shared patterns of anterograde labeling which included: 1) bilateral, but predominately ipsilateral, labeling in the nucleus tegmenti pontis of Bechterew responsible for smooth pursuit eye movements; 2) the paramedian pontine reticular formation (PPRF) including dense labeling of the region responsible for saccadic generation; and 3) divisions of the gigantocellular field. Both perisomatic and peridendritic presumptive boutons outlined the somatic profiles of individual large neurons in each of these loci. PPN injections were unique in labeling cardiorespiratory related regions of the ventrolateral medulla (e.g., surrounding the nucleus ambiguus) and dense midline labeling in the raphe magnus. MEA injections were unique in labeling large reticulospinal neurons of the dorsal gigantocellular field of the medulla and dense bilateral labeling of longitudinal cell columns of the inferior olive.

Conclusions: This study demonstrates unique PPN efferents with respect to cardiorespiration and nociception while the MEA has unique efferents with respect to reticulospinal and cerebellar related motor pathways. At the same time this study demonstrates shared efferents of the PPN and MEA with respect to modulation of the physiological hallmarks of rapid eye movement (REM) sleep. Convergence of PPN and MEA efferents upon sites modulating smooth pursuit and saccadic eye movements may account for disease and behavioral state specific eye movement alterations (e.g. in schizophrenia and Parkinson's disease).

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1687.A

Endogenous Adenosine Inhibits The Excitatory Synaptic Transmission In The Laterodorsal Tegmentum

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Introduction: Cholinergic neurons of the laterodorsal tegmentum (LDT) are known to be involved in electroencephalographic arousal and synaptic inputs onto these neurons may contribute to their state-dependent activity. We previously showed that electrical stimulation of the ipsilateral border of the LDT nucleus evokes synaptic responses in LDT neurons in an in vitro preparation. This protocol has proven to be a good model for studying excitatory and inhibitory inputs onto LDT neurons. Using this protocol, we have reported that the excitatory component of the evoked synaptic transmission is glutamatergic and is presynaptically inhibited by exogenous adenosine application through activation of adenosine receptors type A1 (Arrigoni et al. 1999). Moreover, it has been shown that LDT neurons are under tonic inhibitory control by endogenous adenosine in vitro (Rainnie et al. 1994). Here, we extend these studies by investigating the effects of endogenous adenosine on excitatory synaptic transmission in LDT neurons. During these studies two approaches were taken: 1) we antagonized endogenous adenosine effects with the A1 receptor antagonist CPT, and 2) we induced an increase in the extracellular levels of endogenous adenosine by blocking adenosine metabolism. Adenosine metabolism is primarily controlled by adenosine kinase, and inhibitors of this enzyme are known to induce an increase in extracellular adenosine levels (Pak et al. 1994). For our study, we have applied the adenosine kinase inhibitor, 5-iodotubercidin (ITU), and examined its effects on evoked synaptic transmissions.

Methods: Whole-cell patch-clamp records were obtained from rat LDT neurons, in coronal brainstem slices, using an Axopatch-1D preamplifier. Slices, 400µm thick, were prepared from 20-28 day old Long Evans rats and incubated in oxygenated ACSF. Excitatory postsynaptic currents (EPSC) were elicited with a bipolar stimulating electrode placed close to the dorsolateral border of the ipsilateral LDT nucleus.

Results: EPSCs evoked by electrical stimulation of the input to the LDT neurons were potentiated by the A1 receptor antagonist, CPT. Application of CPT (200 nM) induced an increase of the EPSC amplitude of 30 ± 4.71% (n = 7), indicating that, in control ACSF, excitatory synaptic transmission was tonically inhibited by basal levels of extracellular endogenous adenosine. In addition to these results, we have induced an increase in extracellular endogenous adenosine levels by apply the adenosine kinase inhibitor ITU. If ITU, by blocking adenosine metabolism, increases extracellular levels of endogenous adenosine, then its application should evoke the same effects as application of exogenous adenosine. These effects should be abolished by application of adenosine antagonists. Analogous to the action of exogenous adenosine (50 µM), application of ITU (10 µM) induced, at –60 mV, a membrane hyperpolarization and a decrease of input resistance (n = 2). In neurons voltage-clamped to –60 mV, applications of both adenosine and ITU, activated an outward current (n = 9). In 3 neurons insensitive to adenosine, ITU did not induce any effect. The voltage-dependent property, and reversal potential, of the current evoked by ITU (IITU) were compared with the adenosine evoked current (IAD), known to be an inwardly rectifying potassium current (Rainnie et al., 1995). IITU showed: 1) an inward rectification similar to the inwardly rectifying potassium current activated by adenosine; 2) the same reversal potential as IAD (EITU = –82.04 ± 9.7 mV n = 5; EAD = –82.6 ± 3.87 mV n = 5); and 3) sensitivity to the A1 receptor antagonist CPT (200 nM) (n = 5). Moreover, ITU attenuates evoked excitatory transmission in the LDT nucleus whereby ITU application induced a reduction in the EPSC amplitude of 48.81 ± 4.39% (n = 6). The inhibitory effect of ITU on EPSC amplitude was blocked by CPT (n = 4) and partially blocked by the application of the enzyme adenosine deaminase (0.8 IU/ml) (n = 2), which convert adenosine to inosine.

Conclusions: LDT neurons are under inhibitory tone by endogenous adenosine through the activation of A1 receptors. Endogenous adenosine not only inhibits LDT neurons by activation of postsynaptic receptors (Rainnie et al., 1994), but also by activation of presynaptic adenosine receptors on excitatory terminals. In addition, endogenous adenosine inhibition can be modified, it can be increased by applying the adenosine kinase inhibitor ITU to block adenosine metabolism, or it can be removed by application of A1 receptor antagonists.

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1621.A

Hypothalamic Regulation of Hippocampal Theta Activity

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Introduction: Rhythmic sinusoidal waves occurring at 5-9Hz, which are referred to as theta activity, are generated in the hippocampus during certain behaviors in wakefulness, paradoxical sleep, or an intermediate stage occurring prior to paradoxical sleep. Theta burst neurons in the medial septum are critically important for the expression of the hippocampal theta rhythm (e.g., Gottesmann 1992, Kitchigina 1999, Leung 1998). The brainstem and the hypothalamus may regulate theta activity by influencing theta burst neurons in the medial septum nucleus. Among

the brainstem structures, the reticular formation and raphe nucleus have been shown to be involved in theta regulation. Theta activity occurs during certain behaviors in wakefulness, such as grooming, drinking and running. Therefore, in this study, we used retrograde tracing to identify the neurons of the hypothalamus which have projections to the medial septum and thus may also be involved in theta regulation.

Methods: Cholera toxin B subunit (CTB) was injected into the medial septum of two rats. After five days, the rats were deeply anesthetized and perfused transcardially with 0.9% saline and 4% paraformaldehyde. The brains were removed and processed for immunohistochemistry.

Results: CTB-labeled neurons were detected in the lateral hypothalamus, and many of those neurons were found to be orexin-positive. Numerous CTB-labeled neurons were found in the lateral preoptic area of the hypothalamus, including the ventral lateral preoptic (VLPO) area. Densely labelled fibers as well as CTB-labeled neurons were seen in the diagonal band of Broca. Absolute majority of the CTB-labeled neurons was found on the ipsilateral side to the injection site.

Conclusions: It has been previously shown that the VLPO contains sleep-active neurons. Because VLPO neurons project to the medial septum, they may inhibit its activity, which would explain why theta rhythm is never seen during slow wave sleep. On the contrary, orexin-containing neurons, which are mostly wake-active, could probably induce hippocampal theta by activating neurons of the medial septum.

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1232.A

Gene Expression Profiling of the Response to Sleep Deprivation in Mouse Brain Using cDNA Arrays and Real-Time PCR

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Introduction: The two-process model of sleep regulation predicts that a molecular basis exists for the homeostatic regulation of sleep and that some molecules are expressed during the waking state that relate to sleep propensity. Since the slow wave activity measured in the EEG during slow wave sleep is generally accepted as being due to thalamocortical activity, we focussed our initial efforts on gene expression in the cerebral cortex. cDNA arrays were used for initial candidate gene screening. Conventional PCR and TaqMan analysis were used to confirm candidates obtained from the arrays and to evaluate the expression of these genes in other brain regions.

Methods: C57BL/6 mice were implanted with electrodes for EEG and EMG for sleep analysis. Experimental and control mice were sacrificed at ZT6, after a 6h sleep deprivation (SD) period, and at ZT10, after a 4h period of recovery sleep following 6h SD. Brains were dissected into 7 regions and total RNA was isolated from individual tissues. Aliquots were DNase treated and used for first strand cDNA synthesis to be analyzed by RT-PCR and TaqMan. Additional aliquots were pooled from at least 10 individuals from each group for poly A+ RNA purification. [32P]-labelled cDNA probes were synthesized from the pooled polyA+ RNA samples, hybridized to replicate mouse Atlas cDNA Expression Arrays and analyzed by AtlasImage 1.01 software. The candidates identified were verified by RT-PCR and/or Northern analyses; the genes that were confirmed by these methods were assayed by TaqMan.

Results: From an initial screen of 728 genes using the Mouse General and Stress/Toxicology arrays, 17 genes were determined to be differentially expressed during 6h SD in cerebral cortex. Subsequent confirmation by RT-PCR and TaqMan analyses revealed that 6 of 17 candidates were upregulated by 6h SD: c-fos, FosB, Egr1, nur/77, junB, ERp72. Of these genes, c-fos, Egr-1 and Nur77 have previously been shown to increase expression during SD by other investigators. We also used a candidate gene approach and found that Arc, GRp78, and c-jun were also upregulated in cortex in response to 6h SD. (Verification of changes in the expression of the candidates during recovery sleep is ongoing). These 9 genes were further analyzed by TaqMan in the other 6 brain areas with variable responses. As assessed by changes in the expression of this panel of 9 genes, the cortex and basal forebrain appear to be the most SD-responsive brain regions and hypothalamus is the least responsive.

Conclusions: These results indicate that the expression of a subset of genes in the cerebral cortex change in response to SD. Of the 728 genes analyzed to date, the SD-responsive genes fall into two classes: immediate early genes (c-fos, FosB, junB, c-jun, Egr1, Nur77, and Arc) and glucose-regulated proteins (ERp72 and GRp78). About half of the candidates emerging from the arrays were verified by RT-PCR and/or Northern analysis; of this subset, all were confirmed by TaqMan. The combination of cDNA arrays and TaqMan analyses will be a powerful method for identifying genes involved in sleep homeostasis.

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1393.A

Expression of Fos/Jun Family Members in Response to Sleep Deprivation in Mouse Brain

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Introduction: c-fos mRNA and Fos protein expression has been used as a functional marker in sleep research. This "immediate early gene" (IEG) is of interest because c-fos encodes the transcription factor Fos which, when induced by exogenous stimuli, dimerizes with members of the Fos/Jun family to form AP-1 which then binds the promoter region of "target" genes. Several laboratories have found lower levels of Fos in the cortex during sleep relative to wakefulness; Fos expression also reportedly increases in the VLPO in association with sleep. To affect transcriptional activity, Fos must dimerize and is more likely to form heterodimers with members of the Jun family than to form Fos/Fos homodimers. Since little information exists about the expression of other members of the Fos/Jun family in relation to sleep, we analyzed the expression family members in response to sleep deprivation (SD).

Methods: C57BL/6 mice were implanted with electrodes for EEG and EMG for sleep analysis. Experimental and control mice were sacrificed at ZT6 after a 6h sleep period of SD, and at ZT10, after a 4h period of recovery sleep following 6h SD. Brains were dissected into seven regions. mRNA levels were quantified using a real-time fluorescence detection method. After RNA isolation, genomic DNA contamination was removed by treatment with RNase-free DNase I in the presence of

anti-RNase and first-strand cDNA was prepared from each sample. A "target" cDNA (cFos, FosB, junB, c-jun, junD and, for comparison, the IEGs zif/268, nur/77 and ARC) and a reference cDNA (glyceraldehyde-3-phosphate dehydrogenase, G3PDH) were PCR-amplified simultaneously using an oligonucleotide probe with a 5'fluorescent reporter dye (6FAM for the target genes and VIC for G3PDH) and a 3' quencher dye (TAMRA). Target cDNA and G3PDH amounts were determined by fluorescence, normalized and the resultant ratios subjected to MANOVA and post-hoc tests.

Results: The expression of c-fos was significantly elevated during SD in all brain regions examined except hypothalamus; cerebellum was the most responsive brain region (>7-fold increase). FosB was elevated during SD in all brain regions examined; in contrast to c-fos, the hypothalamus underwent a significant 3-fold elevation during SD. Changes in the expression of members of the Jun family were more restricted: JunB mRNA levels were significantly increased in response to SD only in the cortex and pons; c-jun expression was elevated in the cortex and basal forebrain; and junD expression was invariant. Expression of nur/77 was similar to c-fos; zif/268 and ARC were similar to c-jun, although mRNA levels were consistently greater.

Conclusions: These results indicate that the expression of Fos/Jun family members is diverse during SD and raises questions about the significance of Fos expression in brain regions in which no corresponding dimerization partner is induced. The present study is limited to examination of mRNA levels at one time point and a more complete picture would be obtained by measurement of the corresponding proteins. The similarity of FosB and nur/77 (NGFI-B) to c-fos expression suggests that these genes might also be useful functional markers.

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1040.H

Interleukin-1 Enhances NREM Sleep in Adult, but not in Old (25-27 Months) Fisher Rats

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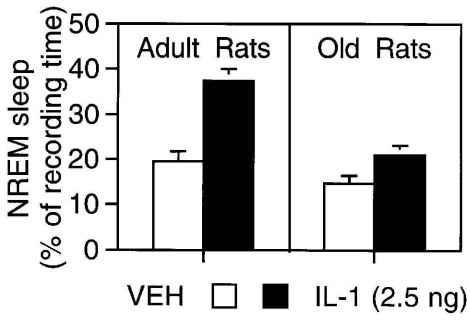
Introduction: Interleukin-1 (IL-1) enhances non-rapid eye movement (NREM) sleep in adult animals of several species.[1] Sleep response to IL-1 in old animals is unknown. Since the response to an immune challenge is affected by aging, the aim of this work was to investigate sleep and febrile responses induced by IL-1 in young/adult and old rats.

Methods: Seven freely moving adult (three/four months) and six old (25-27 months) Fisher (F344) rats were chronically implanted with electrodes for standard polygraphic recordings of sleep-wake activity (EEG, neck EMG), a thermistor for the measurement of brain cortical temperature (Tcort) and a polyethylene cannula for intracerebroventricular administration of phosphate buffered solution (PBS - control) and IL-1 (2.5 ng) dissolved in PBS (1 µl) and given 15 min prior to dark onset. Animals were individually housed in sound proof and temperature controlled (21 ± 1°C) cages, maintained on 12:12 h light:dark cycle, with ad libitum access to food and water. Recordings began at dark onset and continued for 20 h. Polygraphic signals were digitized and computer stored until visual scoring and calculation of EEG power density values by means of fast Fourier transform.

Results: In control conditions, time spent in the different phases of the the sleep-wake cycle, as well as Tcort values were not significantly different in adult and old animals, during both dark and light periods. In adult rats, in comparison to control conditions, IL-1 i) induced fever (maximal increase: 1.1 ± 0.2 °C during the third post-injection hour), ii) significantly enhanced NREM sleep (see Figure, left panel) and EEG power density values in the delta range (0.5 – 4.0 Hz) during NREM sleep, iii) inhibited REM sleep. In old rats, febrile response to IL-1 was maintained (maximal increase: 1.4 ± 0.1 °C during the third post-injection hour), but in the first six post-injection hours neither NREM sleep (see Figure, right panel) nor EEG power density values in the delta range during NREM sleep were enhanced. REM sleep was inhibited.

Figure 1



Conclusions: The results of this study for the first time show that sleep response to an immune challenge is affected by aging. Since it has been proposed that a prolonged pattern of increased NREM sleep is associated with a more favorable clinical prognosis after microbial challenge and it has been shown that animals responding to immune challenge with a robust enhancement of the amount of NREM sleep and of the amplitudes of EEG delta waves during NREM sleep have a greater probability of surviving than animals not showing these responses[2], the results of this study, by showing that old animals do not responde with NREM sleep increase to immune challenge, might explain the increased difficulty observed in aged organisms to combat infections and support the hypothesis that NREM sleep promotes recuperation.[2] The results of this study also confirm that sleep and temperature regulatory mechanisms, although closely linked, can be dissociated.

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1612.H

Caffeine Decreases Sleep in Middle-Aged and Old Rats but not Young Rats

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Introduction: A significant decline in sleep occurs with age. We have shown that this decline is not due to a loss of sleep-active cells (Shiromani et al. 2000). Another possibility is that a decline in the sensitivity or number of receptors might contribute to the sleep loss with age. The present study focused on the adenosinergic receptors, because

of the role of adenosine in sleep regulation. Caffeine, an adenosine receptor antagonist, is widely consumed as a wake-promoting alerting agent, and it was used to determine whether the sensitivity of adenosine receptors could change as the animals get older.

Methods: Young (2 mos), middle aged (10 mos), and old (21 mos) F344 rats were implanted under deep anesthesia with electrodes to record sleep. Ten days later, two 24h sleep recordings were obtained. Subsequently, the rats received saline, 10 mg/Kg or 20 mg/Kg of caffeine (I.P.) in a randomized fashion (Square-Latin design), 30 minutes before the start of the dark active phase (19:00 hrs). Investigators blind to the age and drug treatment of the rats analyzed the sleep recordings.

Results: When compared to saline treatment, both doses of caffeine significantly reduced sleep in old and middle aged rats ($p<0.01$). No changes in sleep were observed in young rats (Table 1).

Table 1. SLEEP VARIABLES IN THREE GROUPs OF RATS (12 hours nighttime values)

	Saline	10 mg/kg	20 mg/Kg
Young rats	2.21±1.3	2.8±1.8	1.18±1.1
Middle rats	3.3±2.5	1.21±1.1 *	0.7±0.7 *
Old rats	4.5+3.5	1.38±1.05 *	1.25± *
NREM			
Young rats	17.5±6.01	17.07±3.6	13.4±3.1
Middle rats	27.6±9.1	19.4±9.9 *	11.1±5.5 *
Old rats	28.4±12.08	15.02±6.5 *	15.02±8.2 *

*** P<0.05 Student "t" test for repeated measurements.**

Conclusions: These findings suggest that a change in the sensitivity and/or number of adenosine receptors contribute to the sleep deficits found with aging. Equally interesting is that the change in receptor sensitivity and/or number begins in middle age. This may explain why coffee has a much more disruptive effect on sleep as we get older.

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1490.I

Individual Differences in Sensitivity to Aircraft Noise during Sleep

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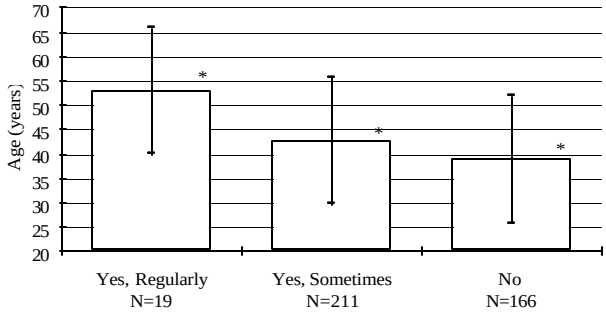
Introduction: Various studies have been carried out to look at the overall relationship between aircraft noise and sleep disturbance,[1,2] and aspects of that relationship, such as noise and annoyance. Some people may be more sensitive to the effects of aircraft noise than others, and may be described as 'noise sensitive'.[1] As field studies give quite different results from laboratory studies,[3] any investigation of noise-sensitive people needs to be undertaken at home rather than in a laboratory. Previous research has not established just how sensitive these more sensitive people are, and to what levels of noise are they sensitive.

Methods: This research was part of a larger study,[1,2] and looked at the effects of aircraft noise on the sleep of 400 participants sleeping at home, under the flight paths of 4 of the UK's largest airports. Sleep was monitored by actigraphy. Noise was measured outside. Daytime sleepiness was measured using the KSS at two hourly intervals. Those participants who claimed to be noise sensitive were identified by self-report, using the questionnaire item "Once you have fallen asleep does aircraft noise disturb your sleep at night ?"

Figure 1. Response to Questionnaire item "Once you have fallen asleep does Aircraft noise disturb your sleep at night?" by age. * = significant difference between means.



Results: Out of the total sample of 400, 19 participants responded "Yes, regularly" (11 Males, 8 Females), 166 "Yes sometimes", 211 "No", and 4 subjects "Don't know" category.There were significant age differences across these groups, with the mean age for the "Yes regularly" group being 52.9y, (SD=12.9y),"Yes sometimes" being 42.7y, (SD=13y), and the "No" being 38.8y,(SD=13.y). 1-way analysis of variance indicated a significant differences between the groups, ($F=12.28$, $df=2,393$ $p=0.000$) and post hoc analysis (Tukey) at the 5% level indicated that there were significant age differences between all the groups. To eliminate the strong age effect, the 19 participants claiming disturbed sleep were matched for age, sex, and geographical site (to eliminate possible effect of differing noise levels or flight schedules) with 19 other participants who claimed their sleep was not disturbed by aircraft noise. Actigraphic data from the two groups were compared for evidence of sleep disturbance. No significant differences were found between the groups in the amount of movement in epochs during which aircraft noise was recorded, or the onsets of movement in aircraft noise epochs.

Conclusions: Participants claiming to be sensitive to aircraft noise showed no evidence of any increase in either movement (sleep disturbance) related to aircraft noise epochs, or in total movement across the night. Research is underway to identify and further investigate 'noise sensitive' subjects using more sophisticated techniques.

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1439.I

Is There a Link Between Daytime Somnolence and Sickness Absenteeism? A Study in a Working Population.

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Introduction: A number of studies have highlighted the increasing incidence and financial cost of sleep-related disorders in the general population, but little research has been done on the impact of severe daytime somnolence as seen from the point of view of a company. The existence

of the GAZEL cohort, a long-term national survey of the health of employees of the French National Gas and Electricity Board, has allowed us to investigate this question and measure the link between daytime somnolence and sickness absenteeism.

Methods: We excluded all subjects taking psychotropic medication and/or working shifts. Each participant received a questionnaire to evaluate the quality of sleep over the previous three months and the incidence of daytime somnolence as measured on a frequency scale ranging from 0 (never or less than once a month) to 5 (almost every day or every day). These data were stored and subsequently compared with company registers of sickness absenteeism for the following twelve months.

Results: 6.7% of our 1105 subjects reported severe daytime somnolence 3 or more days a week. Mean age of participants was 51±3 years and 63% were male. A strong association was observed between daytime somnolence and absence for ill health, which remained very significant even after adjustment for potential confounding variables (age, sex, number of sicknesses and grade of employment). The odds-ratio for sickness leave during the follow-up period associated with daytime somnolence on 3 or more days a week was 2.4 (95% CI : 1.4 – 4.0).

Conclusions: Somnolence is becoming a problem which physicians and employers need to recognise. Employees suffering from severe daytime somnolence lose more working days than their more alert colleagues. This may have long-term implications for the employees themselves and for the productivity of companies.

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1377.I

The Recuperative Value of Brief Versus Long Daytime Naps

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Introduction: Recent evidence indicates that both brief naps (<30 minutes) and long naps (>30 minutes) are effective strategies for improving alertness, mood and performance. While three studies have compared brief naps with longer naps,[1,2,3] no experimental study has compared brief with longer naps following acute nocturnal sleep restriction while precisely controlling nap duration. Accordingly, the present study compares the recuperative value of an EEG determined 10-minute and 30-minute mid-afternoon nap following a night of sleep restriction.

Methods: Twelve (6 male, 6 female) young adult self-reported good sleepers with no history of sleep complaints or daytime napping participated in three napping conditions (no nap, a 10-minute nap and a 30-minute nap) presented in counterbalanced order. On the evening prior to the laboratory sessions subjects slept for five hours between 2400 and 0500 hours. The Stanford Sleepiness Scale (subjective alertness), Profile of Mood States (fatigue and vigour) and cognitive performance tasks (symbol-digit substitution and letter cancellation) were administered three times during each laboratory session; pre-nap, 5 minutes post-nap and 35 minutes post-nap. Objective alertness was assessed by sleep onset latency (SOL) measured both pre nap (the latency to the nap) and one hour after the nap.

Results: The 10-minute nap yielded significant increases in subjective alertness and cognitive performance 5 minutes and 35 minutes after napping. Vigour was also improved 35 minutes after napping. However, immediately following the 30-minute nap there were decreases of subjective alertness, mood, and performance comparable to the no nap condition. This was followed by trends of recovery on all measures with letter cancellation performance showing significanct improvement 35 minutes after the 30-minute nap. One hour after napping, both the 10-minute and 30-minute naps resulted in significantly improved objective and subjective alertness to the same extent.

Conclusions: A 10-minute nap produces an immediate and sustained recovery in alertness, mood, and performance. On the other hand, a 30-minute nap produces an immediate decline in alertness and performance followed by a degree of recovery 35 minutes after awakening. This may indicate a relatively brief detrimental effect of sleep inertia following the 30-minute nap. An hour after awakening from the 30-minute nap, and presumably after the dissipation of sleep inertia, there are improvements of alertness comparable to those from the 10-minute nap. At no point up to an hour following the naps does the benefit from the 30-minute nap exceed those following the 10-minute nap. The findings from this study suggest that a brief 10-minute nap may be a practical solution for ameliorating the adverse effects of nocturnal sleep restriction.

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1847.I

What Are The Chances That a Daytime Nap Will Disturb Subsequent Nighttime Sleep?

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Introduction: According to the widely accepted two-process model of sleep regulation, naps can be viewed both as an expression of a circadian, albeit polyphasic, oscillation, and of homeostatic control. With respect to the latter conceptualization, naps have been characterized as a response to residual sleep pressure on one hand, and as a factor in diminished quality of subsequent nighttime sleep, on the other. The implication of napping as a factor in poor nighttime sleep has led advocates of sleep hygiene to recommend against napping as a means of enhancing 24-hour sleep amounts. Yet, there is little objective evidence to support the popular notion that naps have a negative impact on the subsequent major sleep episode. In this study, we examined the effects of spontaneous naps on nighttime sleep quality.

Methods: Nine adult subjects were studied. Two successive nights of ad libitum sleep, were immediately followed by 72 consecutive hours in the sleep lab; behavioral options to sleep were limited and subjects were instructed to sleep whenever they felt inclined to do so. EEG activity was continuously recorded and scored off-line according to standard criteria. The subjects had a "nap day" (N) (>30 minutes of sleep) during one daytime period (0900 – 1800) and a "wake day" (W) (<30 minutes of sleep between 0900-1800) during another daytime period. The nighttime sleep episodes (> 4 hrs, starting between 2000 and 0300) immediately following these daytime periods were used for analysis. Nocturnal sleep was analyzed for duration, efficiency, and the proportions of both REM and slow wave sleep (SWS). Paired t-tests were performed to compare sleep measures across these post-nap day and post-wake day nighttime sleep episodes.

Results: Six subjects had N followed by W, while the reverse sequence occurred for the other three subjects. Analysis of nocturnal sleep dura-

tion revealed that sleep preceded by a nap (mean=9.5±2.9h) did not differ significantly from the sleep obtained after a day of wakefulness (mean=8.2±2.2h). Likewise, nighttime sleep efficiency, for all subjects, did not differ significantly based on prior daytime state (post N:80.9±8.3%, post W: 84.6±8.1%). However, analyses of nocturnal sleep composition, based on prior daytime state, showed an age-related difference. Within young (<30 yrs) and middle-aged (30-60 yrs) subjects (n=5), napping had no appreciable effect on the contribution of either REM (post N:21.8±6.9%, post W:23.6±8.6%;n.s.) or SWS (post N:10.2±3.1%, post W:12.1±4.2%;n.s.) in the subsequent sleep period. However, amongst older subjects (>60 yrs, n=4) nighttime REM differed, such that, significantly lower levels were detected following a nap (post N:13.9±2.0%, post W:22.6±3.2%;$p<0.05$). These differences were not found in SWS measures.

Conclusions: These results indicate that naps do not occur at the expense of nighttime sleep. Sleep duration, sleep efficiency and SWS levels were similar in nighttime sleep periods following a daytime nap and sleep periods following a day without napping. At the same time, older subject's sleep composition appears to be influenced by prior daytime state; reduced levels of REM sleep are observed in nighttime sleep episodes preceded by daytime naps. Analyses are underway to look at the effects of nap composition and circadian placement on nocturnal sleep measures.

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1172.I

Do the Benefits of Brief Naps Suggest a Fourth Biological Process Determining Sleepiness?

Lack LC, Tietzel A

Introduction: The current model of biological determination of sleep propensity includes three processes.[1] Circadian "Process C" sleep propensity is inversely related to the core body temperature rhythm. Homeostatic "Process S" sleep propensity increases with continuous wakefulness and its reversal during sleep is dependent on delta wave activity (DWA). Sleep inertia, "Process W", is a temporary increase followed by rapid decay of sleep propensity immediately upon awakening from a substantial period of sleep. We suggest from recent studies of brief naps that a fourth process, sleep onset, may need to be added to complete the biological determination of sleep propensity. Considerable anecdotal evidence suggests that a brief (10-20min) "power" nap can noticeably reduce drowsiness as much as can longer sleeps. Only recently has objective experimental evidence confirmed the anecdotal impressions by comparing brief (15min) with longer (45min) naps.[2] Process S would predict that a nap of 45min should be three or more times as effective as a 15min nap depending on how much more DWA is in the 45min nap. Allowing for the dissipation of the sleep inertia, Process S would predict considerably more benefit following the longer nap.
Methods: Our own study has extended this research by comparing naps of 10min and 30min with a no nap condition on a number of objective and subjective measures of daytime alertness.(See Tietzel and Lack, this volume, for details.)

Results: When tested an hour following both nap lengths, sleep latencies were increased equally. In general, performance measures and subjective alertness showed immediate improvement after the 10min nap which was maintained 35min later. However, the 30min nap showed no immediate improvement in any measure. Thirty-five minutes later, allowing for the dissipation of sleep inertia, the benefits of the 30min nap were only comparable to the 10min nap. Therefore, our objective results confirm that the brief nap is more effective than a longer nap in the short term and at least equally effective 35min later despite considerably more DWA in the 30min nap (7.4 times more).

Conclusions: These results are not predicted by Process S. One explanation would be that alertness can be increased a constant amount simply through the process of sleep onset. How brief the period of sleep can be and still satisfy this process needs investigation. It appears that the benefit of increased alertness continues for at least an hour following the nap, but the precise time course has yet to be explored. The main point is that new evidence from napping studies suggests that the three-process model of sleep propensity is not totally adequate. A fourth process, sleep onset (or Process O) appears necessary to explain the significant improvement of alertness following very brief naps.

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1620.I

Effect of Knowledge of Bedtime on Sleep Onset and Body Temperature

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Introduction: A close causal relationship between the decline in nocturnal core body temperature, increase in peripheral body temperature, and sleep onset has been previously reported.[e.g.,1,2,3] The exact trigger for these thermoregulatory changes around the time of sleep onset, however, is not known. We hypothesize that pre-sleep or 'nesting' behaviors, in particular cognitive processes, may influence physiological process associated with sleep onset. The aim of the present study was to examine one possible component (i.e., prior knowledge of bedtime) on subsequent changes in body temperatures and sleep onset latency.

Methods: Seventeen young, healthy male subjects (mean age ± sem: 21.9 ± 0.6 yrs), participated in a randomized, single-blind crossover study, where knowledge of bedtime was manipulated. Following a baseline night, subjects completed three experimental nights, where they were: (A) aware of their bedtime; (B) had no knowledge of their bedtime; (C) or were misinformed about their bedtime. However, in all conditions the lights were turned off at subjects' individual habitual bedtime (determined from sleep diaries), to standardize the circadian time of lights off for each subject. On each experimental night from 1900h, until waking the following morning, subjects maintained a supine position, with polysomnography, rectal and peripheral (foot) temperatures recorded continuously.

Results: There was no significant difference in sleep onset latencies between the three conditions (mean ± sd: 1155h ± 0.73 mins). There was a trend over the pre-sleep onset period for elevated core body temperatures in conditions B and C relative to condition A, and also a significantly greater rate of decline in core body temperature in condition C compared to condition A ($F(1,13)=4.8$, $p<0.05$). Consequently, in all three conditions sleep onset occurred at the same core body temperature. In comparison, however, at the time of sleep onset there was a significant difference in peripheral temperature between the three conditions ($F(2,20)=5.5$, $p<0.01$). Specifically, condition A had significantly higher

peripheral temperature than conditions B and C ($p<0.05$). Further, there was a significantly greater rate of change in peripheral temperature from 120 mins to 10 mins prior to sleep onset in conditions B and C compared to condition A. This process of enhanced peripheral heat loss may underlie the increased rate of decline in core temperature observed in condition C.

Conclusions: The present findings suggest that knowledge of bedtime may modulate changes in temperature around the time of sleep onset. It appears that there is an optimal core body temperature at which to initiate sleep, and changes in the rate of peripheral heat loss may assist in achieving this optimal temperature, and hence facilitate sleep onset. Consequently, it is possible that cognitive and/ or behavioral ('nesting') processes may play an important role in the physiological preparation for sleep. These findings also raise the possibility that sleep incompatible conditions, such as those reported by sleep-onset insomniacs, may affect the physiological mechanisms that promote sleep onset.

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1308.K1

The Prevelance of Obstructive Sleep Apnea in Women with Polycystic Ovary Syndrome and Increased Testosterone versus Matched Controls

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Introduction: Obstructive sleep apnea (OSA) is substantially more common in men than in women, for unclear reasons. Preliminary data also suggest that androgens can precipitate or worsen sleep apnea in both men and women.[1] We therefore compared the prevalence of sleep apnea in a group of women with Polycystic Ovary Syndrome (PCOS, a disorder which is characterized by central obesity and overproduction of ovarian androgens) with that in a group of age and weight matched control women.

Methods: Women with untreated PCOS were recruited from the Division of Women's Health and age/weight matched controls were recruited by means of advertisement (all had regular menstrual cycles and no clinical signs of androgen excess). All subjects underwent standard polysomnography (+ nasal pressure measurement) in addition to measurement of serum androgens. To date, we have studied 18 women with PCOS and 8 controls.

Results: As can be seen in Figure 1, the AHI was significantly greater in women with PCOS than in controls (23.2 vs. 6.1 events/hr, $p < 0.05$) and this difference was more pronounced during REM sleep. Using an AHI cutoff of > 15 events per hour of sleep to define OSA, the prevalence of sleep apnea was higher in women with PCOS than in the control group (44 vs. 0 %, $p = 0.03$, Fisher Exact Test). In addition, the serum level of free testosterone correlated significantly with the measured Apnea Hypopnea Index ($r = 0.56$, $p = 0.006$). The groups were not different in terms of age (31.4 vs. 33.3) or body mass index (35.6 vs. 36.7 kg/m2).

Figure 1: AHI in PCOS Vs. Controls

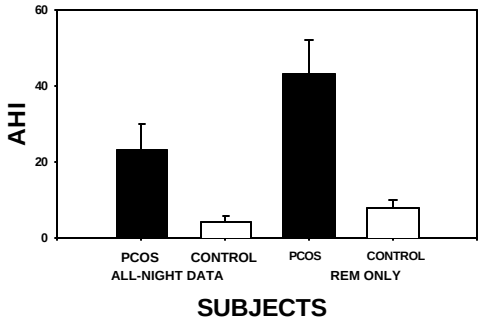
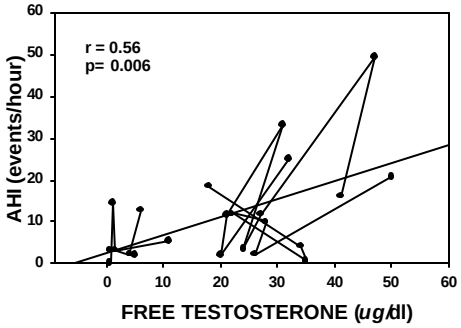


FIGURE 2: TESTOSTERONE VS. AHI



Conclusions: Obese women with polycystic ovary syndrome have an increased prevalence of obstructive sleep apnea when compared to age/weight matched controls. We hypothesize that the elevated androgen levels in these women lead to structural and/or functional changes in the pharyngeal airway that renders it more collapsible during sleep. Whether treatment of PCOS would improve the sleep-disordered breathing in these women is unclear.

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1229.K1

A Population-Based Longitudinal Epidemiologic Study of the Association of Body Habitus and Sleep-Disordered Breathing

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Introduction: Sleep-disordered breathing (SDB) is prevalent in the general population, and has been associated with multiple harmful sequelae including hypertension, cardiovascular disease, and automobile acci-

dents. Obesity is a relatively strong correlate of SDB in cross-sectional epidemiology studies, and surgical or dietary weight loss has been found to reduce measures of SDB in morbidly obese patients. However, there is scant prospective data relating changes in weight or other body habitus measures to progression or incidence of SDB in population-based samples. This report from the Wisconsin Sleep Cohort Study is the first large population-based examination of the longitudinal relationships between change in body habitus and incidence and progression of SDB.

Methods: Baseline and four-year follow-up polysomnography, body habitus and health history data from 827 participants from the Sleep Cohort were analyzed. Changes in body habitus variables including weight, body mass index (BMI), skinfold thickness, and neck, waist and hip girth, were used to predict changes in SDB. In particular, multiple linear regression was used to estimate the association of change in body habitus and percent change in the apnea-hypopnea index (AHI, apnea plus hypopnea events per hour of sleep), controlling for possible confounding variables such as change in alcohol or cigarette use. In addition, changes in body habitus variables were used to estimate odds ratios for occurrence of moderate or worse SDB (AHI>15 events per hour) in conditional logistic regression models, also controlling for potential confounding variables.

Results: Of the body habitus measures examined, change in BMI was found to be the best predictor of change in AHI. Each 1 kg/m^2 increase in BMI predicted an approximate 9% (95% confidence interval: 7% to 12%) increase in the AHI. Likewise, a 1 kg/m^2 decrease in BMI predicted a 9% decrease in the AHI. Weight gain was associated with increased odds of developing moderate or worse SDB and weight loss with increased odds of reversing SDB: the odds ratio for a 1 kg/m^2 change in BMI was 1.8 (95% confidence interval: 1.3 to 2.5).

Conclusions: Weight increase is a predictor of progression and incidence of SDB. Conversely, weight loss was associated with regression and remission of SDB. Because obesity is a growing world-wide health problem and its association with SDB is likely to be causal, it follows that SDB will continue to grow in prominence. Clinical and public health strategies utilizing weight control are attractive approaches to the management of SDB.

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1101.K1

Sleep-Disordered Breathing and Neuropsychological Functioning: A Study in Non-Patient Adults Age 45-75

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Introduction: The Sleep Heart Health Study (SHHS)[1] investigates sleep-disordered breathing (SDB) as a risk factor for the development of cardiovascular diseases. The Cognitive Substudy examines the effects of SDB on neuropsychological functioning. In previous studies, a broad range of cognitive deficits (e.g., vigilance, memory, psychomotor efficiency, executive functions) have been found in patients with severe SDB but results have been mixed in untreated individuals with SDB.[2,3] We hypothesize that persons with mild-to-moderate SDB, compared to those with little or no SDB, exhibit poorer psychomotor efficiency, executive function (e.g., mental flexibility, inhibition, set shifting) and working memory, and report more depression.

Methods: The Cognitive Substudy was conducted at the Tucson and New York sites of SHHS. This report includes results from 104 (60 men and 44 women) of an expected 150 participants. They all had an in-home polysomnogram 1 to 2½ years prior to neuropsychological assessment, reported no current alcohol abuse, were in good health and between the ages of 45 and 75. The controls (CTL) had RDIs of \leg 5. The index cases (IDX) (31 men and 22 women) had RDIs between 20 and 50, inclusive, and had not had any treatment for SDB. Attempts were made to match CTL and IDX by age (± 5 years) and sex. The protocol consisted of standardized administration of a 2½-3 hour battery of neuropsychological measures and self-report questionnaires, some of which are reported here.

Results: Selected measures, group mean ± standard deviation (SD), reported in the table below include the Wechsler Adult Intelligence Test (WAIS-III) Index Scores for Working Memory Index (WMI) and Processing Speed Index (PSI), Stroop Color-Word Test, Trail Making Test part A (TrA) and B (TrB), Grooved Pegboard of dominate hand (PgD) and non-dominate hand (PgND) and the Center for Epidemiologic Study-Depression Scale (CES-D). WMI and PSI are standardized scores (X ± SD = 100 ± 15) derived from WAIS-III Subtests; they are measures of working memory, and information processing and psychomotor speed, respectively. Stroop score is presented in standardized score (X ± SD = 50 ± 10) for Color-Word trial, which is a measure of ability to inhibit dominate response. Psychomotor efficiency was assessed by PSI score, Trail Making Test and Grooved Pegboard. Executive function was assessed by Stroop and Trails B.

Table 1. Two-tailed between-group t-test: * = p < .01 ¥ = p < .20 ‘ in years ° time to completion in seconds

	* RDI	Age	ɔEdu	CES-D	* Stroop
IDX	33.4	60.0	14.8	7.7	48.0
n=53	(7.3)	(9.0)	(2.6)	(5.9)	(7.9)
CTL	2.7	58.2	15.0	7.7	53.0
n=51	(1.4)	(9.4)	(2.7)	(8.0)	(7.4)

	∞ WMI	∞ PSI	°TrA	∞ °TrB	°PgD	∞ °PgND
IDX	107	107	30.5	80.4	79.5	91.3
	(12)	(13)	(9.4)	(34.4)	(13.6)	(20.3)
CTL	111	110	29.5	71.7	79.8	85.1
	(14)	(11)	(11.4)	(27.5)	(17.2)	(18.8)

Conclusions: As intended, CTL and IDX did not differ on any of the measured demographic variables. IDX and CTL also did not differ on self-reported depression; both groups scored within normal range. The largest group differences were on measures of executive function (i.e., Stroop Color-Word (p = .0014) and Trails B (p = .1571)). In contrast, differences for measures of psychomotor efficiency and attention/working memory were smaller or less consistent. Results suggest that although there are some measurable differences in neuropsychological functioning in individuals with mild-to-moderate SDB, when compared to control subjects with little or no SDB, these differences are smaller than those reported in clinical studies.

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1824.K1

Correlations Between Polysomnography Parameters and Quality of Life Measures in Sleep Apneics

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Introduction: Polysomnography (PSG) is the gold standard for assessing severity of obstructive sleep apnea (OSA). These physiologic metrics are assumed to estimate symptoms and quality of life (QOL) deficits associated with OSA. We hypothesized that sleepiness, depressive symptoms, and self-reported health status are associated with OSA severity as measured by polysomnography.

Methods: This cross-sectional study involves all patients who underwent full, monitored, in-lab PSG at the UW Sleep Lab between 7/1/98 and 1/31/99 and were diagnosed with OSA (n=95). Only the diagnostic portion of split-night studies was used. Apnea-hypopnea index (AHI), Arousal Index (ArI), and hypoxemic burden measured by percent of sleep time with an oxygen saturation < 90% (T90) were measured. Immediately before the PSG, each patient completed the Epworth Sleepiness Scale (ESS), Short Form 36 mental health domain (SF36MH), and self-reported health status (SRHS). Spearman rho correlation coefficients (r_s) were computed for the associations between PSG and QOL measures (nine comparisons). Group correlation results are reported as mean $|r_s|$ ± standard deviation. We used multivariate logistic regression to model dichotomized SRHS (outcome variable) with each trichotomized PSG parameter (AHI, ArI, and T90), adjusting for gender, age, body mass index, and comorbidity.

Results: Our sample (n=95) consists of middle-aged (mean age 51 years), obese (mean body mass index 36 kg/m2), predominantly male (69 male, 26 female) patients. PSG parameters correlate poorly with QOL measures (mean $|r_s| = 0.10 \pm 0.20$, mean $p = 0.43$). However, ordinal SRHS correlates statistically significantly, albeit weakly, with ArI ($|r_s| = 0.21$, $p = 0.05$) and T90 ($|r_s| = 0.24$, $p < 0.05$). Multivariate logistic modeling reveals that ArI category (Normal, Moderate, Severe) is significantly associated with SRHS category (Poor-Good vs. Very Good-Excellent): OR 0.37, 95%CI (0.17, 0.84). T90 category (Normal, Mild, Severe) is significantly associated with SRHS category: OR 0.32, 95% CI (0.13, 0.78). AHI category (Mild, Moderate, Severe), however, is not significantly associated with SRHS category: OR 1.03, 95% CI (0.45, 2.36).

Conclusions: In our sample, polysomnography correlates poorly with sleepiness and depressive symptoms and weakly with self-reported health status. Even though certain PSG parameters are associated with a subset of QOL measures, in general, one should not assume that physiologically-measured OSA severity is significantly associated with patient-reported symptoms and quality of life. Interestingly, the AHI, which is the most commonly reported parameter of OSA severity and currently defines our clinical categories of OSA, is not associated with sleepiness, depressive symptoms, or self-reported health status. These data suggest that sleep disruption frequency (ArI) and hypoxemic burden (T90) may be more important to quality of life than frequency of obstructive events (AHI) in sleep apneics. Furthermore, physiologic measures alone may assess inadequately the clinically important outcomes of symptoms and quality of life.

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1506.K1

The Association Between Sleep Disordered Breathing and Cardiovascular Abnormalities

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Introduction: It is well established that obesity and age each have a strong independent association with cardiovascular abnormalities. The relationship between sleep disordered breathing (SDB) and cardiovascular abnormalities is, however, complex and not completely understood. This may be partially due to the fact that the effects of age, while controlling for weight, on the association between SDB and cardiovascular abnormalities have not been well studied.

Methods: We examined this question in a large study which was based on a two-stage general randomized sample of men and women. The first phase interviewed 4,364 men and 12,219 women ranging in age from 20-100 years. In the second phase of this study, 741 men and 1,000 women previously interviewed were selected based upon the presence of risk factors (snoring, daytime sleepiness, obesity, hypertension and for women menopause). Each subject selected for laboratory evaluation completed a comprehensive history and physical examination and were evaluated for one night in the sleep laboratory. Our two outcome measures, blood pressure and an electrocardiogram (ECG), were measured in the evening during the physical examination. Blood pressure was the average of three estimates using an automated device following five minutes in the supine position. Hypertension (HTN) was defined as diastolic pressure >90 mmHg or systolic pressure > 140mmHg or currently treated for hypertension. ECG abnormalities were categorized into eight possible types. Three levels of severity of SDB were identified: O/HI≥15 (obstructive sleep apnea +hypopnea index); SNORE+ (snoring + 0<O/HI<15); and SNORE (snoring + O/HI=0).

Results: SDB was observed to have an independent added risk for HTN when age, BMI, menopause and hormone replacement therapy status, race, alcohol and smoking were controlled in the logistic regression analysis. All three levels of severity were significantly associated with HTN: O/HI≥15 [OR=6.8(2.0,26.4),P=0.003]; SNORE + [OR=2.3 (1.4,3.6),P=0.0004] and SNORE [OR=1.5(1.1,2.2),P=0.01]. This association interacted with age and BMI, indicating that the association between SDB and HTN is strongest in the young, especially the normal weight. In men we were able to detect an independent added risk for an abnormal ECG in the presence of O/HI ≥15 [OR=2.0(1.0,3.7), P=.03]. There was no interaction with age or BMI. Two specific types of abnormal ECGs appeared to be independent added risks in the presence of O/HI ≥15; atrial premature complex [OR=5.1(1.3, 19.5), P=0.02] and old infarct [OR=2.5(1.2, 5.4), P=0.02]. In both cases no gender effect was detected.

Conclusions: This study indicates that the presence of SDB, even simple snoring, has an independent association with HTN in both men and women. This relationship is strongest in the young, especially the normal weight, which is consistent with our previous findings.[1] In terms of ECG findings, men and women showed an increased risk for coronary artery disease in the presence of SDB.

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1141.K1

Sleep Apnea and Hypertension: Moderating Effect of Age

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Introduction: Accumulated evidence links Sleep Apnea (SA) and hypertension.[1] Sleep apnea contribution to hypertension has been shown to be independent of potential confounding variables such as BMI, smoking and gender. In view of reports[2,3] that the risks of mortality in SA peaks at 30-50 yrs and decreases afterwards, we examined the association between SA and hypertension as a function of age.

Methods: Two large databases of SA patients, of the Technion Sleep Laboratories in Israel and the St. Michael's Hospital Sleep Laboratory in Toronto, were analyzed. They included 7704 and 2700 patients, respectively, referred for a whole-night polysomnographic evaluation because of suspected SA. Both comprise demographic information, results of polysomnographic monitoring (sleep stages, RDI, nadir of nocturnal oxygen saturation, etc), and medical history. In Haifa, the definition of hypertension solely relied on the reported use of antihypertensive medications. This definition relied on either actual blood pressure measurements or medical history in Toronto. A patient reported using antihypertensive medication or having blood pressure levels higher than 140 mmHg systolic or 70 mmHg diastolic, during either morning or evening measurements, was defined as hypertensive. Blood pressure was measured 3 times in the supine position before and after sleep in the lab. The two populations were comparable with respect to age and gender distributions but not with respect to BMI. In Toronto there were 2-fold more patients with BMI>35. Comparing the two populations with respect to RDI after matching for age and BMI revealed almost identical results. Only data of male patients were analyzed. In Haifa, patients were stratified to 5 age groups (20-39, 40-49, 50-59, 60-69, >70 yrs), and 4 BMI subgroups (<25, 25-29, 30-34, >35). Respiratory disturbance index of matched patients with and without hypertension were compared. In Toronto, SA patients were matched for age and BMI with those not having SA. Morning systolic and diastolic blood presures were compared between matched patients stratified to 4 age groups (<40, 40-50, 50-60, >60 yrs).

Results: Haifa data revealed significant differences for RDI between hypertensive and nonhypertensive patients for 2 age groups: 40-49 yrs for the BMI groups 25-29 ($p<.02$), 30-34 ($p<.009$), and >35 ($p<.04$), and 50-59 yrs, for BMI groups 25-29 ($p<.03$) and 30-34 ($p<.04$). There were no significant differences for patients older than 60 years. In Toronto, 675 patients could be matched within ± 5 years of age and ±2 BMI units. Significant differences in systolic and diastolic blood pressures were found only for age groups 40-50 (120.7 vs 116.4 $p<.004$; 75.2 vs 71.8, $p<.002$) and 50-60 yrs (124.3 vs 119.2, $p<.01$; 75.4 vs. 72.4, $p<.03$).

Conclusions: Analysis of both databases showed that the association between hypertension and sleep apnea may be limited to patients aged 40-60 yrs. These results may have important implications for interpretation of studies employing elderly cohorts for investigating the impact of sleep apnea on the cardiovascular system.

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1169.K1

Increased Diastolic Blood Pressure Associated With Obstructive Sleep Apnea Independently of Overweight

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Introduction: It has been debated whether obstructive sleep apnea causes hypertension or it merely is a marker of obesity and aging. To investigate this we conducted a population-based study of middle-aged adults.

Methods: 10,221 persons above 20 years of age were examined between 1991-1993 in The Copenhagen City Heart Study, a cardiovascular health study initiated in 1976. The examination consisted of a self administered questionnaire on health, disease symptoms, level of physical activity, lifestyle factors, education and household income. Measurements included height, weight, blood pressure, spirometry, ECG, blood glucose, -cholesterol and -triglycerides. In 1998 a questionnaire containing the Epworth Sleepiness Scale (ESS) and questions about snoring and breathing pauses during sleep was sent by mail to all of the 10,221 persons still alive. 9,139 received the questionnaire and 6,987 responded. To estimate the prevalence of OSA among middle-aged a subgroup of the participants aged between 30-69 years at the examination in 1991-93, were selected. The 5% of the study population with the highest score on the ESS scale, and all persons who reported to have habitual breathing pauses during sleep observed by others, were selected as candidates for a home sleep study. 298 persons, out of 4,822 in the selected age group, met these criteria. 210 of those agreed to participate. 166 underwent a home sleep study with EEG, EOG, EMG, and measurements of oronasal airflow, -respiratory movements and pulse oximetry. 44 would only accept a pulse oximetry. 88 refused participation.

Table 1

	AHI>10		AHI>20	
	OR	95% CI	OR	95%CI
Sex	3.0	1.6 - 5.8	2.3	1.1 - 5.0
BMI > 25 kg/m2	5.7	2.4 - 13.7	5.1	1.7 - 14.7
DBP > 95 mmHg	1.9	1.1 - 3.3	3.1	1.5 - 6.2

Results: Of the 210 examined 52 had an apnea-hypopnea index (AHI) above 10. 33 had an AHI above 20. In a logistic regression model (Table 1.) sex, body mass index (BMI), and diastolic blood pressure (DBP) were the only independent predictors of OSA. The following were not independently associated with AHI scores in the model: age, blood glucose, -cholesterol and -triglycerides, FEV1, FVC, tobacco smoking, alcohol consumption, physical activity, level of education, household income, use of hypnotics or tranquillizers, a history of myocardial infarction, ischemic heart disease, stroke, asthma or chronic bronchitis.

Conclusions: This investigation supports data showing a link between OSA and hypertension that is not explained by increased BMI in OSA-

patients. We found no association between age and sleep apnea. This contradicts the view that OSA is a symptom of aging.

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1328.H

Excessive Daytime Sleepiness and Sleep Disordered Breathing in Older Men and Women

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Introduction: Excessive daytime sleepiness (EDS) is a significant contributor to decreased quality of life and is a known risk factor for accidents. Individuals with obstructive sleep apnea also have EDS. Less well known is the relationship between sleep disordered breathing (SDB) and EDS in a nonclinical, community-based population of older men and women (Gottleib et al., 1999). The purpose of this analysis was to examine the relationship between two indices of SDB and EDS in community-dwelling older adults.

Methods: Three hundred eighty five individuals from the Western Collaborative Group Study, a long-term health and aging study, were included in this analysis. Men (n = 256) were of mean age 80.0 ± 3.7 (SD) years and women (n = 129) were of mean age 75.6 ± 5.4 years at the time of examination. As part of the 36-year follow-up of this cohort, all participants completed the Epworth Sleepiness Scale (ESS; Johns, 1991), provided an updated medical history, and wore an Edentrace II sleep monitor for the duration of an in-home sleep period. Participants were monitored for airflow, respiratory effort, body position, heart rate, oxygen desaturation, and snoring. After completion of scoring of the sleep data, apneas (chest or airflow pause of 10 seconds or longer) and hypopneas (decreased airflow of 50% or more for an interval of 10 seconds or longer and a 4% or larger drop in O2) per hour were summed to create an apnea/hypopnea index (AHI). A desaturation index (DI) was also created by determining the number of desaturations less than 90% per hour. EDS was defined by ESS scores ≥ 11. All individuals with a history of stroke were excluded from the analysis.

Results: Compared to women, men had a higher mean ESS score, 9.04 ± 4.77 vs. 7.02 ± 4.36, $t(383) = 4.04$, $p < .0001$, a higher mean AHI, 4.35 ± 4.88 vs. 1.60 ± 2.13, $t(377) = 7.69$, $p < .0001$, and a higher DI, 13.32 ± 13.00 vs. 6.17 ± 6.78, $t(380) = 7.06$, $p < .0001$. The gender difference in mean ESS scores persisted after multivariate adjustment for age, BMI, AHI, $F(1,372) = 7.24$, $p < .01$, and DI, $F(1,368) = 4.30$, $p < .04$. Compared to women, men were 2.81 (95% CI, 1.52, 5.17) to 2.88 (95% CI, 1.57, 5.29) times more likely to report EDS (37.9% vs. 15.5% prevalence) independently of age, BMI, AHI, and DI. In men, the prevalence of EDS increased significantly with increasing severity of AHI (defined using clinical cutpoints of < 5, 5 to 14, ≥ 15), 33.9%, 47.6%, and 50%, respectively, chi-square[1] = 4.07, $p < .05$. A similar increase in EDS prevalence was also observed across AHI values divided into tertiles, 30.2%, 38.8%, and 44.7%, chi-square[1] = 3.84, $p < .05$. These associations remained significant after multivariate adjustment for age and BMI. In women, no corresponding increase in rate of EDS as a function of increasing AHI severity (defined either clinically or by tertile rank) was observed. The prevalence of EDS was also examined as a function of DI values grouped into tertiles. In men, EDS prevalence increased from 31.0%, 37.7%, to 45.9% as a function of increasing tertile, chi-square(1) = 3.98, $p < .05$, whereas in women, EDS prevalence remained similar across tertiles, 14.3%, 16.3%, 16.3%. After adjustment for age and BMI, the increase in EDS prevalence in men across DI tertile became marginally significant, chi-square[1] = 3.30, $p < .07$.

Conclusions: In this sample of older adults men had higher mean levels of SDB and ESS scores than did women. EDS was approximately three times more common in men than in women. Increasing levels of AHI and DI severity defined either clinically or empirically were associated with increasing prevalence of EDS in men but not in women, perhaps because of the comparatively low levels of SDB in women in this sample. The results for men in the present study support similar recent findings in a somewhat younger elderly cohort (Gottleib et al., 1999). The fact that mean ESS and prevalence of EDS remained higher in men than in women even after adjustment for age, BMI, and indices of SDB suggests the contribution of other non-SDB risk factors to the presence of EDS.

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1323.P

Sleep, Waking and Neural Plasticity: New Insights From the Expression of P-CREB, BDNF and Arc Across the Sleep-Waking Cycle and After Sleep Deprivation

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Introduction: It has been suggested that sleep may be important for learning and memory. However, establishing a specific role for sleep in learning and memory requires an understanding of the differences between sleep and waking with respect to the molecular mechanisms of plasticity. It has been pointed out that the expression of plasticity-related genes should be triggered when the animal is acquiring new information about the environment, i.e. during waking.[1] On the other hand, it has been proposed that hypersynchronous firing during sleep may lead to a massive influx of calcium into neural cells, which may in turn induce genes involved in plasticity.[2] Recently, a number of molecular markers have been identified, whose increased expression is involved in the occurrence of long-term memories. Among them P-CREB, BDNF, and Arc are particularly noteworthy. Here we examined whether the expression of these genes 1) changes in relation to sleep and waking, and 2) is dependent on the activity of the noradrenergic system of the locus coeruleus, which is active in waking and promotes synaptic plasticity in relation to salient or novel stimuli. Since behavioral data suggest that learning is impaired in sleep-deprived subjects, we also examined how the expression of P-CREB, BDNF and Arc is modified by long-term sleep deprivation.

Methods: Wistar WKY rats were sacrificed after 2-9 h of sleep (n=9), spontaneous waking (n=7) or sleep deprivation by gentle handling (n=9), or after 5-14 d of long-term total sleep deprivation by the disk-over-water method (n=14). BDNF and Arc mRNA levels were measured with ribonuclease protection assays and in situ hybridization. Protein levels were measured with an ELISA immunoassay (BDNF) and immunocytochemistry (P-CREB and Arc). In a third set of rats (n=8), the noradrenergic innervation to the cerebral cortex was destroyed bilaterally using systemic injections of DSP-4 or unilaterally with local injections of 6-OHDA in the locus coeruleus.

Results: BDNF and Arc mRNA and protein levels were 2-3 fold higher after spontaneous waking and after short periods of sleep deprivation

than after sleep. In awake animals Arc protein was expressed in layers II-VI of most cortical areas and was restricted to glutamatergic neurons (Arc immunostaining did not colocalize with either parvalbumin or GFAP immunostaining). P-CREB positive cells were also more numerous in awake rats than in sleeping rats, and were present in most cortical neurons, both glutamatergic and GABAergic. BDNF and Arc expression in the cerebral cortex was reduced by 50-60% after lesions of the noradrenergic fibers. In long-term sleep deprived rats, P-CREB, BDNF and Arc expression was lower than in their yoked controls and similar to that observed in sleeping animals.

Conclusions: The expression of the molecular markers of plasticity P-CREB, BDNF and Arc is high in waking and low in sleep and is modulated by the noradrenergic system.

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1538.P

Genetic Aspects of Slow-Wave Sleep Homeostasis

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Introduction: EEG delta power (1-4 Hz) in slow-wave sleep (SWS) exhibits a predictive quantitative relationship with the duration of prior wakefulness and sleep in that it increases during wakefulness and decreases during SWS. SWS delta power is therefore thought to reflect a homeostatic process underlying the regulation of SWS propensity. Although substantial progress has been made on the understanding of the neurophysiological mechanisms underlying the generation of slow-waves, little is known about the mechanisms that homeostatically modulate delta power. We have previously reported on the dynamics of SWS delta power in six inbred strains of mice. The amplitude of the changes in delta power in baseline and the positive rebound after 6 h sleep deprivation (SD) varied with genotype and were largest for AKR and smallest for DBA mice. The relationship between delta power and the sleep-wake distribution was quantified with computer simulations. The time constant of the increase of SWS propensity during waking was smaller in AKR than in DBA (3.3±0.2h vs. 7.0±0.4h) whereas the decreases rate during SWS did not differ. This suggests that SWS propensity increases at a faster rate in AKR mice and thus that the homeostatic regulation of SWS is under genetic control. In this study we first seek to confirm the results of the computer simulations by performing a 'dose-response'-experiment in AKR and DBA mice. Subsequently, genomic regions associated with the changes in delta power in baseline were determined in BXD Recombinant-Inbred (RI) mice by means of Quantitative-Trait-Loci (QTL)-analysis.

Methods: For AKR and DBA mice (n=6-7/strain) dose-response curves were constructed for SDs lasting 35, 70, and 140 min and 6 and 9 h, all ending in the last 4h of the 12-h light period. Delta power was calculated over the first 15 min of SWS after the onset of recovery sleep. In 25 BXD RI-strains (n=4-6/strain) and their parental strains (C57BL and DBA; n=7/strain) the amplitude of the changes in delta power in baseline were calculated by expressing the delta power over the first 15 min of SWS in the major rest period relative to the level reached at the end of the rest period. QTLs were determined by correlating the strain distribution pattern of the phenotype with those of the >1700 polymorphic genetic markers.

Results: Even the shortest SDs resulted in significant increases in delta power over its prevailing level in the last 4 h of the baseline rest period. In both AKR and DBA mice delta power increased according to a linear function for SDs <9 h. However, the increase was faster for AKR resulting in significantly larger values after 140 min and 6 h of SD. Compared to the level reached after 6-h SD, after 9-h SD delta power did not further increase for DBA mice whereas for AKR mice it even significantly decreased, thereby reducing the genotype difference observed after 6-h SD. The doubling of the attempts to enter SWS (and thus of SWS amount) in the last 3 h of the 9-h SD might have contributed to the lack of a further increase or even a decrease of delta power compared to the value attained after 6-h SD. The decrease of delta power in the course of recovery followed an exponential function of which the time constant did not differ between strains (AKR: 4.6±1.2 h; DBA: 3.9±1.4 h).QTL-analysis of the amplitude of the changes in SWS delta power during baseline revealed a significant QTL on chr.7 between 19-44 cM with marker D7Ncvs40 having the best correlation (p=0.00004 point-wise, lod-score 3.62; p=0.01 genome-wide). Candidate genes in this region include TPH, NGF, GABA-A Receptor subunits, and the transcription factor DBP. We recently demonstrated that a lack of DBP results in a profound reduction of the amplitude of the changes in delta power.

Conclusions: These results imply that SWS homeostasis is under genetic control which possibly could lead to the identification of its molecular basis. Especially, the rate of increase of SWS propensity strongly varies with genotype. It remains to be established whether differences in the 'quality' of wakefulness (e.g. locomotor activity) contributes to the strain differences in the dynamics of SWS delta power. That locomotor activity might affect the level of delta power was shown in DBP knock-out mice where a reduction in the amplitude of the changes in delta power was paralleled by a reduction in locomotor activity.

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1712.P

Genetic Influences on Methamphetamine-Induced Compensatory Sleep in Mice

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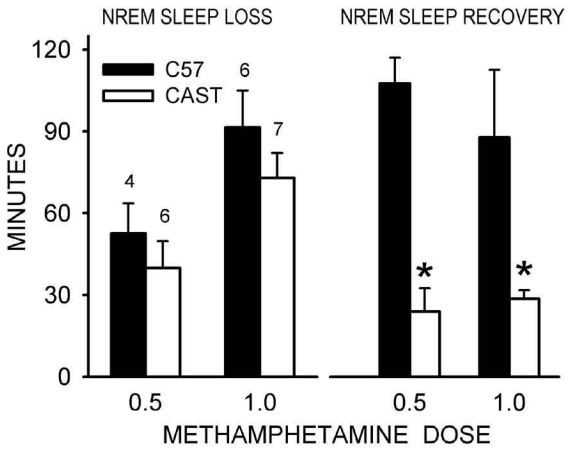
Introduction: Sleep is a homeostatic process that is reflected in the uniform daily sleep times (TST) among genetically identical individuals and in the compensatory sleep response (CSR; increased sleep time and increased electroencephalographic slow wave amplitude) that occurs following sleep deprivation. Treatment of rodents with methamphetamine provides a pharmacological model of sleep loss and the CSR. Here we examined the wake promoting effect of methamphetamine in two genetically diverse strains of mice.

Methods: Male mice of the C57BL/6J and Cast/Ei strains, age 3-8 months were anesthetized with isoflurane and surgically prepared for electroencephalogram (EEG) and electromyogram (EMG) recording. Following recovery, mice were isolated in separate compartments of a sound-attenuated stainless steel recording chamber with ad libitum food and water in an LD12:12 cycle. The chambers allow continuous recording of EEG, EMG, wheel running and drinking data. Digitized EEG (bandpass 1-30 Hz, digitization rate 100 Hz), integrated EMG (bandpass 10-100 Hz) and wheel and drink signal (binary variables) were stored in ten second epochs. Epochs were classified as wake, rapid eye movement sleep (REM), or non-REM sleep (NREM) by a pattern-matching algorithm (SCORE). Pharmacological treatments were delivered intraperi-

toneally five hours into the daily light period (+ 30 minutes). Data were collected for at least 24 h before (baseline day) and after (treatment day) injection. 'NREM sleep loss' and 'NREM sleep recovery' are determined based on the cumulative change in NREM time (treatment day vs. baseline day) on an hour-by-hour basis. 'NREM sleep loss' is the maximal deviation (in minutes) of NREM time during the treatment day from the baseline day. 'NREM sleep recovery' is the magnitude of recovery of NREM time (in minutes) that occurs following methamphetamine-induced NREM loss.

Figure 1. Sleep loss and sleep recovery following methamphetamine treatment in C57BL/6 mice (C57) and Cast/Ei mice (CAST). NREM recovery sleep was significantly less in the Cast/Ei group (p<0.02, Independent measure T test). Numbers associated with bars in the left panel indicate sample sizes.



Results: Methamphetamine produced a significant, dose-dependent loss of NREM sleep time in both strains (Figure 1, left panel). There were no strain differences in NREM sleep loss at either dose of methamphetamine. Following methamphetamine-induced sleep loss, there was a robust increase in NREM sleep time in C57BL/6 mice (Figure 1, right panel). In contrast, Cast/Ei mice exhibited markedly attenuated CSRs to methamphetamine-induced wakefulness. Despite the fact that 0.5 and 1.0 mg/kg of methamphetamine produced statistically similar amounts of wakefulness (plotted as NREM sleep loss) in both strains, compensatory NREM sleep in the Cast/Ei mice was very significantly attenuated.

Conclusions: The CSR that occurs following methamphetamine-induced wake in C57BL/6 mice indicates that methamphetamine treatment is a useful pharmacological model of sleep homeostasis in mice. Furthermore, the absence of CSR following methamphetamine-induced NREM sleep loss in Cast/Ei mice suggests that the CSR is genetically determined. Since Cast/Ei and C57BL/6 mice are genetically diverse, we hypothesize that the dramatic deficit in compensatory sleep in the Cast/Ei strain is a product of discrete genetic differences. This observation raises the possibility that the genetic, and thus physiological, underpinnings of NREM sleep homeostatic regulation, may be determined through breeding and gene mapping studies of the C57BL/6 and Cast/Ei strains.

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1823.P

Development of Sleep-wake Patterns in Two Inbred Rat Strains: A Longitudinal Study

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Introduction: Genetic differences in the characteristics of sleep-wake states in adult animals offer a potential window for examining how the neonatal and adult behavioral states are related to one another. Our recent finding that adult Wistar Kyoto (WKY) rats show pronounced genetic differences in sleep-wake patterns relative to the Wistar (WIS) control strain (Dugovic et al 1999) led us to investigate the relationship between these behavioral states in neonates and adults in a longitudinal study in these two inbred rat strains.

Methods: Spontaneous sleep-wake recordings were obtained from eight WKY and eight WIS rats, all males, at 8 days (3-h recording during the light phase) and at 3 months (24-h recording) of age in the same animals. In pups, the behavioral states of wake, quite sleep (QS) and active sleep (AS) were differentiated by recording EMG activity with temporary fixed muscular electrodes. When adults, the rats were chronically implanted with EEG, EMG and EOG electrodes for standard polygraphic sleep monitoring. Sleep-wake parameters were compared between WIS and WKY rats, as neonates and as adults, using the unpaired two-tailed Student t'test.
Results: Similar pronounced differences in the sleep-wake states were found between WKY and WIS rats in adult and in neonatal animals. Compared to WIS rats, WKY rats showed a marked increase in total AS time (+55%, p<0.0001) at 8 days of age during the 3-h recording session, and later in life at 3 months of age in total REM sleep time (+46%, p<0.0001) during the 12-h light phase. In addition, neonatal as well as adult WKY rats exhibited an increased sleep fragmentation relative to WIS rats, as indexed by a larger number of episodes in each vigilance state associated with a shorter mean duration of episodes.

Conclusions: This is the first longitudinal study (repeated measures in the same animals) on two strains of rats demonstrating that genetic differences in sleep architecture that are observed in adult animals are already present in neonatal rats at 8 days of age. The finding that these differences can be detected even before EEG-defined sleep-wake states can be differentiated, indicates that the neonate can be used to screen for genetic abnormalities in sleep and wake states.

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1456.P

Possible Association of Polymorphisms in the HLA and Monoaminergic Systems in Kleine-Levin Syndrome

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Introduction: Kleine-Levin syndrome (KLS) is characterized by recurrent episodes of hypersomnia associated with binge eating, hypersexual-

ity, and personality changes (irritability, aggression, confusion, and hallucinations). Males are predominantly affected, with an age of onset typically in adolescence. Hypersomnia is often precipitated by an acute febrile episode, alcohol, or severe stress. Although its etiology remains unknown, a neurotransmitter imbalance in the serotonergic pathway[1] and a possible association with the HLA antigens have been suggested.[2,3] However, since the disorder is very rare, only sporadic cases have been so far reported. We have therefore initiated a collaborative project to systematically investigate KLS subjects ascertained together with their families from several European countries.

Methods: To date, twenty-three KLS subjects (21 males and 2 females) entered the study. In 16 cases both parents (and in 7, other family members) were also available while in 5 cases only mothers were available (in 2 with a sibling). Detailed clinical description of these patients will be reported elsewhere. As a first step in this project, two main candidate systems (HLA and serotonergic) were investigated. Thus, the HLA-DQB1, the tryptophan hydroxylase (TpH), and the catechol-O-metyltransferase (COMT) genes were analyzed in all patients and their relatives and results were contrasted with 27 ethnically matched controls for HLA and COMT, and 94 French normal controls for TpH. DQB1 typing was performed by combination of group-specific amplification and restriction fragment length polymorphism. The TpH polymorphism (A to C substitution in intron 7) was resolved by the restriction enzyme BfaI (alleles A and C). TpH is the rate limiting enzyme in the synthesis of serotonin and has been strongly associated with impulsive personality. The COMT functional polymorphism (G to A substitution at codon 158) was resolved by the restriction enzyme NlaIII (alleles L and H). COMT is the key enzyme in the dopaminergic and noradrenergic neurotransmission and has been associated with obsessive-compulsive disorder.

Results: HLA-DQB1: Twelve out of 23 KLS subjects were DQB1*0201 against 7 out of 27 control subjects (51.2 vs. 25.9 %; chi2=2.73, uncorrected p = 0.09). Also, 2 KLS subjects but none of the controls were DQB1*0201 homozygous. In 11 DQB1*0201 heterozygous parents 8 had transmitted the DQB1*0201 (72.7 %), strongly suggesting a preferential transmission of this allele.TpH: There was no significant difference at genotype level between KLS and control subjects. However, the frequency of allele A tended to be increased in the patient group (43.5 % vs. 32.0 %; chi2=2.2, uncorrected p = 0.14). However, in 12 heterozygous parents, allele A and C were transmitted 6 times each, suggesting a homogeneous transmission.COMT: Neither the genotype nor the allele frequencies significantly differed between groups. However, in 16 heterozygous parents, 10 (62.5 %) had transmitted allele L, which is associated with 3-4 fold reduction in COMT enzyme activity (ie. increased dopaminergic transmission).

Conclusions: These preliminary data suggest that DQB1*0201 may confer susceptibility to the development of the KLS. The extended haplotype DRB1*0301, DQA1*0501, DQB1*0201 is associated with many autoimmune disorders (Addison's, Grave's, and Celiac disease and Myasthenia gravis). The age of onset and the infectious origin of KLS are in good agreement with this hypothesis. Also, the TpH showed a trend for positive association while COMT allele L showed a preferential transmission from heterozygous parents to the affected child. Larger samples will be needed for replication/extension of the present results.

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1057.M

The Differential Effect of Nefazodone, Psychotherapy and Combination Treatment on Sleep Disturbance in Chronic Depression

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Introduction: Insomnia is a key feature of depression and there is evidence that residual symptoms, including disturbed sleep, after treatment of depression are associated with higher rates of relapse. The design of the present study afforded the comparison between the effects of three treatment modalities for depression on the resolution of insomnia symptoms.

Methods: The Acute phase of the study was an open trial in which patients were randomized to one of three treatment conditions: Nefazodone alone (226), CBASP therapy (a variant of cognitive behavioral therapy designed for the treatment of chronic depression) alone (228), and their combination (227). Participants were 681 patients (65.3% female) from 12 academic institutions who met DSM-IV criteria for a Major depressive Episode that was either chronic (i.e., criteria for MDD was met continuously for at least 2 years - 35.1%), superimposed on antecedent Dysthymia (42.3%), or recurrent with incomplete interepisode recovery and the total duration was at least two years (22.6%). Mean age was 43 ± 10.7 years. The acute phase of treatment lasted 12 weeks. CBASP consisted of 16 - 20 sessions of manualized psychotherapy provided by certified therapists. Pharmacotherapy consisted of open label Nefazodone, 300-600 mg per day in two divided doses administered in a standardized manner. Measures included HAM-D (24 items) conducted by blind certified raters, the IDS-SR (a self report measure of depressive symptoms), and sleep diaries (7 days). Measures were completed weekly for the first 4 weeks and biweekly thereafter. An insomnia factor consisting of 3 items was extracted separately from the HAM-D and the IDS-SR. Other study measures remain beyond the scope of this abstract. Intent-To-Treat analyses were performed using the last-observation-carried-forward principle. Separate analyses of covariance on change to week 4 and change to end-point were performed. These analyses included baseline scores as covariate and treatment and site as factors. These analyses were performed separately for each of the three sleep measures. Pair-wise comparisons of the three treatment groups were performed using the least-squares means method, with Bonferrroni-corrected alpha level of 0.0167.

Results: Patients treated with nefazodone (alone or in combination with CBASP) experienced statistically significant improvement in sleep as measured by the HAM-D sleep factor at week 4, week 12, and endpoint compared with CBASP alone ($p < 0.01$). The differential improvement in sleep in the nefazodone treated groups was independent of overall treatment response, suggesting a drug mediated effect.

Conclusions: This finding is consistent with an existing report that sleep disturbance is resistant to change with psychotherapy. The clear implication from this large-scale study is that insomnia symptoms need to be specifically addressed as part of the treatment of depression either by using antidepressant medication, that improves sleep such as nefazodone, or by the addition of an empirically supported insomnia module to existing cognitive behavioral psychotherapy for depression.

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1525.M

Characteristics of Sleep Quality in Depressed and Healthy Adults

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Introduction: "Sleep quality" is a generic term used by clinicians, researchers, and lay people. Despite the frequency of its use and importance in evaluating sleep disorders, there is little consensus on how sleep quality is defined. The aim of the current study was to model subjective sleep quality in a large sample of adults, using structural equation modeling of a post-sleep questionnaire. We also evaluated differences in the structure of subjective sleep quality among depressed and healthy controls.

Methods: Archival data were available for a sample of 722 men and women (398 with major depression, 324 healthy controls) between the ages of 19-92 years. At the time of sleep studies, depressed subjects were unmedicated and symptomatic (mean Hamilton = 19). A post-sleep evaluation form was used to assess subjective sleep quality data and was administered in the laboratory on the morning following the second or third night of polysomnographic sleep studies. The post-sleep evaluation form contained semi-quantitative questions related to the amount and continuity of the previous night's sleep (e.g., sleep latency, time spent asleep) as well as 10 visual analog scales (VAS) that addressed more phenomenological aspects of sleep (e.g., difficulty falling asleep, feeling poorly rested). A series of three analyses were used to model subjective sleep quality. First, exploratory factor analysis was used to identify orthogonal dimensions of subjective sleep quality using the full sample of subjects. Second, confirmatory factor analyses were conducted in the depressed and control samples to identify stable factors across samples. Finally, stable factors were modeled and tested for goodness of fit using structural equation modeling procedures, with group as an independent factor. ANCOVAs, controlling for age and sex, were used to test group differences on all measures that were entered into the structural equation model.

Results: Through the use of structural equation modeling, we identified three stable dimensions of sleep quality: difficulty initiating sleep, difficulty staying asleep, and difficulty with the transition from sleep to wakefulness. Goodness of fit indices indicated that the data fit the model well (gfi = .982, rmsea = .03). Difficulty initiating sleep was measured by estimates of latency to sleep and a VAS item that specifically asked about difficulty falling asleep. Difficulty staying asleep was measured by the number of awakenings and the number of sleep complaints during the previous night's sleep. Difficulty with the sleep-wake transition was a function of three VAS items: difficulty awakening, feeling poorly rested upon awakening, and not feeling alert. The structure of sleep quality was similar in depressed patients and healthy controls, despite group differences in mean values on 6 of the 7 specific measures that comprised the three sleep quality dimensions (p values < .0001).

Conclusions: "Sleep quality" can be modeled by three factors that make intuitive sense: difficulty falling asleep, difficulty staying asleep, and difficulty awakening. These dimensions are similar in depressed and healthy adults. We plan to use structural equation modeling to characterize visually-scored and quantitative sleep EEG measures in this sample, with the goal of modeling overall relationships between subjective and EEG sleep measures.

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1849.M

REM Sleep Microarchitecture in Depression

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Introduction: There is a substantial literature on the microarchitecture of NREM sleep in patients with major depressive disorders (MDD), particularly with regard to slow-wave or delta activity. Most studies indicate that slow-wave activity amplitude is reduced in those with MDD. Our own work has shown that SWA abnormalities are prevalent in men, but not women, with MDD.[1] By contrast, few studies have evaluated the EEG frequency characteristics or temporal organization of REM sleep in MDD.

Methods: This report focused on period amplitude analysis (PAA) of sleep EEG across successive REM periods in 12 symptomatic, unmedicated outpatients with MDD (6 men, 6 women), mean age 30.8 ± 4.2 years and 12 healthy normal controls (6 men, 6 women), mean age 31.4 ± 5.1 years. Each participant spent two consecutive nights in the laboratory. All analyses were based on night 2 data. All-night PAA quantified amplitude and incidence in each EEG frequency band.[2] PAA data were then averaged in each REM period, identified by visual stage scoring,[3] and coded for group and sex. ANOVA evaluated between-group differences, treating REM period as a repeated measure.

Results: Results indicated a significant overall group by sex interaction for both beta and delta measures ($p<.04$). No sex differences were evident in healthy controls, whereas dramatic sex differences were evident in the MDD group ($p<.008$). Moreover, hemispheric asymmetries during REM were significantly larger in the MDD group ($p<.04$) with greater fast-frequency activity in the right hemisphere. Most importantly, healthy controls and MDD women showed significant changes in beta and delta activity across successive REM periods ($p<.02$). By contrast, MDD men showed no change in EEG amplitude or incidence from the first to the fourth REM periods.

Conclusions: These results suggest that the temporal organization of REM sleep is abnormal in men with MDD, as reported in studies of NREM sleep. Women with MDD, however, showed little evidence of abnormal temporal organization of REM sleep. These findings suggest that both REM and NREM sleep regulation is impaired in men with MDD and provide further evidence that the pathophysiology of depression differs between men and women.

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1711.M

New Cholinergic Test of Sleep/Mood Dysregulation in Familial Depression

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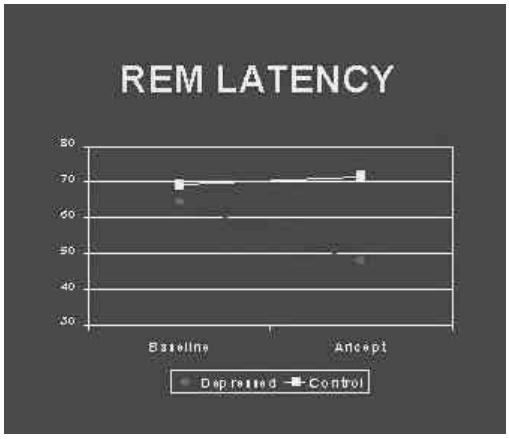
Introduction: Major Depression is reliably associated with REM sleep abnormalities, suggesting increased cholinergic activation, enhanced cholinergic sensitivity and/or an imbalance in cholinergic and monoaminergic tone (e.g. Gillin et al 1991). A number of investigations have determined that depressed patients and/or family members can be differentiated from controls based on response to intravenously administered, centrally active cholinergic agents like arecholine and physostigmine. These agents preferentially shortened REM latency or reduced REM interval times in those at risk for depression (e.g. Sitaram et al. 1987). We tested an orally administered cholinergic agonist to determine whether it could be used effectively to alter REM timing preferentially in depressed patients and, as such, serve as a probe for cholinergic abnormalities in our family cohort (e.g. Giles et al 1998). Specifically, we evaluated Donepezil HCl 10 mg (Aricept: Pfizer-Eisai), a cholinergic agent used to treat Alzheimer's disease. Donepezil is orally administered, with peak plasma levels at 3-5 hours, a half-life of 60 to 100 hours and is well tolerated.

Table 1

GROUP	AGE	SEX (F)	HT (in)	WT (lbs)	HRSD
DEPRESSED n = 8	36.8 ±10.5	75%	66.5 ± 3.2	164.6 ±30.9	19.4 ±2.3
CONTROL n = 8	39.8 ±5.4	75%	64.6 ±4.6	153.6 ±32.9	0.1 ±0.4

Figure 1



Methods: Depressed patients (n=8) were age- and sex-matched to controls (n=8) for a 3-night sleep laboratory study. Patients had nonpsychotic, recurrent depression. Subjects maintained a medication-free, stable, diurnal sleep/wake schedule for two-weeks prior to laboratory study. Night 1 was the adaptation night. On night 2, the baseline night, placebo was administered at 8:00 p.m. On night 3, Donepezil was administered at 8:00 p.m. Subjects were assigned to a fixed placebo-Donepezil protocol due to the half-life. Bedtime for all subjects was between 11:00 p.m. and midnight.

Results: The cholinergic challenge distinguished the groups. Onset to REM sleep was shorter in depressed patients compared with controls (47.6 vs. 71.7, p=.02). REM latency after Donepezil in depressed patients was also reduced compared with baseline (47.6 vs. 64.4, p =.04). Control subjects showed no response: REM latency after Donepezil was virtually identical to baseline REM latency (71.7 vs. 69.3).

Conclusions: The three-night protocol and the differential response to a cholinergic challenge in the depressed group strongly support the validity of the procedure. These data also support our model that cholinergic sensitivity may mediate mood dysregulation observed in our cohort and that REM sleep dysregulation may be an expression of this effect.

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1049.M

Towards a Neurobiology of Dysfunctional Arousal in Depression: NREM Sleep [18F]FDG PET/Spectral EEG Sleep Studies

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Introduction: Symptoms of depression suggest dysregulation in brain systems that regulate physiological arousal. EEG sleep measures of arousal are among the more reliable and well-studied of biological alterations in depression and these measures have been linked with the clinical course of a depressive episode. These studies suggest that the identification of the functional neuroanatomical correlates of these shifts in cortical function to a more aroused state may help to define the brain systems that relate to clinical response in depression. Within this framework, we correlated high frequency beta EEG power spectral density and regional cerebral glucose metabolism using [18F]2-fluoro-2-deoxy-D-glucose ([18F]FDG) PET scans during NREM sleep in healthy and depressed subjects.

Methods: Twelve depressed and nine healthy subjects underwent concurrent EEG sleep studies and [18F]2-fluoro-2-deoxy-D-glucose ([18F]FDG) PET scans during their first NREM period of sleep. PET studies used a 4-6 mCi dose of [18F]FDG. The time of injection was either 5-7 minutes following the identification of the first sleep spindle (6 subjects) or after 20 minutes from sleep onset (3 subjects). Spectral analyses of the sleep EEG during the first 20 minutes of NREM sleep [18F]FDG uptake was performed. For the current analysis, we examined the beta frequency range of 20-32 Hz. Subjects also completed sleep quality visual analog scales. Statistical parametric mapping was used to identify brain structures where there was a relationship between beta power and relative regional cerebral glucose metabolism (rCMRglu) during NREM sleep. A simplified kinetic method was used as an indirect measure of absolute glucose metabolism (Hunter et al 1996).

Results: Depressed patients demonstrated greater relative beta power in

relation to an age- and gender-matched healthy control group. In both healthy and depressed subjects, beta power negatively correlated with subjective sleep quality. Healthy and depressed subjects demonstrated correlations between beta power and relative cerebral glucose metabolism in the ventromedial prefrontal cortex, bilaterally, and the right lateral inferior occipital cortex. In the depressed group, there was a trend for beta power to correlate with an indirect measure of absolute whole brain metabolism during NREM sleep.

Conclusions: The findings from this study help to define brain mechanisms related to psychophysiological arousal and sleep disturbances in depressed and healthy subjects. In the context of prior work, these findings suggest an important role for the ventromedial prefrontal cortex in mediating dysfunctional arousal in depressed and healthy subjects. Reductions in prefrontal cortex function have been demonstrated during NREM sleep (Maquet et al., 1997; Hofle et al., 1997; Braun et al., 1997). The orbitofrontal cortex has widespread connections with a distributed ascending activating system, placing it in a position to integrate limbic-paralimbic afferents with those coming from more higher order association cortex and subsequently influence motivational, emotional and arousal systems in the brain. Mayberg (1997) has suggested that ventrally located anterior paralimbic structures have increased functional activity that relates to vegetative and somatic features of the depressive syndrome. Rolls (1999) has implicated the ventromedial prefrontal cortex in rapid stimulus-reinforcer association learning, and the correction of these associations when reinforcement contingencies in the environment change. Behaviorally and anatomically, therefore, the ventromedial prefrontal cortex appears to be a brain region that has increased function in relation to abnormal emotional arousal in depression. Given the role of abnormal arousal in predicting treatment response, functional activity in the ventromedial prefrontal cortex may play a significant role in determining which depressed patients will respond to treatment.

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1757.L

Sleep Disorders in a Population-Based Study of Chronic Fatiguing Illnesses Identified with the Sleep Assessment Questionnaire© 1-H. Moldofsky, 2-A.Cesta, 3-C.Sammut, 4-E. R. Unger, 5-R. Nisenbaum, 6-W. C. Reeves

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Introduction: The 17 item Sleep Assessment Questionnaire (SAQ (c)) has been shown to have favourable sensitivity and specificity for identifying patients with sleep disorders and more specifically, for differentiating patients with a primary diagnosis of sleep apnea, fibromyalgia/chronic fatigue syndrome, insomnia, excessive daytime somnolence (EDS), and restlessness during sleep, from subjects free of any sleep disturbances. The purpose of this study was to evaluate the results of the SAQ(c) in a group of subjects enrolled in a longitudinal epidemiological study of chronic fatigue.

Methods: A random-digit telephone survey of the population of Wichita, Kansas was used to interview 7176 people to identify subjects with fatigue of greater than 6 months duration and no psychological or medical exclusions. Fatigued subjects and non-fatigued controls were further evaluated at a clinic visit that included a detailed interview, physical examination and laboratory testing. At the 12 month follow-up period, the phone survey was repeated and all subjects previously evaluated at the clinic as well as any newly identified fatigued subjects were seen at the clinic and in addition to the previous studies were given the 17 item SAQ(c) to evaluate sleep disorders. Of the 354 clinically evaluated subjects, 328 had complete data (45 population-based controls and 283 subjects with fatiguing illnesses). The SAQ(c) was blindly analyzed for severity of sleep disturbances and symptoms of specific sleep pathology. Receiver Operator Curves were used to identify cut-off scores that maximized sensitivity and specificity for global severity and SAQ(c) factor scores (non-restorative sleep, sleep apnea, excessive daytime sleepiness, insomnia and restlessness) in patients with a polysomnographic-confirmed diagnosis of sleep disorder versus "normals". The sensitivities and specificities of these scores, which ranged between 64% to 85% and 83% to 100% (Cesta et al 1996, 1997, 1999), were used to predict the prevalence of sleep disturbances in the Wichita sample.

Results: An analysis of the SAQ(c) factor scores showed that 15 (33.3%) of the 45 controls vs. 254 (89.8%) of the 283 subjects with fatiguing illnesses had sleep disturbances identified in one or more of the SAQ(c) factors, (chi-squared p value = 0.001). The number and proportion of controls and subjects above the cut-off score for each of the SAQ(c) factor(s) are shown in Table 1.

Table 1

Number of Subjects with Elevated SAQ© Factor Scores

SAQ© Factor(s)	Controls (%) N=45	Fatiguing Illness (%) N=283
Non-Restorative sleep	2 (4.4%)	47 (16.6%)
Sleep Apnea	4 (8.9%)	15 (5.3%)
Excessive Daytime Sleepiness (EDS)	5 (11.1%)	46 (16.2%)
Sleep Apnea / EDS	2 (4.4%)	34 (12.0%)
Non-Restorative / Sleep Apnea	0	18 (6.4%)
Non-Restorative / EDS	0	47 (16.6%)
Non-Restorative / EDS / Sleep Apnea	1 (2.2%)	22 (7.8%)
Insomnia	0	5 (1.8%)
Restlessness	1 (2.2%)	20 (7.1%)
Normal Sleep Factors	30 (66.7%)	29 (10.2%)

Conclusions: In a population-based study of fatiguing illnesses, sleep-related pathologies are quite common. Sleep disorders are significantly associated with fatiguing illness when compared to non-fatigued controls. Further study of the inter-relatedness of sleep pathology and chronic fatigue is warranted.

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1461.L

Alpha Sleep Patterns in Fibromyalgia

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Introduction: Disturbed sleep is a prominent symptom in fibromyalgia, present in up to 90% of the patients. Not only bad sleep influence pain symptoms,[1] but also chronic pain conditions exert a variable influence over sleep parameters.[2] Sleep architecture alterations described in fibromyalgia reflect a tendency towards a more superficial sleep and the alpha/delta sleep pattern may be related to musculoskeletal complaints.[3] The aim of this study is to characterize the different alpha rhythms during sleep in fibromyalgia and the repercussion of them on pain manifestations.

Methods: Forty fibrornyalgia female patients, aged 45.3+4.5 year, average disease duration 5.5+2.6 years and forty-three female controls aged 46.6+5.1 years, were randomly selected. The study comprised pain evaluation before and after sleep recording by means of visual analogic scale (VAS) for pain symptoms, tender points count and VAS for evaluation of sleep in the laboratory. After a first night of adaptation, the sleep of all subjects was recorded by polysomnography (3). Architecture of all-night sleep and frequency analysis along the first two sleep cycles was performed blindly.

Results: Post-sleep increase in tender points count occurred in 25 (62.5%) fibromyalgia patients and 6 (13.9%) of the healthy controls ($p< 0.01$). Polysomnography showed a tendency to superficial sleep among fibromyalgia subjects and three distinct conditions in regard to alpha activity in non-REM sleep: Phasic alpha sleep pattern (episodic, occurring simultaneously to delta activity), in 20 (50%) subjects; tonic alpha rhythm (continuous along non-REM sleep, independently of delta activity) in 8 (20 %) and low alpha activity in the remaining 12 (30%). In the control group, 3 (6.9%) subjects presented phasic alpha sleep pattern, 4 (9.3%) tonic alpha and 36 (83.7%) low alpha rhythm. All patients with phasic alpha sleep activity presented worsening of scores for pain evaluation after sleep, comparing to 7 (58.3%) of fibromyalgia patients with low alpha activity ($p< 0.01$) or 2 (25%) of patients with tonic alpha activity ($p<0.01$). The same significance of differences were observed in regard to increase in tender points count after sleep , presented by 18 (90%) of patients with phasic alpha, in comparison to 5 (41.7%) patients with low alpha activity and those with tonic alpha activity, 4 (25.0%). Poor sleep scores by VAS was obtained in all patients who presented phasic alpha sleep activity, 7 (58.3%) patients with low alpha ($p<0.01$) and 1 (12.5%) patient with tonic alpha sleep activity ($p<0.01$). Pain complaints duration was longer in phasic alpha sleep patients than in other subgroups (ANOVA $F(2,72) = 26.5$, $p< 0.01$). In regard to polysomnography data, phasic alpha sleep patients presented shorter total sleep time than the other subgroups (ANOVA $F(3, 72) = 13.3$, $p< 0.0\ 1$), longer sleep latency than controls (ANOVA $F(3,72) = 3.6$, $p< 0.0\ 1$), lower sleep efficiency than controls (ANOVA $F(3,72) = 7.9$, $p< 0.0\ 1$), decreased slow wave sleep amount than other subgroups (ANOVA $F(3,72) = 10.1$, $p< 0.01$), and increased arousal index than other subgroups (ANOVA $F(3,72) = 13.\ 1$, $p< 0.0\ 1$).

Conclusions: Three patterns of alpha activity were observed in fibromyalgia. The phasic, or alpha-delta sleep rhythm, presented prominent association with poor sleep sensation, superficial sleep parameters and worsening of the pain condition after awakening.

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1402.L

Sleep Spindle Activity in Women with Fibromyalgia: Preliminary Findings

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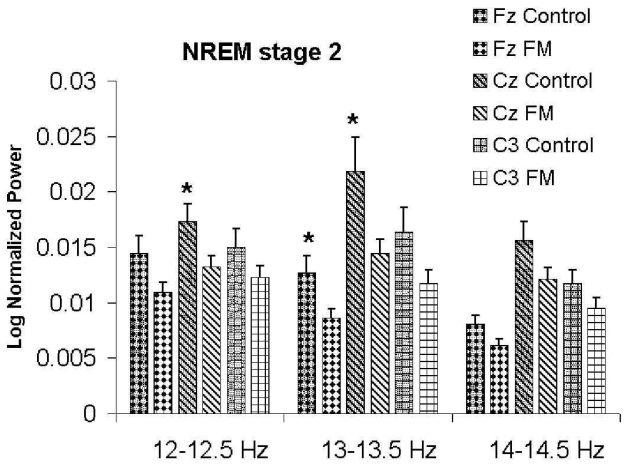
Introduction: Fibromyalgia (FM) is a chronic pain condition manifested also by fatigue and poor sleep (Harding, 1998). Altered blood flow in the thalmus and cortex have been documented (Mountz et al, 1995) and central nervous system dysfunction probably contributes to altered pain perception in FM. Because sleep spindles are associated with hyperpolarization of thalamocortical neurons, and are considered critical to maintaining NREM sleep (Steriade et al, 1993), we examined sleep spindle characteristics and spindle frequency activity in our ongoing study of women with and without FM.

Figure 1



Methods: Polysomnographic (PSG) data from 18 women with and 15 women without FM were used in this analysis. Women were excluded for a current psychiatric or sleep disorder diagnosis. Women with FM stopped taking all hypnotic, sedative, or psychotropic medications for two weeks prior to the 3 night laboratory study. Control women were pain free with good PSG sleep. Women with menstrual cycles were studied during days 5 to 10. Sleep was recorded and scored (night 2) in 30-sec epochs with the Oxford Sleep Acquisition Computer (SAC) System. A standard EEG montage (C3-A2) was used with additional midline (Fz and Cz) electrodes. Sleep spindles were defined by the SAC system and quantified in NREM stage 2 (C3) according to number of spindles/min, duration (sec), and index of spindling for the entire night. The raw EEG data from C3, Fz and Cz were screened of artifact. Spectral analysis was performed (0.5Hz resolution) with a discreet fourier transform algorithm. The power spectra (0 to 30Hz) for each epoch were matched with scored sleep data and summarized for NREM stage 2 in 12-12.5, 13-13.5 and 14-14.5 Hz bins for the entire night for each lead (Figure 1). To compensate for variability in EEG power among subjects and across the night, the spectra were normalized and then log transformed.

Results: Women with FM were slightly older (46.3±7.5 yrs) than control women (41.2±7.6 yrs, $p = .065$). Women with FM had fewer spindles/min (4.35±2.3) of slightly longer duration (1.2±0.16 sec) than control women (number, 5.9±2.5; duration, 1.07±0.15 sec). Spindle index was lower in FM (6.6±4.2) compared to controls (9.9±5.8, $p = .072$).

Women with FM showed lower spindle power in Cz in the 12-12.5 Hz (f = 4.7, p = .041) and 13-13.5 Hz (f = 5.27, p = .032) bins, and in Fz in the 13-13.5 Hz (f = 5.31, p = .031) bin (Figure 1).

Conclusions: Women with FM have altered sleep spindle charactistics and reduced power in frequency activity compared to healthy women of similar age. These differences in spindle power were most evident in the midline EEG central lead and in the lower spindle frequency range. These data imply that thalamocortical mechanisms of spindle generation might be impaired in women with FM

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1669.L

Pathological Sleepiness in Patients on Chronic Hemodialysis

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Introduction: Increased sleep propensity in the chronic hemodialysis (HD) population has been described for over 30 years and attributed to a variety physiologic and psychologic factors. Although recent research has demonstrated that sleep apnea and periodic leg movements are very prevalent in this group, the extent to which they contribute to daytime sleepiness remains to be established. Most prior studies have been limited by the fact that the subjects were preselected on the basis of sleep/sleepiness complaints, that potentially confounding variables such as co-morbidity and medications were not controlled, and because daytime sleepiness was not formally assessed. Thus, whether sleepiness in these patients is determined by the presence of sleep disorders versus effects of the disease or its treatment is not clear. We, therefore, studied a sample of well-controlled HD patients to explore variables related to sleepiness.

Methods: The sample included 29 chronic, metabolically stable HD patients (see Table 1). Potential subjects with other major chronic conditions such as heart failure, cancer, chronic lung disease, immunological disorders, organic brain disease, drug/alcohol abuse, or past psychiatric disorders were eliminated from the study. In addition, patients on medications known to have CNS effects such as beta-blockers, centrally acting antihypertensives, antidepressants, sedatives, activating agents, or pain medications were also eliminated. Potential subjects were carefully screened via a structured interview to exclude those with a clinical history suggestive of sleep apnea, periodic leg movement disorder, and restless leg syndrome. Subsequently, all subjects underwent one-night of laboratory-based polysomnography followed by an MSLT and completed the Epworth Sleepiness Scale (ESS).

Results: Polysomnography revealed that mean, general sleep measures for the sample including sleep latency, REM latency, sleep staging, sleep efficiency, and total sleep time were unremarkable in comparison to normative data. Although the MSLT revealed a group mean sleep latency of 10.5 minutes (±4.3), 13 of the 29 subjects had unsuspected moderate to severe sleepiness and 10 subjects had sleep onset REM periods (SOREMPS) that were unrelated to sleepiness severity (Chi-square analysis; see Table 1). There were no significant correlations between MSLT scores and respiratory disturbance (RDI) or brief arousals (BAI) and no significant differences in these indices when groups based on sleepiness severity were compared. In addition, when groups based on sleepiness severity were considered, those subjects with moderate sleepiness had a significantly higher PLMI in comparison to those with mild (p = 0.000) or severe (p = 0.000) sleepiness (ANOVA, post hoc testing using Dunnets C). There was no significant difference among the groups based on sleepiness in body mass index, ferritin, or iron levels. The ESS scores were not correlated with the MSLT, RDI, PLMI, or BAI. (insert Table 1)

Table 1

Demographics, Sleepiness Severity, and Sleep Disorder Related Indices (Mean ± Standard Deviation)

Sleepiness Severity		MSLT < 5	MSLT 5 to 10	MSLT >10	Total
n		4	9	16	29
AGE*		51.8+11	52.6+ 8	52.3+11	52.3+10
M		3	6	7	16
F		1	3	9	13
RDI*		21.1±17	6.0 ± 6	6.8 ±12	8.5±12
PLMI**		12.6±19	56.5 ± 57	11.2±14	25.5±39
BAI*		43.5±23	25.8±21	24.2±20	27.3±21
SOREMPS	**0**	1	8	10	19
	1	1	1	3	5
	2	2	0	3	5
ESS*		5.3+5.7	7.6+5.3	6.7+4.4	6.8+4.7

* differences among groups NS, ANOVA ** ANOVA, p = 0.01

Conclusions: Our experience is noteworthy in several respects. First, pathological sleepiness was present in over one-third of the patients, a finding that may underestimate the actual prevalence of the problem in the HD population as these subjects were well controlled. Second, impaired modulation of arousal state was manifested as SOREMPs in another 20% of patients with essentially normal daytime alertness. Third, patients inaccurately reported their level of subjective sleepiness regardless of its severity. Finally, the effects of renal disease or its treatment on arousal systems likely contribute to these findings, as underlying "primary" sleep disturbances did not correlate well with sleepiness levels. Thus, renal disease or animal models of such may provide unique insights into the modulation of normal and pathological arousal states. Increased awareness of sleepiness and delineation of its pathophysiology will result in more rational treatments, better functional outcomes, and maximize the benefits of HD.

Research supported by RO1 NR04340

1683.L

The Use of Autonomic Activity During Sleep As a Marker of Functional Gastrointestinal Disorders

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Introduction: Previous work from our laboratory and others has demonstrated differences between patients diagnosed with irritable bowel syndrome (IBS) and healthy controls in the autonomic regulation of heart rate variability (HRV) during REM sleep. The present study was designed to replicate and extend these findings, by examining whether this difference is unique to IBS or is a generalized characteristic of all

individuals with a functional gastrointestinal disorder (FGD).

Figure 1. HF Band Power

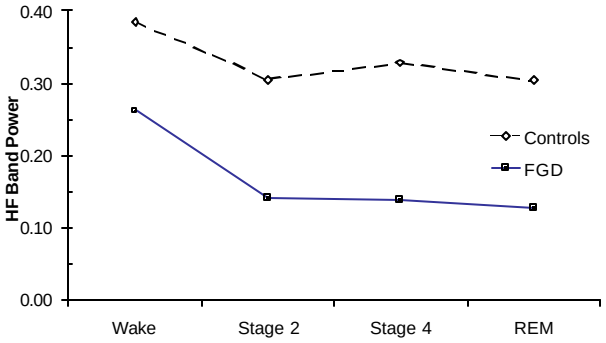
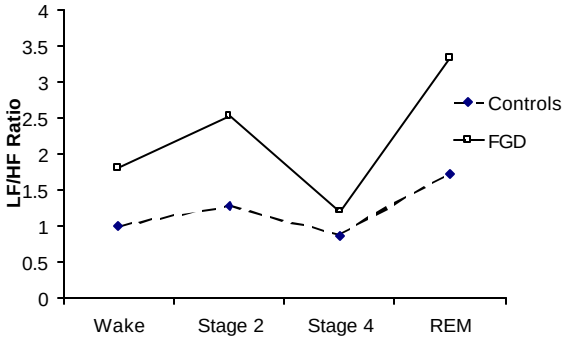


Figure 2. LF/HF Ratio



Methods: Fourteen individuals with a diagnosis of a FGD (i.e., either IBS and/or non-ulcerative dyspepsia), along with eleven healthy volunteers participated in the study. Each subject spent one night in the laboratory, during which they underwent a standard polysomnographic (PSG) recording which included one channel for ECG sampled at a frequency of 500 Hz. Sleep stages were determined using the standard R&K criteria. Fifteen minute segments of artifact-free ECG were selected and analyzed for four different sleep stages: Wake, Stage 2, Stage 4, and REM sleep. After detrending, total power between 0.04 Hz and 0.5 Hz was calculated, along with the power in the low frequency band (LF, 0.04 Hz to 0.15 Hz) and high frequency band (HF, 0.15 to 0.5 Hz). The LF band represents predominantly the sympathetic nervous, while the HF band reflects vagal (parasympathetic) activity. The LF to HF ratio (LF/HF) was also computed for each segment as a way of representing sympathetic-parasympathetic balance. The data were then analyzed using a 2x4 repeated measures ANOVA and post-hoc pairwise comparisons were carried out. In addition, a preliminary stratification of the FGD group, based on symptomatology was also carried out in order to explore the possibility of differences between subtypes of the heterogeneous FGD group.

Results: As can be seen in Figure 1, the FGD group demonstrated a lower HF band power at all measurement points; these differences reach significance during both SWS and REM sleep ($p<.05$). This difference in HF band power also contributed to a trend ($p<.08$) towards a difference in the LF/HF ratio, particularly during REM sleep (Figure 2). Preliminary analysis of subgroups of FGD demonstrated differences between those with predominantly diarrhea vs. constipation, with diarrhea-predominant patients demonstrating more sympathetic dominance (i.e., higher LF/HF) during REM sleep than constipation-predominant individuals.

Conclusions: 1) Patients with FGD clearly have an abnormal autonomic regulation of cardiac activity during sleep. This was characterized by an increase in sympathetic dominance during REM sleep and vagal withdrawal during slow wave and REM sleep.2) These data suggest that alterations in autonomic functioning during sleep may indeed be useful in describing differences among patients with FGD.

1680.A

Plasma Cortisol Changes Following Chronic Sleep Restriction

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Introduction: Previous studies have reported both no effect[1] and significant alterations[2] in cortisol secretion following total or partial sleep deprivation. The aim of the present study was to investigate the effects that chronically reduced nocturnal sleep time, with and without a daytime nap has on plasma cortisol profiles.

Methods: A total of 13 subjects (8m; 5f; mean age ± sd: 28.5 ± 4.9) attended the sleep laboratory for a 14-day protocol. Following 2 nights of baseline sleep (8.2h between 2154h-0606h) subjects were randomly assigned to a sleep restriction condition, that was maintained for 10 consecutive days, followed by 2 recovery days (14h sleep). In condition A [control condition] (N=5) subjects were allowed an 8.2h anchor sleep between 2154h-0606h; in condition B (N=4) subjects were allowed a 4.2h anchor sleep between 2354h-0406h; and in condition C (N=4) subjects were allowed a 4.2h anchor sleep between 2354h-0406h and a daily 1.2h nap sleep between 1324h-1440h. On the first baseline day (day 1) and the final condition day (day 12), starting at 1630h, subjects were maintained in a quasi-constant routine paradigm for twenty-four hours. During this time subjects were near-supine in bed, and allowed to sleep at the allocated times, with blood samples collected at 15 minute intervals via an indwelling nonthrombogenic venous catheter. From these samples plasma cortisol concentrations were determined at hourly intervals, using an RIA (Diagnostic Systems Laboratories, Inc, TX). Cortisol secretion was analyzed using within-subjects repeated-measures ANOVA comparing day 1 with day 12.

Results: For all three conditions there was a significant time of day variation, reflecting the well established circadian changes in cortisol levels ($P<0.001$). On day 1 in all three conditions (8.2h sleep period), and day 12 in control condition A (8.2h sleep period), there was a peak in plasma cortisol levels evident just subsequent to the offset of sleep. This peak was also evident on day 12 in condition B following the offset of the 4.2h sleep period (i.e. a 2h earlier clock time relative to baseline). Hence there was a significant difference between the plasma cortisol levels on day 1 and day 12 for condition B ($p=0.05$). In condition C (4.2h + 1.2h nap), the peak in cortisol secretion on day 12 did not occur directly following sleep offset, but rather occurred at the same time as on baseline day 1 (i.e. at 0745h). In this condition, there was no difference in the timing of the peak in plasma cortisol levels between day 1 and day 12, and no significant difference between the overall plasma cortisol levels on the two days.

Conclusions: Cortisol secretion is modulated by the interactions of the circadian, sleep and stress systems. Consistent with Born and colleagues[3] conditions A and B of this study suggest that the early morning peak in cortisol is related to sleep offset. However, in condition C, the

peak in cortisol on day 12 was not associated with sleep offset. The midafternooon nap appears to have prevented the phase advance of the circadian peak of peripheral corticotrophic hormone concentration associated with anticipation of awakening. Polysomnographic data from the present study are currently being analyzed, to investigate the relationship of sleep architecture and cortisol secretion.

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(2) Spiegel K., Leproult R, van Cauter E, Impact of sleep debt on metabolic and endocrine function. Lancet, 1999, 354: 1435-1439.
(3) Born J, Honsen K., Marshall L, Molle M, Fehm H.L. Timing the end of nocturnal sleep. Nature, 1999, 397: 29-30.

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1737.J

Circadian Rhythm Amplitude of Leptin is Reduced by Chronic Sleep Restriction to 4 Hours Per Night

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(1) Neurology, Beth Israel Deaconess Medical Center and Harvard Medical School (2) Psychiatry, Unit for Experimental Psychiatry and Center for Sleep and Respiratory Neurobiology, University of Pennsylvania School of Medicine

Introduction: Leptin is a recently discovered hormone that is produced by adipose tissue and is involved in controlling body weight and energy expenditure. Leptin shows a prominent circadian rhythm, with a gradual rise through the day, peaking around midnight, and falling to its nadir around the time of awakening, out of phase with the diurnal rhythm of cortisol (Bornstein et al., 1998). It has recently been suggested as a regulator of the hypothalamo-pituitary-adrenocortical (HPA) axis and the immune response (Heiman et al., 1997). Since sleep loss is known to affect metabolic, HPA and immune function, we investigated the effects of partial sleep loss on the circadian variation of leptin in peripheral circulation.

Methods: Thirty-five healthy volunteers between the ages of (21-38 yrs) participated in a larger study of the neurobehavioral consequences of sleep restricted to 4, 6 or 8 hours per night, for 14 days. One of the subject selection criteria was evidence (>1 wk sleep log and actigraphy) of regular sleep wake patterns with an average of 7-9 hrs sleep per night, and randomly assigned to one of the 3 conditions. Following 3 nights of baseline sleep of 8h/night, subjects began the experimental schedule that continued for 14 days, followed by 2 days of recovery sleep. This study was performed with four subjects from the 4h/night condition who volunteered to wear an indwelling forearm catheter on one baseline night, on the 7th and again on the 12th night of sleep restriction. During the baseline sleep episode they were permitted to sleep between 2325-0725h, during the 4h/night condition 0325-0725h. Plasma was assayed for several neuroendocrine and neuroimmune parametere, including leptin (R&D systems, Minneapolis, MN). Only the leptin results are reported here.

Results: The individual leptin profiles are provided in Figure 1, and the z-transformed data for each subject are averaged together and presented in Figure 2. As can be seen, the amplitude of the circadian rhythm of leptin has dropped substantially by the 7th day of sleep restriction in subjects 1 and 2, and in all 4 subjects it was reduced by the 12th day.

Figure 1

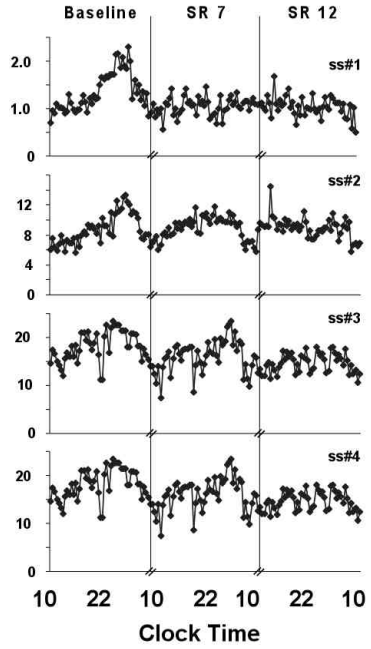

Figure 1. Leptin (ng/ml) profiles for individuals participating in a 14-day sleep restriction laboratory protocol.

Figure 2

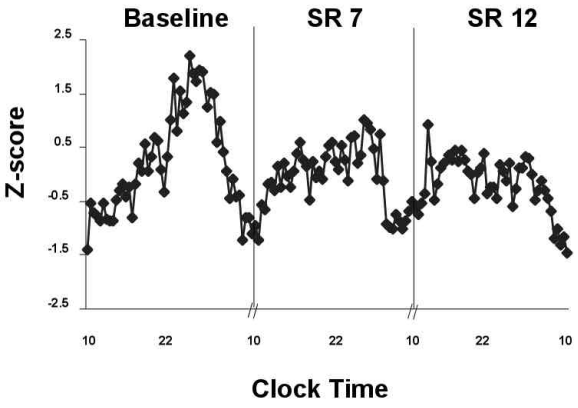

Figure 2. Z-score transformed data for 4 subjects through baseline, and at the 7th and 12th day of chronic sleep restriction (to 4 hrs per night).

Conclusions: These data are the first to show that leptin is affected by sleep loss. In addition, they are consistent with findings of Spiegel et al., (1999), who showed that sleep restricted to 4 hours per night for even 6 nights alters glucose tolerance. This study adds to the growing body of evidence that sleep is an important regulator of neuroendocrine and metabolic systems.

References:
(1) Bornstein SR, et. al. 1998 J Clin Endocrinol & Metab, 83:280-283;
(2) Spiegel K. et.al. 1999 Lancet, 354:1435-1439
(3) Heiman et al., 1997 Endocrinology, 138:3859-3863

Research supported by NIH grant NR04281; NASA cooperative agreement NCC958 with NSBRI

1463.J

Evidence for an Adaptive Process Associated with Cumulative Sleep Loss

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Introduction: It is well recognized that acute total and partial sleep loss have impairing effects on alertness.[1] In addition, there is increasing evidence that chronic partial sleep deprivation can have detrimental effects on cognitive performance as a sleep debt accumulates across time.[2] However, no study has compared the alertness and performance impairing effects of an equal amount of sleep loss experienced at different rates of accumulation. In order to directly compare the effects of different rates of sleep loss we assessed physiological sleep tendency, memory, and psychomotor performance following three schedules of 8 hours of sleep loss (slow, intermediate, and rapid accumulation) in comparison to a "normal" 8 hour time in bed (TIB) sleep schedule.

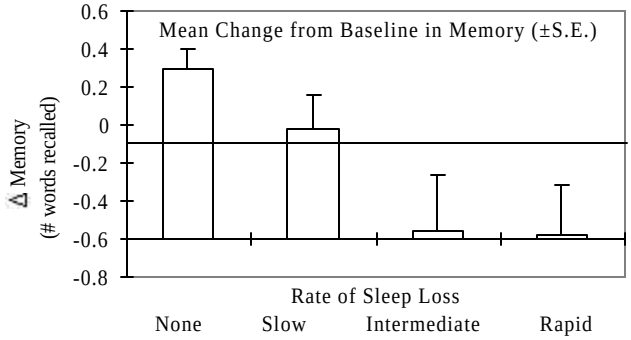
Methods: Twelve healthy individuals aged 21-35 years (5 females, 7 males), were screened using standard clinical polysomnographic techniques and the multiple sleep latency test (MSLT) and were free of psychiatric and medical disease including apnea and PLMs. During screening, all participants had nocturnal sleep efficiencies above 85% and daytime mean sleep latencies of 8-14 minutes. Prior to the experimental conditions, each participant completed a standard 8-hr PSG and MSLT as a baseline assessment. Participants then completed each of the following conditions according to a Latin Square design: no sleep loss (8-hr TIB for 4 nights; 2300-0700), slow (6-hr TIB for 4 nights; 0100-0700), intermediate (4-hr TIB for 2 nights; 0300-0700), rapid (0-hr TIB for 1 night). Thus, individuals in each sleep loss condition (Slow, Intermediate, and Rapid) accumulated a total sleep debt of 8-hr but at different rates. On the baseline day and each experimental day, participants completed a 5-nap MSLT, a memory recall test (MRT), a psychomotor vigilance task/simple reaction time (PVT), and a divided attention task (DAT). Change scores were calculated (last day of each condition minus baseline) for each dependent variable and submitted to separate 1 factor (condition, 4 levels) repeated measures analysis of variance (ANOVA). Trend analysis was also used to identify significant polynomial effects across conditions.

Table 1

Planned Comparisons	*MSLT*	*Memory*	*PVT*
Omnibus F-value	10.86	3.82	4.10
"Deprivation Effect" (8 vs. 0)	$p < .001$	$p < .01$	$p < .05$
Slow vs. Rapid (6 vs. 0)	$p < .06$	$p < .01$	$p < .03$
Intermediate vs. Rapid (4 vs. 0)	n.s.	n.s	$p < .01$
Slow vs. Intermediate (6 vs.4)	n.s	n.s	n.s.

Results: A significant main effect for condition was found for each dependent measure (see table). In addition, trend analysis revealed significant linear trends for each dependent measure across conditions ($p < .05$ for all; see figure). Second and third order trends were not significant. Planned comparisons were undertaken to identify differences between rapid, intermediate, and slow accumulations of 8 hours of sleep loss. For all measures, the 8-hrs of "rapid" sleep loss produced significant impairments compared to the 8-hr TIB condition (see table) indicating that each measure was sensitive to the effects of 8 hours of acute sleep loss. Importantly, the "slow" accumulation condition produced significantly less impairment compared to the "rapid" sleep loss condition for the MRT (see figure) and PVT (approached significance for MSLT). Finally, the "intermediate" condition produced significantly less impairment compared to the "rapid" sleep loss condition on the PVT (see table) and was intermediate to the "slow" and "rapid" conditions.

Figure 1



Conclusions: The impairing effects of 8 hours of sleep loss on alertness and performance appear to be more severe when experienced acutely as compared to cumulatively, suggesting the presence of a compensatory adaptive mechanism operating in conjunction with the accumulation of a sleep debt.

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(1) Rosenthal L, Roehrs TA, Rosen A, Roth T: Level of sleepiness and total sleep time following various time in bed conditions. Sleep. 1993;16(3):226-32.
(2) VanDongen HPA, Maislin G, Dinges DFC. Chronic partial sleep deprivation: neurobehavioral response and slep architecture. Third International Congress of the WFSRS. Dresden, Germany; 1999: 735.

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1577.J

Neurobehavioral Performance Decrements Associated with Sleep Loss and Circadian Phase are Exacerbated by a Supine Body Position

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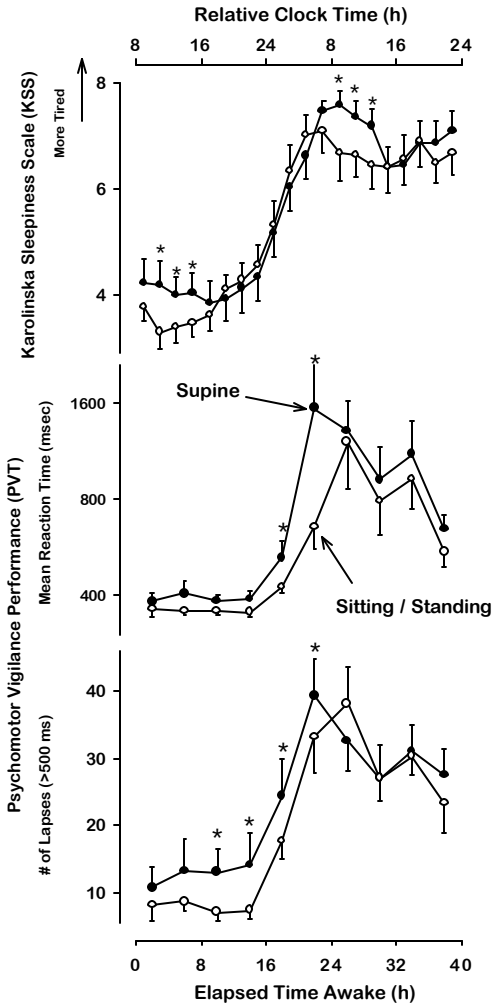
Introduction: Human cognitive performance and vigilance are modulated by an interaction of circadian and sleep-wake dependent processes. Here we investigate whether neurobehavioral performance during wakefulness is modulated by behavioral concomitants of wakefulness such as the upright posture.

Methods: Following three 24-h baseline days (16h scheduled wakefulness and 8h of sleep) in which subjects slept at their habitual bedtime, 7 male and 5 female healthy adults, age range 19-28 years, underwent one of two 40-h posture modified constant routine protocols (CR), in a balanced cross-over design. Subjects were randomly assigned to start with either a sitting/standing CR or supine CR. The supine CR consisted of subjects remaining in bed with a bed angle of 0° and in a supine position, while in the sitting/standing CR subjects alternated between 40 minutes of sitting upright in a chair and 20 minutes of free standing

throughout the entire 40 hours. After an 8-h sleep episode following the CR, subject were scheduled to two standard 24-h days and then underwent the other 40-h posture modified CR, i.e. either supine or sitting/standing. Light levels were maintained at < 50 lux for the entire study except during sleep episodes (0 lux). Neurobehavioral performance was assessed throughout each posture modified CR with a 10-min Psychomotor Vigilance Test (PVT) every 120 min (only during the sitting portions in the sitting/standing CRs). Subjective sleepiness was assessed every 20 min on the Karolinska Sleepiness Scale (KSS). Due to a technical problem, PVT data from one subject were not included.

Figure 1



Results: In the sitting/standing condition the time course of subjective sleepiness exhibited fairly stable levels throughout the first 10 hours of wakefulness followed by an increase in sleepiness during the phase of melatonin secretion and a decline of sleepiness after approximately 26 hours of wakefulness. In the constant supine posture condition the evening increase in subjective sleepiness occurred later than in the sitting/standing condition, i.e. after about 16 hours of wakefulness rANOVA: interaction posture x time: $p < 0.04$). During the biological day, subjects were significantly more sleepy when in a supine position (asterisks indicate significant post-hoc comparisons, LSD test). Significant posture x time interactions were also observed for the mean reaction times ($p < 0.03$) and performance lapses (>500ms; $p < 0.07$) in the PVT. In contrast to subjective sleepiness, most of the effects of body posture on PVT performance occurred during the early evening and the biological night.

Conclusions: The present data indicate that a constant supine posture exacerbates decrements in neurobehavioral performance in a time dependent manner, similar to the reported effects of reduced stimulation on performance during sleep deprivation.[1] Interestingly, most of the negative performance effects induced by a supine posture occurred during the biological night when subjectively rated sleepiness did not differ between the posture conditions (supine vs. sitting/standing). This dissimilar time course of subjective sleepiness and objectively evaluated psychomotor vigilance performance implies that subjective assessments are more unreliable under bedrest conditions. We conclude that postural changes associated with the sleep-wake cycle reinforce the circadian and homeostatic regulation of neurobehavioral performance.

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Research supported by a grant of NASA Cooperative Agreement NCC 9-58 with the National Space Biomedical Research Institute.

1171.J

Equating the Effects of Acute and Cumulative Partial Sleep Deprivation on Performance

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Introduction: Shiftworkers typically experience reduced opportunity for sleep and reduced sleep quality. Not surprisingly, the combination of these factors leads to increased fatigue, lowered levels of alertness and impaired performance on a variety of neurobehavioural performance tasks. Several recent studies have used alcohol as a standard with which to equate impairment in psychomotor performance caused by acute sleep deprivation (e.g., Dawson & Reid, 1997). While the results of such studies provide a useful comparative index, they have limited generalisability. Shiftwork related fatigue is not caused solely by the effects of acute sleep deprivation, rather, it is more often the result of cumulative partial sleep deprivation over a series of nights. Using alcohol as a reference point, we aim to compare the performance decrements associated with acute sleep deprivation and cumulative partial sleep deprivation.

Methods: Two age-matched groups each participated in a randomised cross-over design involving two experimental conditions: a sleep deprivation condition and an alcohol condition. In the first group, twenty-two healthy subjects, aged 19 to 26 years, were kept awake for twenty-eight hours. In the second group, twelve healthy subjects completed a sequence of seven consecutive eight-hour nightshifts. In the alcohol condition, subjects consumed an alcoholic beverage at half-hourly intervals, until their blood alcohol concentration reached 0.10%. In each condition, performance was measured at hourly intervals using three tasks from a standardised computer-based test battery.

Results: Preliminary analysis indicated that as blood alcohol concentration increased performance significantly decreased. Similarly, as hours of wakefulness increased performance significantly decreased. Equating the performance impairment in the acute sleep deprivation condition and the alcohol condition indicated that a period of approximately 20 to 25 hours of wakefulness produced performance decrements equivalent to those observed at a BAC of 0.10%. Further analysis will similarly equate the effects of partial sleep deprivation for each of the seven consecutive nightshifts.

Conclusions: The study is still in progress (data collection in the partial sleep deprivation condition is continuing); however, the preliminary analyses indicate that moderate periods of total sleep deprivation produce performance decrements equivalent to or greater than those observed at levels of alcohol intoxication deemed unacceptable when driving, working and/or operating dangerous equipment.

References:
(1) Dawson D, Reid K: Fatigue, alcohol and performance impairment. Nature, 1997, 388-235.

Research supported by the Australian Research Council.

1615.J

Manipulation of the Recuperative Value of Sleep with Behavioral Sleep Fragmentation

Dumont M Paquet, J, Bergevin, A, Mecteau, M, Jomphe, C, Clossey, G, Lavoie, S

Introduction: To study the interaction between the circadian and homeostatic processes on sleep and vigilance, it is necessary to alter the recuperative or homeostatic aspect of sleep without changing the circadian sleep-wake cycle. Selective slow-wave sleep (SWS) deprivation by acoustic stimulation may increase sleep pressure (Dijk & Beersma 1989; Ferrara et al 1999). However, this technique is extremely difficult to apply because of large variations in acoustic thresholds. Sleep fragmentation by behavioral awakenings is easier to implement, and partial deprivation of stage 2 or REM sleep also seems to decrease the recuperative value of sleep (Glovinsky et al 1990). Even if the latter technique induces some degree of sleep deprivation, it can be used without changing the timing or the duration of the sleep episode. In the present study, we used repeated behavioral awakenings to decrease the recuperative value of sleep and we measured the impact of this procedure on sleep and vigilance.

Methods: Thirteen young adults spent 5 consecutive nights (00:00h to 08:00h) in the laboratory: one adaptation night, one baseline night (BL), two fragmentation nights (FR1 & FR2), and one recuperation night (RN). During FR1 and FR2, the subjects were awoken 15 times: 5 min of verbal interaction in the dark, separated by 25 min of sleep. Sleep was recorded and scored according to standard procedures and power spectral analysis was conducted on C3/linked ears derivation. Daytime vigilance levels and mood were measured after BL, FR1 and FR2 with waking EEGs, sleep latency tests, analog scales of alertness, and the Profile of Mood Scales (POMS).

Results: Total sleep time was on average 7.6 h during BL, 5.9 h during FR1, and 6.4 h during FR2. Sleep efficiency was 74.9% on FR1 and 80.9% on FR2, compared to 96.7% on BL. Most sleep parameters showed a profound deterioration during FR1, followed by some recuperation during FR2. Specifically, SWS decreased from 72.7 min during BL to 36.8 min during FR1, then increased to 56.7 min during FR2. SWA (0.75-4.5 Hz) showed a large decrease on FR1 compared to BL, but no difference between FR2 and BL. Both SWS and SWA increased above baseline during RN. All indicators of vigilance levels revealed a significant deterioration after each of the fragmentation nights: increased activity in the theta frequency band (4.00-7.75 Hz) of the waking EEG, shorter daytime sleep latencies, decreased subjective alertness, higher scores on fatigue and confusion scales with lower scores on the vigor scale of the POMS.

Conclusions: Our technique of behavioral sleep fragmentation significantly impaired the recuperative value of sleep. One night of sleep fragmentation, which produced only a moderate degree of sleep deprivation, had a significant impact on both sleep and vigilance measures. The level of recuperation observed during the second night of sleep fragmentation might be a useful indicator of the strength of the homeostatic process when challenged by external perturbations.

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1768.I

Effect of Chronically Reduced Nocturnal Sleep, with and without Daytime Naps, on Neurobehavioral Performance

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Introduction: Recent experiments have demonstrated that chronic sleep restriction produces a progressive decrease in neurobehavioral functioning.[1,2] One possible countermeasure for adverse neurobehavioral effects in real-life scenarios where sleep restriction cannot be avoided is to supplement reduced nocturnal sleep with a daytime prophylactic nap.[3] This strategy has never been experimentally tested in a chronic sleep restriction paradigm. To address the issue an experiment was designed to test the effectiveness of 18 nocturnal sleep and nap sleep combinations for maintaining alertness during chronic partial sleep loss (i.e., <8h TIB per day).

Methods: A total of n=90 healthy adult subjects will be studied. To date n=58 (28m; 23f; M=28.1 ± 6.6yr) have participated in a 14-day laboratory protocol involving 2 nights of baseline sleep (8.2h TIB between 2154h-0606hr) and 2 nights of recovery sleep, separated by 10 nights of sleep restriction involving random assignment to one of 18 different nocturnal+nap sleep combinations. The 18 conditions consist of 4 nocturnal sleep durations (4.2, 5.2, 6.2, 8.2 hr) and 7 nap sleep durations (0.0, 0.4, 0.8, 1.2, 1.6, 2.0, 2.4 h.) crossed to yield a total of 4 nocturnal-sleep-only conditions and 14 nocturnal+nap conditions. Subjects are tested on a 30-minute computerized neurobehavioral assessment battery every 2h while awake. Performance and mood scores from this neurobehavioral test battery serve to quantify the cumulative performance deficits (across days) that are associated with each sleep restriction condition. Random coefficients regression models were used to estimate subject-specific mean decrements associated with cumulative exposure to the chronic sleep ration protocols performed to date for key performance, subjective, and physiological variables. These subject-specific slopes will be subjected to response surface modeling allowing identification of the optimal nocturnal anchor sleep / daytime prophylactic nap combination that minimizes adverse neurobehavioral effects subject to any specified constraints on maximum TIB. The spatial location of optimal solutions will be graphically illustrated by plotting the expected slope as a function of the response surface model.

Results: To date, 11 of the 18 sleep restriction conditions have been

studied, with the remaining 7 to be completed in the coming months. With all conditions completed the full response-surface model will be developed for each of a number of key neurobehavioral performance, subjective, and physiological variables. For the purpose of this preliminary comparison, performance degradation slopes were calculated for PVT performance lapses for each of 32 subjects and averaged across sleep condition (see Table). With the exception of a control condition subgroup (nocturnal = 8.2h TIB with no nap), the data shown derives from subjects who were randomized to one of the 4.2h TIB nocturnal sleep conditions, which varied in the length of the daily daytime nap TIB (i.e., 0.0 to 2.4h). The mean slopes in the Table serve to illustrate 1) that when 8.2h TIB is provided nocturnally each day, there is no deficit slope for PVT lapses (M=0.000, SD=0.008); 2) as less sleep is provided each day, as in the 4.2h nocturnal+0.0h or 0.4h nap, deficit slopes occur in most subjects (M=0.076 and M=0.150); 3) when 4.2h nocturnal TIB was supplemented daily by a nap TIB between 0.8h and 2.4h, the PVT lapse deficit slopes are intermediate between those found for no nap and those for 8.2h TIB (range from M=0.022 to M=0.045); and 4) the magnitudes of the minimum, maximum and SD values suggests the existence of heterogeneity among subjects in their responses to chronic partial sleep loss challenges.

Table 1

PVT lapses over 10 days of sleep restriction

sleep restriction condition (nocturnal+nap TIB)	n	mean slope across days	sd	min	max
8.2 + 0.0	4	0.000	0.008	-0.01	0.01
4.2 + 2.4	4	0.044	0.093	0.00	0.21
4.2 + 2.0	5	0.022	0.057	-0.02	0.12
4.2 + 1.2	4	0.045	0.079	-0.02	0.16
4.2 + 0.8	5	0.036	0.080	-0.06	0.16
4.2 + 0.4	5	0.150	0.206	0.00	0.49
4.2 + 0.0	5	0.076	0.057	0.01	0.14

Conclusions: The above data suggest that the addition of a prophylactic nap does attenuate neurobehavioral performance deficits during a period of chronic sleep restriction when nap length is at least 0.8h. The surface response model we will generate when the remaining 7 conditions are studied will provide a clear indication of what combinations of nocturnal sleep duration and nap sleep duration afford the "best" return (in terms of performance capability and alertness) relative to the time invested in sleep. Furthermore, future PSG analyses of both nap and anchor sleep will help determine the role of sleep stages in attenuating cumulative neurobehavioral deficits from sleep restriction.

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1864.I

Sleepiness and Car Accidents: Epidemiological Survey on Motorways of Emilia-Romagna and Lombardia (Northern Italy)

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Introduction: Correlation between car accidents and somnolence is widely recognized but very difficult to demonstrate on the road. Epidemiological data based on police 's report in all countries showed very low percentages of sleep related crashes , ranging from 1% to 3%.[1] However Horne and collaborators found indirect evidence of impairment of vigilance in almost 20% of car accidents.[2] Since epidemiological data on Italian motorways are lacking we started collaboration with two Police Departments of Northern Italy in order to collect epidemiological data on prevalence and characteristic of crashes attributed to excessive sleepiness (ES).

Methods: We evaluated all crashes monitored by Police Department of Emilia -Romagna and Lombardia on motorways during 12 consecutive months (November '98-November '99). Before starting the study we trained the policemen on the issue ofsleepiness. At the crash site the policeman administered a two-part questionnaire. Part 1 consisted of detailed information on crash aspects and was always completed. Part 2 investigated driver's behavior and possible cause of ES and was completed only when he was present and accepted to collaborate. The driver possibly responsible for the accident was outlined. We considered 1) reliable "ES crashes" those attributed to falling asleep at the wheel by policeman 2) "possible ES crashes" those fitting the Horne's criteria on the basis of crash characteristics.

Figure 1

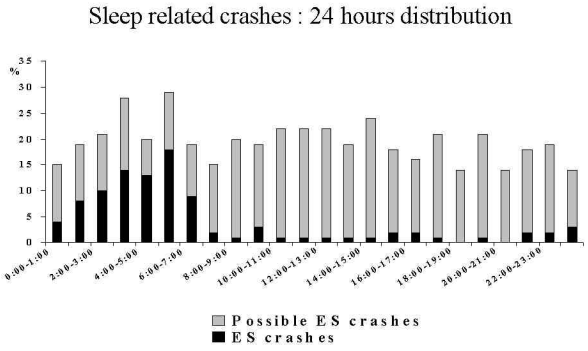
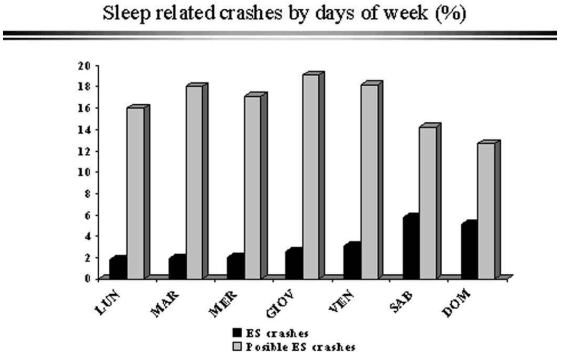


Figure 2



Results: Up to now we examined 7913 vehicle accidents occurred between November '98 and March '99 : 246 (3.1%) were ES crashes and 1278 (16.2%) "possible ES crashes"; altogether 19.3% of accidents could be attributed to somnolence as main cause or contributing factor. Since we have a small preliminary sample, in order to obtain more reliable data we considered only ES crashes for the analysis of sleep-related accident's distinctive features. ES crashes were significantly more common during late night hours (1 AM - 7 AM) with percentages ranging from 7.8 % to 17.8% ($p<0.01$)(Fig. 1).Young subjects with less than 30 yrs were significantly more at risk than older subjects (4.2% vs 2.3%, $p <0.05$)Men had significantly more ES crashes than women (4% vs 2%, $p <0.05$) didOur data demonstrated that it was more common to fall asleep when during on Saturday and Sunday than during weekdays (fig.2). This difference were mainly explained by ES crashes occurring between 1 an 6 AM (16% Saturday, 10 % Sunday, 4.8% Monday, $p<0.01$) rather than during daytime hours (2.3% Saturday, 3.1% Sunday ,1.1 %Monday). Sleep related crashes are more often fatal than other crashes (5.2% vs 2.2 % , $p<0.01$).Seventy four percent of ES crashes involved a single vehicle that typically left roadway. Moreover sleep related accidents occurred more on freeways (4% of total crashes) than in other motor ways (2.6%).

Conclusions: Our data demonstrated that 19.3 % of vehicle accidents can be attributed to sleepiness as main cause or contributing factor. Sleep related crashes were more common in late night hours and were more often involving young men (<30 yrs old) and people driving on late night hours on weekend.ES crashes typically involved only one vehicle leaving the roadway and were more often fatal.These Italian data are perfectly in accordance with those reported in other countries. More information on sleepy drivers is expected by the analysis of part 2 of the questionnaire.

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1637.J

Effects of a Medial Prefrontal Cortex Lesion on a PS Deprivation-Sensitive Version of the Morris Water Maze in the Rat

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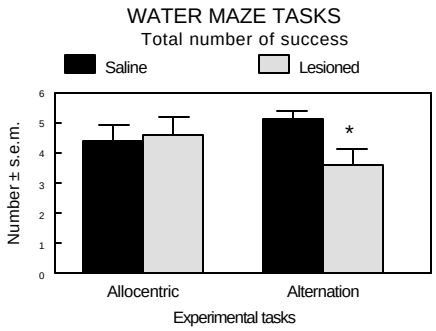
Introduction: We have shown that deprivation of Paradoxical Sleep (PS) for 8 hours impairs learning an alternation task in the Morris Water Maze (WM-alt) while performance on its standard (allocentric) version (WM-allo) does not.[1] Based on previous lesion studies by others,[2,3] we suggested that tasks involving the frontal cortex are more sensitive to short-term PS deprivation than tasks related to hippocampal structures.[1] The aim of the present study was to verify the effect of an excitotoxic lesion of the medial prefrontal cortex (mPFC) on the same two versions of the WM.

Methods: Bilateral lesions of the mPFC were performed in 21 adult rats by injecting 1 µl of ibotenic acid (2 µg/µl) at three anterior-posterior placements over a period of 6 minutes; an equal volume of saline was injected at the same placements in 14 other rats that served as control. Seventeen days later, rats were submitted to one test session, on either one of the two versions of the WM; a test session consisted of six learning trials. In the WM-allo version of the test, rats must rely on external cues to reach the hidden platform while departing from a different quadrant of the pool at every trial. In the WM-alt version, the hidden platform alternates between two quadrants while the rats always starts from the same quadrant. Rats have six trials of 60 seconds maximum to locate the platform. If the platform is found, rats remain on it for 30 seconds; if not found before 60 seconds, they are placed on it by the experimenter and left there for 30 seconds. Seventeen days after surgery, 10 lesioned and 7 saline rats were tested in the WM-allo version and 11 lesioned and 7 saline rats were tested in the WM-alt version. Number of successful attempts to escape onto the platform was compared between the two groups using Mann-Whitney U-tests.

Results: Lesioned and saline rats had the same total number of success on the WM-allo. In the WM-alt however, lesioned rats had significantly less success compared to saline rats.

Figure 1



Conclusions: Like mPFC-lesioned rat, rats deprived of PS show an impairment to learning the WM-alt version while their performance on WM-allo is normal.[1] This supports the hypothesis that frontal tasks are more sensitive to PS deprivation than hippocampal tasks.

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1550.J

Regional Differences in the Dynamics of Slow-Wave Activity in Two Strains of Inbred Mice

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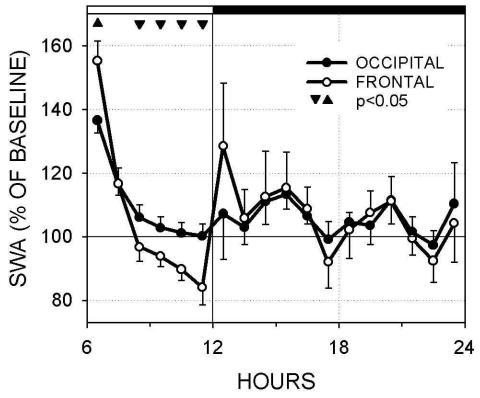
Introduction: It is well established that SWA is a function of the prior history of sleep and wakefulness. It is thought to reflect the homeostatic component of the two-process model of sleep regulation. Krueger and Obál (1993) hypothesized that sleep is a use-dependent local phenome-

non. In humans, local activation of the left somatosensory cortex by vibration of the right, dominant hand resulted in a shift of power in the sleep EEG toward the left hemisphere (Kattler et al. 1994). Recently, Schwierin et al. (1999) showed a larger increase of slow-wave activity (SWA) in NREM sleep after sleep deprivation (SD) in rats in a frontal compared to an occipital derivation. Thus these recent results show that sleep and sleep regulation are not only global phenomena but have local features.

Methods: Adult, male mice of the inbred strains C57BL/6J (n=9) and 129/Ola (n=8) were chronically implanted with three epidural EEG electrodes (right occipital cortex, right frontal cortex and cerebellum) and two EMG electrodes inserted into the neck muscles. A 24-h baseline (BL) recording was followed by 6-h SD. SD started at light onset and was performed with the aim of minimizing stress. Objects of interest were introduced into the cage whenever the mice appeared drowsy and/or slow-waves occurred in the EEG. Recovery was recorded for the remaining part of the 24 h.

Figure 1



Results: Mean integrated power (0.25-25.0 Hz) over the three vigilance states did not differ between the frontal and occipital derivation. Both derivations showed a significant increase in SWA in NREM sleep after SD in both strains. SWA was more prominent in the initial 1-h interval after 6-h SD in the frontal derivation, and showed a faster decline compared to the occipital derivation (Figure). This faster decrease was reflected in the value of the decreasing time constant which was estimated according to the adapted tenets of the two-process model of sleep regulation. The value of the decreasing constant of the frontal derivation was smaller than the one obtained for the occipital derivation indicating a faster decline (occipital: 3.5 (0.4) h; frontal: 1.7 (0.3) h; $p<0.005$). Similar results were obtained in the 129/Ola mice.

Conclusions: The results indicate regional brain differences in the increase of SWA after SD and its subsequent decline during sleep in mice. This suggests regional differences in the dynamics of the homeostatic component of sleep regulation. The observation supports the notion that sleep is not only a global phenomenon but has also local, use-dependent features, as has been shown for humans (Kattler et al., 1994) and rats (Schwierin et al., 1999).

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1539.K1

The Prediction of Suitable Candidates for Split-Night Protocols in OSA Populations

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Introduction: Pulse oximetry (Ox) has been proposed as a potential screening tool for the identification of cases of obstructive sleep apnea (OSA). However, concerns about its relatively low sensitivity or low specificity (depending on the algorithm being used for the interpretation of the Ox), has prompted some researchers to suggest that a higher reliance on split-night protocols represents the most rational use of sleep laboratory resources. Unfortunately, all too often split-night protocols are problematic as they frequently result in patients requiring a second laboratory study (Strollo, 1996). Split nights may not be suitable for all patients, but rather for patients in whom there is reasonable certainty that they will have a positive diagnosis of OSA. The purpose of this study was to identify an algorithm that would enable the identification of patients suitable for split-night protocols.

Table 1

	BMI and NC	BMI, NC, EDS	BMI, NC, Ox	BMI, NC, EDS, Ox
Sensitivity	53	27	52	27
Specificity	76	92	94	97
PV-	54	47	58	49
PV+	76	82	93	93

Methods: The development of the algorithm was based on a retrospective analysis of 172 consecutive polysomnographic studies for diagnostic purposes (112 M, 60F, mean age=48, range=16-83 years). Prior to polysomnography (PSG), all patients completed a Sleep-Wake Questionnaire, and had a consultation with an AASM Board Certified physician. The parameters used to develop the algorithm were based on previous clinical research (Rosenthal et al, 1993, Rosenthal et al, 1997). The following parameters were judged to be predictors of a positive PSG diagnosis of OSA: Body mass index (BMI)>32, neck circumference (NC)>17, a sleepiness (EDS) score on the Sleep-Wake Activity Inventory<50, and overnight oximetry (at the time of the PSG) with an index of >3% desaturation events of >10. The PSG diagnosis of OSA was derived if the respiratory event index (REI) was >10. Using the parameters described above, the sensitivity, specificity, predictive value negative (PV-), and predictive value positive (PV+) were derived for each of the models below.

Results: The results of this study showed overall low sensitivity levels. However, the specificity of 3 out of 4 algorithms was relatively high (see table). Critical to the viability of developing an algorithm to identify those patients best suited for split-night protocols is the positive predictive values of BMI, NC, Ox, and BMI, NC, EDS, Ox models. Interestingly, nocturnal Ox had a specificity of 88% while daytime measures (BMI, NC, EDS) had a specificity of 92.

Conclusions: The results of this study suggest that our algorithm using BMI, NC, and Ox would enable to successfully identify candidates for a split-night protocol. However, its effectiveness needs yet to be evaluated in a controlled prospective trial. The use of at home Ox evaluation, in the context of this proposed model, needs to be implemented to deter-

mine if it proves effective in reducing the number of PSG studies for the detection and treatment of OSA.

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1120.K1

Relationship Between Depressive Symptoms and REM Sleep in Subjects with and without Obstructive Sleep Apnea

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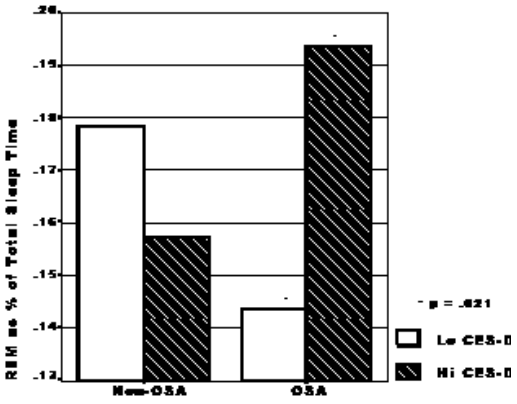
Introduction: This study examined the relationship between depressive symptoms and rapid eye movement (REM) sleep in subjects with and without obstructive sleep apnea (OSA). OSA patients generally experience less REM sleep than normals, likely secondary to sleep fragmentation. Also, several studies have reported increased REM sleep in depressed patients. We wondered if the relationship between depressive symptoms and REM sleep would differ between subjects with and without OSA.

Methods: Subjects (n=107) were recruited by advertising and word of mouth, were between 100 and 150% of ideal body weight and free of major illness other than OSA. Subjects were studied for two nights with polysomnography. REM sleep was calculated as a percentage of total sleep time. OSA was defined as a respiratory disturbance index (RDI) ≥ 15. For OSA subjects (n=68), RDI ranged from 15 to 142 (mean = 51.5) and REM ranged from 1% to 38% (mean = 16%); for Non-OSA subjects (n=39), RDI ranged from 1 to 14 (mean = 5.8) and REM ranged from 0% to 32% (mean = 17%). Subjects completed the Center for Epidemiological Studies-Depression (CES-D) scale and were divided into Hi/Lo groups using a commonly-accepted cut-off score of 16 (Hi CES-D indicates more depressive symptoms). Data were analyzed using a 2-way analysis of variance: OSA/Non-OSA and Hi/Lo CES-D.

Figure 1



Results: OSA and Non-OSA subjects did not differ significantly in terms of CES-D (12.6 vs. 13.7, p=.601) or REM (15.7% vs. 17.2%, p=.334). Using REM as the dependent variable, no significant main effects were found for either OSA or CES-D; however, a significant OSA X CES-D interaction emerged (p=.036). Post-hoc analyses revealed OSA/Hi CES-D subjects experienced more REM than OSA/Lo CES-D subjects (19.3% vs. 14.3%, p=.021). Non-OSA subjects did not differ in terms of REM regardless of CES-D level; Hi CES-D subjects did not differ in terms of REM regardless of apnea diagnosis; and, Lo CES-D subjects did not differ in terms of REM regardless of apnea diagnosis.

Conclusions: Depressive symptoms help explain variations in REM sleep among OSA but not Non-OSA subjects: OSA subjects who reported high levels of depressive symptoms spent 35% more time in REM sleep than OSA subjects who reported low levels of depressive symptoms. There is a high degree of comorbidity between depression and OSA. Our findings did not replicate previous reports of REM differences between OSA and Non-OSA subjects and between depressed and non-depressed subjects. However, the significant interaction between apnea diagnosis and level of depressive symptoms suggests that depression may be an important factor in understanding variations in sleep architecture among OSA patients.

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1750.K1

Rapid Eye Movement-Specific Obstructive Sleep Apnea: A Demographically and Clinically Distinct Subset of Patients with Sleep-Disordered Breathing

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Introduction: Obstructive Sleep Apnea (OSA) confined to REM Sleep (REM-specific OSA) has been associated with excessive daytime somnolence (EDS).[1] To define the demographic, clinical and polysomnographic profile of these patients, we compared a group of patients with REM-specific OSA to patients with 'conventional' OSA.

Methods: We reviewed the records of patients referred for polysomnography during the 4-year period from September 1995 to September 1999. Using indices derived in a previous study,[1] we randomly selected a group of 40 patients who fulfilled the criteria of respiratory disturbance index (RDI)- Sleep<10 and REM-RDI > 15. The comparison group consisted of 40 patients with OSA, defined as RDI-Sleep>10. Univariate T-test and Chi-square test analyses were used to compare the two groups.

Results: Significant gender differences were observed. The percentage of females in the study group with REM-specific OSA was 42.5% in contrast to 17% in the comparison group (P=0.01). The degree of oropharyngeal crowding was significantly less in the study group (P = 0.01). The ratio of respiratory arousal index (RAI)-REM/RAI-Sleep was significantly higher in the study group (P=0.0001). The groups were significantly different with respect to RDI-Sleep (P<0.001) and RDI-REM (P=0.01) and in the RAI for REM Sleep (P=0.001) and Total Sleep (P=0.001), all of which were greater in the OSA group. There were trends towards younger patients (P=0.056), more daytime somnolence (P=0.064), less snoring (P=0.06) and reduced incidence of hypertension (P=0.054) in the study group. Other relevant parameters compared included BMI, neck size, REM duration, REM latency, sleep efficiency, sleep latency, and total sleep time; among these, there were no significant inter-group differences. Of note was that the patients in the study group had been variously diagnosed with primary snoring (7), idiopathic hypersomnolence (3), and insufficient sleep syndrome (2) and had been treated accordingly. Two patients underwent CPAP titrations and responded well.

Conclusions: Patients with REM-specific OSA comprise a distinct sub-

set of patients with sleep-disordered breathing. Compared to patients with OSA, in whom a striking male predominance has typically been reported,[2] patients in our study with REM-specific OSA had a significantly greater chance of being female. In addition, our results indicate trends for these patients to be younger, to be more somnolent subjectively and to be less likely to be hypertensive. There is significantly less oropharyngeal crowding in this group of patients.To our knowledge, this is the first study to characterize REM-specific OSA as an entity with distinct demographic and clinical features. We propose that this diagnosis be considered in the differential diagnosis of patients with idiopathic hypersomnolence and primary snoring. Further studies to determine the optimal management of patients with REM-specific OSA are warranted.

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1784.K1

MSLT Characteristics in Patients with Sleep-Related Breathing Disorders

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Introduction: The presence of a short mean sleep latency (less than 5 minutes), 2 sleep-onset REM (SOREM) naps, together with pertinent clinical features have aided in the diagnosis of patients with narcolepsy. The occurrence of SOREM(s) on mean sleep latency testing (MSLT) of patients with severe obstructive sleep apnoea (OSA) have also been documented. The mean sleep latency, occurrence and number of SOREM(s) in mild to moderate OSA and other sleep-related breathing disorders is less well defined.

Methods: To investigate the MSLT characteristics in patients with OSA, sleep hypopnoea (SH), upper airways resistance syndrome (UARS), primary snoring (PS) and to assess the relationships of these characteristics with their overnight polysomnography (PSG) findings.MSLT reports between 1 January 1999 to 25 November 1999 were reviewed. Only reports with an overnight PSG the night before and showing sleep-related breathing disorders were selected. Patients with a prior clinical diagnosis of narcolepsy were excluded. MSLT results of mean sleep latency, occurrence and number of naps with SOREM were noted and correlated with patient and PSG data. Chi-squared tests and independent t-tests were utilised to examine for significance of correlation between characteristics.

Results: 68 patients (35 OSA, 8 UARS, 6 SH, 19 PS) had MSLT and PSG records fulfilling selection. There were 33 (48.5%) males and 35 (51.5%) females with a mean age of 47 years (15-91). The mean body mass index (BMI) was 29.8 (19.5-48.5). Comparing patient characteristics across diagnosis groups (OSA vs SH/UARS vs PS), patients with OSA had a significantly greater BMI, and there were significantly more males than females in this diagnostic category. The Epworth Sleepiness Scale (ESS) and mean sleep latency on MSLT did not differ between these diagnostic groups. The sleep architecture on PSG did not differ significantly between these patients though patients with OSA tended to have a poorer sleep efficiency. The mean sleep latency on MSLT did not have any significant correlations with patient characteristics nor PSG data. 16 patients had SOREM on MSLT, 9 only in one nap and 7 (4 OSA, 1 UARS, 1 SH, 1 PS on previous night PSG) in two or more naps. Of the latter patients, 5 had a mean sleep latency on MSLT of less than 5 minutes while the other 2, between 5-7 minutes. These 7 patients all reported excessive daytime somnolence and while 2 reported sleep paralysis, 1 other reported hypnagogic hallucinations. The presence of SOREM on MSLT did correlate with a longer sleep latency on PSG (p=0.004) though it was present in all diagnostic groups. Age (more than 50 years) and a mean sleep latency of less than 8 minutes on MSLT correlated positively with the occurrence of more than one nap with SOREM on MSLT. The number of naps with SOREM did not significantly differ across diagnostic groups. No significant correlation was found between the sleep architecture on PSG and the number of SOREM naps in the ensuing MSLT.

Conclusions: The presence of naps with SOREM on the MSLT correlated with a longer sleep latency on the previous night PSG and the number of naps with SOREM correlated with increasing patient age and a shorter mean sleep latency on MSLT.

1834.K1

Epworth Sleepiness Scale Lability Before and After Office Evaluation, and Correlation to Polysomnography Results

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Introduction: The Epworth Sleepiness Scale (E.S.S.) is a commonly used tool for assessing subjective somnolence in patients presenting for a sleep disorder evaluation. This value was shown to have correlation with the apnea-hypopnea(AFH) index in patients,[1] and there was high test-retest stability in normal medical students over several months.[2] We sought to determine if patients' E.S.S. values would change before compared to after an office evaluation for sleep disordered breathing, and if so, which value would correlate better with polysomnography results.

Methods: One hundred consecutive patients presenting for evaluation of sleep disordered breathing were given the E.S.S. prior to the office interview, and again upon presentation to the Sleep Lab for polysomnography one to three weeks later. The office evaluation was performed by one of two physicians with extensive experience in sleep disordered breathing. Patients were given printed literature to review as well as detailed explanations about the nature of sleep disordered breathing during the course of the office evaluation. E.S.S. scores before and after the office visit were compared by Student's *t* test and Pearson correlation coefficients were generated for the AHI, as well as the arousal index obtained on 12 channel polysomnography in the Sleep Laboratory. Respiratory events and arousals were scored by ASDA guidelines with the exception that 2% desaturation was the threshhold for defining respiratory events without arousal.

Table 1

	E.S.S. Office	E.S.S. Sleep Lab	AHI	Arousal Index
E.S.S. Office	1.000	.75	.12	.22
Sig. (2-tailed)		.000	.22	.03
E.S.S. Sleep Lab	.753	1.000	.13	.21
Sig. (2-tailed)	.000		.19	.04

Results: The mean E.S.S. score rose from 12.6 to 13.4(ns) after the office visit with a standard deviation of 3.2. Age and sex did not affect the degree of variability or the degree of correlation to polysomnography results. Thirty-six percent of patients changed their score by ≥4 with a mean increase in score value of 1.7(p=0.04.) No patients changed their score from <10 to >15 or vice versa. Correlation between AHI or arousal index did not differ between the Office and the Sleep Lab score for the entire group or the subgroup with a difference in score of ≥4. A matrix of the Pearson correlation coefficients between E.S.S. scores and polysomnography results for the entire group is displayed below.

Conclusions: Patient E.S.S. values before and after an office visit for sleep disordered breathing show considerably less test retest stability than in previously described normals. 36% of our patients versus 4% of previously reported normal medical students changed their score by ≥4. However, no patients changed their scores from normal to grossly somnolent or vice versa. In patients that changed their score by ≥4 there was a significant trend toward raising of score suggesting heightened awareness of sleepiness, but there was no improvement in correlation to polysomnography findings as a result of education and reflection after the office visit. In general, our patients' E.S.S. values had much lower correlation to AHI than in previously published studies. There was better correlation with arousal index than with AHI.

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1714.K1

Recovery of Executive Functions in OSAS patients After CPAP Treatment.

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Introduction: Executive functions have been shown to be affected in obstructive sleep apnea syndrome (OSAS).[1] Although some studies report that these functions remain altered after treatment with continuous positive airway pressure (CPAP),[2] these findings are generally based on few measures and heterogeneous groups. In fact, in most studies, only a few measures of executive functions remain altered following CPAP treatment. To further document the recovery of executive functions, OSAS patients were divided into 2 subgroups according to the presence of an initial adaptation deficit on the mirror tracing (MTR) task. This criterion was chosen since it indicates a frontal lobe dysfunction.[3]

Methods: Ten OSAS patients (5 with and 5 without the adaptation deficit on the MTR task) were evaluated before and 6 to 8 months after CPAP treatment. Mean age was 49 and 41 yrs, respectively. Five normal subjects (mean age: 45 yrs) were evaluated at the same interval to control for learning effects. Sleep and nocturnal respiratory variables were recorded and analysed both pre- and post-treatment according to standard methods. The neuropsychological evaluation included the following tests sensitive to frontal lobe dysfunction: WCST, Trail Making Test, Mazes (WISC), Cancellation task, copy of the Rey figure, Picture arrangement (WAIS-R), Written Letter Fluency and the D2 test plus two standard tests of procedural memory (mirror tracing and rotary-pursuit).

Results: No significant changes were noted in normal subjects suggesting the lack of learning effects on most measures of executive functions. Similarly, in the OSAS group without adaptation deficits, most pre-treatment performances were normal and remained the same after treatment except on the picture arrangement; the deficit noted before treatment was no longer present. By contrast, in the OSAS group with adaptation deficits, performance on the picture arrangement remained deficient following CPAP. This group's performance remained deficient on some aspects of the D2 task, the WCST, copy of the Rey complex figure, Trail B, and on the Maze Test. On the other hand, post-treatment improvements were noted on a cancellation task (fewer omissions) and on Trail A (fewer errors) suggesting normalization of some attentional functions. Although a MTR adaptation deficit without subsequent skill learning deficit was present in a subgroup of OSAS patients, post-treatment performance was indistinguishable from that of the other two groups. This suggests normal preservation of skill over time.

Conclusions: Although some aspects of frontal dysfunction (i.e. attention) normalize after treatment, the impact of such dysfunctions on executive functioning appears more important than what had been previously reported and is evident across a greater number of tasks. These results stress the importance of considering patients' pre-treatment neuropsychological functioning in the interpretation of post-treatment changes.

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1794.K1

Subjective Changes in Mood and Daytime Sleepiness in Apnea Patients Treated with Nasal CPAP

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Introduction: Sleep apnea is associated with daytime sleepiness and psychological difficulties including mood and cognitive deficits. Studies investigating the effect of CPAP on mood and sleepiness are inconclusive. Some suggest a placebo effect (Yu et al 1999), otheres no effect (Borak et al 1996), while others find improvement (Engleman et al 1993). Studies are further complicated by disagreement in the definition of compliance. Our investigation attempts to relate changes in mood and daytime sleepiness with specific patterns of CPAP use.

Methods: Twenty-five sleep apnea patients (age=47.8±8.9 years; 20 female, 5 male) completed mood and sleepiness inventories prior to an following a thirty day period of CPAP therapy. Mood was assessed using the Profile of Mood States (POMS) and sleepiness using the Epworth Sleepiness Scale. CPAP data was downloaded via computer from the patient's CPAP device using manufacturer supplied software.

Results: Patients used CPAP an average of 76% of all study nights (range=22% to 100%) with nightly use averaging 4.2±2.5 hours. Fifty-two percent used CPAP four or more hours nightly; 40% used CPAP five or more hours nightly; 24% used CPAP six or more hours nightly. Followup evaluation found decreased sleepiness scores, $t(23)=4.5, p=.000$, decreased POMS measures of 'fatigue-inertia', $t(24)=2.5, p=.02$, and increased POMS measures of 'vigor-activity', $t(24)=-4.9, p=.000$. For the group as a whole, the magnitide of the sleepiness and mood changes was unrelated to compliance variables including percentage of nights with use and average duration of nightly use. Only when compliance was defined as six or more hours of nightly use did the change in sleepiness scores approach significance when compliant and noncompliant patients were compared, $t(22)=-2.2, p=.039$.

Conclusions: Changes in sleepiness and mood were seen in sleep apnea patients following treatment with CPAP. For the whole group, the magnitude of these changes, however, was unrealted to frequency and duration of CPAP use. Studies have typicallydefined compliance as CPAP use exceeding four hours of nightly use. Using this definition, compliant and noncompliant patients in our study improved equally, suggesting that four hours may represent insufficient use for correction of mood problems and sleepiness. Only when compliance is defined as six or

more hours of nightly use does a relationship between improvement in sleepiness and compliance emerge. That six hours of nightly CPAP use may be necessary to significantly improve subjective sleepiness may account for some of the difficulty encountered with CPAP compliance, and the discrepant findings in this area.

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1389.K1

Improvements in OSA Outcomes Relative to Hours of Nightly CPAP Use

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Introduction: Previous research suggests that the frequency of CPAP use affects daytime sleepiness and performance.[1] However, it remains unclear whether the nightly duration of CPAP contributes to treatment outcomes. Therefore, we investigated whether nightly duration of CPAP affected the outcomes of self-reported daytime sleepiness and functional status. In addition to the preliminary findings presented here, analysis is currently underway to examine this issue in other outcomes including objective sleepiness (MSLT) and neurobehavioral performance (Psychomotor Vigilance Test).

Methods: Data from the first 103 subjects (mean RDI=57.2, 87% males) from a target sample for this study of 300 subjects were included in this analysis. Prior to and 3 mo. following CPAP treatment, subjects from 7 sites completed a day of testing that included the Epworth Sleepiness Scale (ESS) and the Functional Outcomes of Sleep Questionnaire (FOSQ). Nightly duration of CPAP use was documented by a microprocessor that detected delivery of therapeutic pressure. Subjects were allocated to one of three groups based on their average nightly CPAP use for all days of monitored use (M = 102 days), including skipped days of treatment (0 hrs.): < 2 hrs., 2-5 hrs., >5 hrs.

Table 1. Change in Outcomes Relative to CPAP Use

Outcome	CPAP Use	Pre-Tx Mean (S.D.)	Post-Tx Mean (S.D.)	Change (S.D.)	Effect Size
ESS					
(n=14)	< 2 hr.	16.53(4.31)	12.88(6.60)	-3.36(6.55)	-0.51
(n=29)	2 – <5 hr.	15.56(5.18)	9.06(5.17)	-6.21(5.87)	-1.06
(n=41)	≥ 5 hr.	14.16(4.73)	7.00(4.54)	-7.09(5.34)	-1.33
FOSQ					
(n=15)	< 2 hr.	13.65(2.98)	16.25(2.05)	2.47(3.75)	0.66
(n=35)	2 – <5 hr.	14.30(3.20)	17.33(2.59)	3.03(3.39)	0.89
(n=50)	≥ 5 hr.	15.24(2.63)	18.11(2.19)	2.94(2.74)	1.07

Results: Higher scores on the FOSQ indicate better function and lower scores on the ESS indicate less sleepiness. As indicated in the table below, there was a consistent trend for greater improvement with longer duration of CPAP use, especially >5 hrs. The apparent dose response produced higher post-treatment responses and greater magnitude of change (effect size). For all subjects collectively, there was a significant, but modest, relationship between mean CPAP use and post-treatment outcome response: Epworth (n = 91, r = 0.36, p = 0.0005) and FOSQ (n = 103, r = 0.34, p = 0.0005).

Conclusions: Optimal benefit occurs with >5 hrs. of CPAP use. However, results also suggest that these improvements may not be simply a function of average nightly use and the relative contributions of other factors, such as respiratory disturbance index and body mass index will be the aim of future analyses.

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1188.K1

Relationship Satisfaction and Nasal Continuous Positive Airways Pressure (CPAP) Therapy for Obstructive Sleep Apnea (OSA): an Investigation of Effects Upon Compliance and Treatment Outcome

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Introduction: Nasal CPAP is an effective treatment for OSA when adhered to, however, up to 30% drop out and compliance is often below therapeutic levels. Yet the physical characteristics of CPAP in relation to compliance appear to have limited predictive power. The wider literature suggests the importance of the marital unit (eg. dialysis, diabetes), but in spite of the impact of OSA and of CPAP upon the partner, few studies have investigated relationship factors. Cartwright and Knight (1987) first described untreated OSA as a cause of friction, and Kiely and McNicholas (1997) reported a cross-sectional, retrospective study where partners experienced improvement in marital satisfaction. The present study set out firstly, to investigate the relationship between pre-treatment marital satisfaction and subsequent compliance with CPAP; and secondly, to investigate treatment-related changes in marital satisfaction.

Methods: Patients who had undergone diagnostic polysomnography to confirm OSA at the Edinburgh Sleep Laboratory and living with a partner were eligible to participate. Of 104 patients, 44 (34 men, 10 women; mean age 49 yr.) agreed to participate (38%). A further 25 (19 men, 6 women; mean age 51 yr.) [out of 45 (55%)] who had to wait a number of months for therapy to commence served as controls. Measures included the ENRICH Marital Satisfaction Scale, 36-Item Short Form Health Survey Questionnaire, Functional Outcomes of Sleep Questionnaire and Epworth Sleepiness Scale scored at baseline and 3 months into CPAP therapy, when compliance data were retrieved from the machines.

Results: Mean compliance was 4.41 hr. per night. Spearman correlations were computed to examine the association between measures at baseline and compliance within the CPAP group. None achieved statistical significance. In particular, neither patient (r = .059; p = .704), nor partner (r = .190; p = .217) marital satisfaction was correlated with compliance. However, compliance was associated with change scores (baseline to 3

months into treatment; see Table 1). Increases in partner marital satisfaction were associated with higher compliance (r = .307;p = .043) and compliance was associated with improvement in the mental component of the SF-36, and with reduction in ESS scores. Factorial ANOVA was applied to consider within (time) and between (CPAP, control) group effects upon marital satisfaction, and other variables (Table 2). Interaction effects confirmed that patients receiving CPAP reported greater improvements in marital satisfaction (p < .001), as did their partners (p < .01). Marital satisfaction in controls tended to deteriorate. CPAP patients also improved significantly compared with controls across the measures of health outcomes. (Insert tables here)

Table 1

	AHI	Compliance	Patient MS	Partner MS	SF 36 Physical	SF 36 Mental	FOSQ	ESS
AHI		.068	-.084	.025	-.327	-.071	-.213	-.464
		.662	**.586**	**.873**	**.030**	**.649**	**.165**	**.002**
Compliance			.254	.307	.192	.484	.570	-.464
			.097	**.043**	**.211**	**.001**	**.000**	**.002**
Patient MS				.543	.352	.294	.382	-.399
				.000	**.019**	**.053**	**.011**	**.007**
Partner MS					.429	.362	.511	-.617
					.004	**.016**	**.000**	**.000**
SF 36 Physical						.259	.473	-.565
						.090	**.001**	**.000**
SF 36 Mental							.699	-.578
							.000	**.000**
FOSQ								-.754
								.000

Spearman Rank Order Correlations between Compliance, AHI and Change Scores (Baseline to Follow-up) on Outcome Measures for CPAP Patients. (n=44)
AHI = Apnea/Hypopnea Index; MS = Marital Satisfaction; FOSQ = Functional Outcomes of Sleep Questionnaire
p values are shown in bold.

Table 2

Variable	cpap n=44		control n=25		group	time	group x time
	Baseline	Follow-up	Baseline	Follow-up	F	F	F
ENRICH Patient marital satisfaction	56.88 (13.18)	61.94 (15.92)	54.71 (15.62)	46.53 (17.97)	6.30	.89	**16.14*** **
ENRICH Partner marital satisfaction	58.18 (13.69)	60.29 (16.51)	53.78 (18.33)	46.75 (18.41)	5.38	3.17	**10.75***
ENRICH Positive couple agreement	68.86 (18.32)	72.50 (15.71)	63.20 (22.86)	52.00 (27.08)	**8.43***	2.58	**9.93***
SF 36 Physical Composite	41.72 (9.86)	48.34 (9.97)	38.59 (8.83)	36.05 (8.46)	**13.40*** **	3.45	**17.38*** **
SF 36 Mental Composite	42.09 (8.44)	50.83 (9.12)	41.06 (9.67)	36.43 (10.51)	**14.01*** **	3.67	**38.78*** **
ESS	14.61 (4.02)	8.18 (5.21)	15.40 (5.03)	16.27 (4.04)	**19.17*** **	**24.59*** **	**42.49*** **
FOSQ Summary score	9.50 (2.16)	12.95 (2.45)	9.63 (2.94)	8.80 (2.88)	**14.18*** **	**14.02*** **	**37.39*** **

Outcome Measures: Means (standard deviations) and Results of Factorial *ANOVA* for CPAP Patients and Controls.
Significant scores are shown in italics and bold
* p<.01
** p<.001
*** p<.001

Conclusions: Multivariate analyses using large samples are required to further investigate relationship factors in CPAP compliance and outcome. Nevertheless, this preliminary study suggests that the marital dyad may be of considerable importance in maximising the treatment plan.

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1125.K1

Treating Sleep-disordered Breathing: A Longitudinal Analysis of Patient Characteristics and Positive Airway Pressure compliance

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Introduction: The use of positive airway pressure (PAP) devices remains one of the most common and effective treatments for sleep-disordered breathing. However, many studies have described relatively poor compliance with this treatment. In addition, few studies have provided identifiable predictors for poor compliance or suggested successful interventions for patients at high risk for treatment failure. A cohort of patients identified as having sleep-disordered breathing and treated with PAP devices is described. Pre-diagnosis clinical features, sleep study findings, and treatment compliance is described.

Methods: Patients identified as having sleep-disordered breathing and prescribed a positive airway pressure device were retrospectively reviewed. Analysis of our standard health intake form including the Epworth, Beck, and SF-36 questionnaires was performed. Sleep study characteristics along with self-report sleep quality immediately post-PAP titration was also reviewed. Post-treatment follow-up included multiple phone contact along with providing a free multidisciplinary evening clinic involving medical equipment providers, respiratory and sleep technicians, a nurse practitioner, psychologist, neurologist, and pulmonologist. A post-treatment self-report symptom survey and SF-36 questionnaire was reviewed. Screening for PAP side effects and PAP compliance downloading was performed in clinic. Home PAP downloading was also performed in a small group of patients unable or unwilling to return to clinic. Patients presenting to clinic without downloadable compliance PAP devices or who did not return for follow-up served as a control population for demographic and sleep study characteristics.

Results: 195 patients were included in this study with 135 patients available for PAP device compliance analysis. A high prevalence of pre-treatment symptoms (91.4% of patients had daytime sleepiness, 64.6% of patients had witnessed respiratory pauses) along with an elevated apnea/hypopnea index (47.6) support a population with significant disease. The majority of patients reported improvement of daytime sleepiness (76.7%) and more refreshing sleep (75.3%) post-treatment. Reported versus measured use of PAP treatment was consistently different over time (6.2 hours of use per day reported compared to 4.8 hours per day measured at month 3) but did loosely correlate (r= 0.441, Spearman correlation). Compliance with treatment as defined as average daily PAP device use greater than or equal to 4 hours remained consistent over a six month follow-up period, ranging from 65-71% of patients. The free evening clinic significantly improved average daily PAP use (4.5 hours pre-clinic vs. 6.2 hours post-clinic, p=.019, t-test). No single patient characteristic was able to predict compliance with treatment. However, PAP device use at week one significantly correlated with use at month one, three and six (r= 0.912, 0.704, and 0.604 respectively, Pearson correlation).

Conclusions: Despite extensive patient profiling, predicting PAP use remains challenging. However, patient PAP use at week one was highly predictive of future device usage suggesting that patients with poor usage in week one may benefit from more aggressive intervention. Reported treatment compliance is consistently overestimated but may correlate with measured compliance. The use of a free evening clinic (possibly by increasing specialized health care accessibility) can enhance patient usage of PAP devices and early intervention of treatment difficulties may allow for a higher long-term compliance rate.

1160.K1

UPPP/LAUP: Indicators for Treatment Success or Failure

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Introduction: Surgical treatment for sleep disordered breathing remains controversial. Success rates, defined as a 50% reduction in apnea + hypopnea index (A+HI) pre- to postoperatively, are generally described

as being approximately 40% for Uvulopalatophyrangoplasty (UPPP) and Laser-Assisted Uvuloplasty (LAUP).[1] Studies to date have not taken into account the more subtle inspiratory associated arousals typically seen in UARS.[2] Moreover, the effect of impaired neuromuscular control, as evidenced by position exacerbated sleep disordered breathing, has not been evaluated as an indicator for success or failure.

Methods: We report 25 patients (23 male, 2 female) who had either UPPP (n=16) or LAUP (n=9) done by various ENT surgeons in central Ohio. All have had preoperative and postoperative nocturnal polysomnogram (NPSG), and a lateral cephalometric x-ray. All NPSG's (aside from four preoperative studies) were done at Ohio Sleep Medicine Institute and all cephalometric analyses were done at Dublin Oral and Facial Surgery Inc. Standardized sleep scoring was performed on all patients. Patients had their postoperative NPSG re-scored to evaluate their inspiratory related arousals or their Respiratory Arousal Index (RAI).[3]

Results: Mean age was 44.9yrs (± 11.9), and mean postoperative body mass index (BMI) 33.9kg/m2 (± 7.4). For the entire group, there was no significant change preoperatively to postoperatively in body mass index (BMI), A+HI, and sleep stage data. Success criterion of a 50% improvement in A+HI indicates that 10 patients, or 40%, achieved "success" (A+HI range = 0.0-31.1). However, two of these ten "success" patients still had an A+HI>25 and six of the remaining eight "success" patients had postoperative inspiratory related arousals or Respiratory Arousal Index (RAI) over 20 (range 23.9-56.0). Using our more strict criteria of a RAI<20, four patients appear to be success cases. However, positional sleep disordered breathing further complicates the results, if sufficient sleep time is spent in the supine position. For instance, one of the four apparent success patients (RAI<20) had a severe position effect for breathing disturbances with a supine A+HI of 46.7 compared to 6.2 laterally. Only three patients out of twenty-five (12%) achieved a postoperative RAI<20/hr and did not have a significant breathing problem in the supine position. These patients were obese (mean BMI=36.2kg/m2, range 28-44), had a normal posterior airway space (mean PAS=13.3, range 11-15), and did not present with supine position exacerbated sleep disordered breathing. Two of the three patients had tonsillectomies as children and one while undergoing UPPP. Two patients had bilateral turbinectomy to alleviate nasal obstruction.

Conclusions: Criteria evaluating inspiratory and snore related arousals (RAI) are recommended to determine success in UPPP/LAUP. In many cases, patients with OSAS are converted diagnostically to UARS following surgical intervention. Surgical interventions are more likely to fail in patients with supine position exacerbated sleep disordered breathing, as this is an indicator of increased upper airway collapsibility and, by inference, impaired neuromuscular control of upper airway muscles in sleep. These results also indicate that a normal posterior airway space cephalometrically, and not the patients body mass index, plays a more critical role in predicting surgical success or failure. Interestingly, despite treatment for their snoring, two of our three success patients continued to complain of hypersomnolence due to the co-existence of narcolepsy, which we believe to be under recognized in patients with UARS and OSAS.

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1159.K1

Simultaneous Uvulopalatopharyngoplasty (UPPP) and Base-of-Tongue (BOT) Radiofrequency Ablation (Somnoplasty) for the Treatment of Obstructive Sleep Apnea (OSA)

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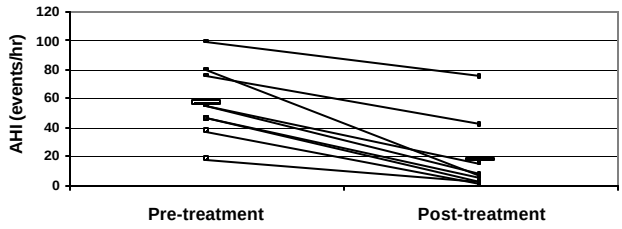
Introduction: Palatal surgery procedures leave the majority of OSA patients inadequately treated. Reports of the efficacy of BOT radiofrequency ablation, somnoplasty, in OSA have been limited to small numbers of patients who had previously undergone palatal procedures (Powell et al 1999). We have prospectively enrolled 35 patients dissatisfied with nasal continuous positive airway pressure (CPAP) in a protocol utilizing simultaneous UPPP and BOT somnoplasty under general anesthesia.

Methods: To date, 35 patients with an apnea-hypopnea index (AHI) greater than 10/hour who expressed dissatisfaction with CPAP have undergone simultaneous UPPP and BOT radiofrequency ablation under general anesthesia. As our confidence in the safety of the procedure has grown, we now initially administer a total of 4,000 joules of energy in 4 lesions. The patients are monitored in the hospital overnight utilizing nasal CPAP for airway protection. Four to 6 weeks later, BOT somnoplasty is repeated with an additional 4,000 joules of energy divided into 4 lesions. Follow-up sleep studies are obtained 2 months later.

Figure 1



Results: Nine patients have completed the protocol and returned for follow-up sleep study. Their body mass index (BMI) ranged from 25 to 41 with a mean of 31.8. Seven of the 9 were treated successfully with a marked reduction in AHI. The mean Epworth Sleepiness Scale (ESS) in the 9 patients dropped from 12.2 to 4.7 (p=<.01). Interestingly, loud snoring persisted in 2 of the 7. Three patients experienced minor superficial tongue ulcerations with infection that responded to oral antibiotics. The remaining 26 patients have undergone the initial surgery, but have not yet completed the protocol. The pre- and post-treatment AHI are shown below.

Conclusions: Simultaneous UPPP and BOT radiofrequency ablation can be performed safely with an acceptable success rate at short-term follow-up. This protocol allows 8,000 joules to be delivered in just two treatment sessions. Post-operative fiberoptic examination in the 2 patients that failed the treatment suggests that persistent lateral pharyngeal wall obstruction may explain the result.

References:
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1853.K1

The Outcome of Patients with Obstructive Sleep Apnea After Gastric Bypass Surgery

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Introduction: There is a strong correlation between a high BMI and the presence of the Obstructive Sleep Apnea Syndrome (OSA). There is also documented evidence that the severity of symptoms improve with weight reduction. However, there have been no studies to date that describe the effectiveness of Roux-en-Y gastric bypass reduction used to treat severe obesity and its impact on the Obstructive Sleep Apnea Syndrome. Therefore, we hypothesized that Roux-en-Y gastric by-pass surgery would have a positive effect on OSA symptoms.

Methods: We reviewed data on severely obese patients with documented OSA and on CPAP or BIPAP therapy who underwent Roux-en-Y gastric by-pass surgery as a treatment of their obesity at Staten Island University Hospital between January 1997 and February 1999. They were then asked to return to the Staten Island University Hospital Sleep Apnea Center for follow-up nocturnal polysomnography and CPAP titration. Comparison data were gathered on the following pre and post surgery variables: Height, Weight, BMI, AHI, and CPAP/BIPAP pressures. We utilized the paired Student t-test for statistical significance. A p value of < 0.05 was considered as statistical significant.

Figure 1

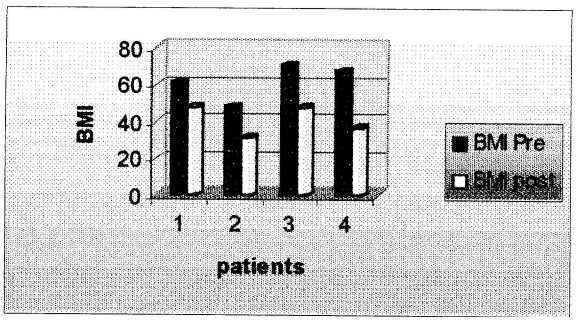
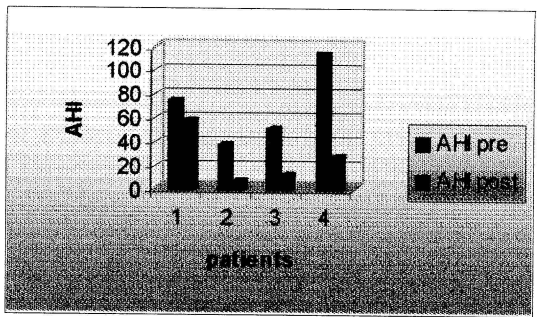


Figure 2



Results: A total of thirty-one patients were enrolled in the study. To date, we have completed data on four. Patients who underwent Roux-en-Y gastric by-pass surgery had a mean reduction in BMI of 20.5 ± 7.1 (Mean BMI pre surgery = 61.25 ± 10.2 vs. BMI post-surgery = 40.75 ± 8.18; p = 0.01). This reduction in BMI was associated with a reduction in AHI (mean reduction = 43.0 ± 30.73; mean AHI pre-surgery = 68.25 ± 33.34 vs. mean AIR post-surgery = 25.25 ± 22.76, p = 0.07; Figure 1) and a reduction in CPAP pressures required for treatment (mean reduction = 10.5 ± 5.06; mean CPAP pressure pre-surgery = 17.25 ± 4.99 vs. mean CPAP pressure post-surgery = 6.75 ± 4.5; p = 0.02; Figure 2).

Conclusions: All patients who underwent Roux-en-Y gastric by-pass surgery for treatment of severe obesity had a significant reduction in BMI. All of them also had a significant reduction in CPAP pressures required to treat OSA; one actually no longer required CPAP after surgery. Our data also shows that there is a non-statistically significant trend towards a reduction of AHI after surgery. As we examine more data, we expect this reduction to become statistically significant. We conclude that Roux-en-Y gastric by-pass surgery is not only effective in the treatment of obesity but when used in obese patients who also have the Obstructive Sleep Apnea Syndrome, it can markedly improve the severity of this syndrome.

1491.K1

Obstructive Sleep Apnea Syndrome and Perioperative Cardiovascular Complications

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Introduction: A surgical procedure is often proposed in treatment of severe obstructive sleep apnea syndromes (OSAS). However, cardiovascular complications (CC) are specially feared during the perioperative period.[1] The aim of this study was to evaluate retrospectively the frequency of CC during the first 48 postoperative hours.

Methods: Fifty five consecutively operated patients with severe OSAS under general anesthesia were analyzed in a retrospective study. Group characteristics were a mean age of 48 ± 9 years, a body mass index of 29 ± 5 kg/m^2 and a mean respiratory disturbance index of 58 ± 15; surgical procedures included uvulopalatopharyngoplasty (n=18; 33 %) or complex maxillofacial procedures (n=37; 67 %). Eighteen patients presented a preoperative systemic hypertension and 12 patients had preoperative clinical or electric symptoms of angina. Thirty nine patients were treated with preoperative application of continuous positive airway pressure. In 80 % patients endotracheal tubes were removed in the post anesthetic care unit (PACU) after few hours of sedation and appropriate analgesia. Immediate postoperative CC was defined as follows: chest pain, new Q wave or ST-T depression longer than 48 hours on daily EKG with elevated cardiac troponin I level, cardiac failure, pulmonary oedema, pulmonary embolism, stroke or cardiac death.

Results: Fifty four patients (98,2 %) did not develop any CC during the first 48 postoperative hours. Moreover the only patient who presented a stroke with herniplegia (thrombosis of the carotid artery) had no preoperative hypertension, no coronary disease and presented no intraoperative CC.

Conclusions: Under postoperative careful supervision in the PACU, we report a very weak rate of CC (< 2 %) among patients operated for severe OSAS under general anesthesia. A prospective study is currently under way to confirm these conclusions, a recent french prospective study showed similar outcome in early postoperative period.[2]

References:
(1) Riley RW, Powell NB, Guilleminault C, Pelayo R, Troell Rj, Li KK. Obstructive sleep apnea surgery: risk management and complications. Otolaryngol. Head Neck Surg. 17:648-52,1997.
(2) Rey S, Lavagne P, Bettega G, Jacquot C, Payen JF. Suites op6ratoires imm6diates dans la chirurgie du syndrome d'apn6es du sommeil. Anal. Franc. Anesth. R6an. 17:R513, 1069,1998.

1829.K1

Efficacy of a Therapeutic Pillow for Snoring and Obstructive Sleep Apnea Treatment

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Introduction: The important influence of body position during sleep on snoring as well as obstructive sleep apnea syndrome is well described in the medical literature and popular press. A wide range of treatments for both have emerged, especially in the last 10 to 20 years. With the extraordinarily high prevalence of both, the need for a simple yet effective method for management is clear. An array of over-the-counter treatments are available, the efficacy of which are almost wholly unknown or dubious at best. Among these devices various 'snoring pillows' are available through retail outlets, some nationally recognized. An important exception is the PillowPositive ™ , having received FDA approval for both the treatment of sleep apnea as well as snoring.

Methods: With little published information available on the PillowPositive™, and nothing comparing it with the current primary intervention, nasal continuous positive airway pressure; this research was designed both to assess the efficacy of the PillowPositive™ and compare it with nasal CPAP.Subjects were patients selected from among those undergoing evaluation in a full-service sleep center accredited by the AASM, the Pacific Sleep Program, for sleep apnea. Patients chosen had apnea indices of < 15, AHI < 40, $Sa0_2 \geq 80\%$, and no life-threatening arrhythmias; classified in the mild to moderate category and included those suspected of having mainly the upper airway resistance syndrome. The pillow size was individually selected following the manufacturer's instructions and custom measuring device by the Program's board-certified sleep physician. It was administered by RPSGT staff, also according to the manufacturer's instructions including use of their custom Reclinometer™. Nasal CPAP titrations were effected following Pacific Sleep Program established protocols. Full diagnostic polysomnography was completed on each patient for a full night, which met or exceeded standards established by the AASM. Therapeutic polysomnography was completed on a separate night following the same standards. An intranight crossover design was followed. Nasal CPAP was administered during the first half of the recording in order to minimize potential problems with adjustment arising from substantial sleep accumulation prior to its initiation; this was felt to be far less likely during the pillow phase which was completed during the second half. Each recording was sleep stage scored according Rechtschaffen and Kales criteria as well as AASM criteria for arousals and abnormal respiratory events.

Results: 25 patients have been studied thus far. Age averaged 49.1 years. Baseline average AHI was 17.4, respiratory arousal index 35.0, $Sa0_2$ low 86%, arousal index 47.0. All patients treated with CPAP had RDI reduced to < 10, except one, average arousal index 39.3 though far less at optimal CPAP settings, and $Sa0_2$ low > 89%. PillowPositive™ treatment phase average AHI was 22.2, RDI 42.9, $Sa0_2$ low 88%, arousal index 59.4. Snoring persisted in virtually all patients. AHI worsened with the PillowPositive™ in 12 (48%), overall RDI in 11 (44%); most did best when also when sleeping on their sides. 4 had the AHI reduced to < 10 and 11 to < 15, none had RDI reduced to < 10, 1 case had RDI level better than the CPAP phase, whose titration was considered unsuccessful. Modifications in the number of inserts as well as use of the Reclinometer™ had no clear effect.

Conclusions: This group of patients with mild to moderate obstructive sleep apnea improved with PillowPositive™ treatment in approximately one half the cases, in terms of respiratory disturbances, but to only a limited degree. Snoring was not eliminated, even in those otherwise improved. The sleep position expected to be of the greatest efficacy did not appear as efficacious as side sleeping. Sleep was more restless than either the baseline measure or the CPAP phase. Of particular concern was the fact that a rather large percentage of patients were worse during the PillowPositive™ phase. Additional patients are being studied and a more detailed data analysis is in progress.

Research was supported by funding through the Pacific Sleep Program.

1778.K1

Modafinil as an Adjunctive Therapy for Excessive Daytime Somnolence in Obstructive Sleep Apnea

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Introduction: Obstructive sleep apnea (OSA) is a common cause of excessive daytime somnolence (EDS). The most common treatment for OSA is continuous positive airway pressure (CPAP), which effectively treats the nighttime respiratory abnormalities asscociated with apnea. However, in many patients, EDS is not completely eliminated even when patients are fully compliant with their CPAP regimen. The etiology of this residual sleepiness is unknown, although in some patients CPAP itself may disrupt sleep quality and contribute to EDS. Additionally, the sequelae of OSA occurring before CPAP therapy is intitiated may cause permanent alterations in nighttime sleep and daytime wakefulness. Use of a wake-promoting medication that does not cause or exacerbate cardiovascular symptoms may be beneficial for patients who are compliant with CPAP therapy but still have residual EDS. Modafinil is a unique wake-promoting agent that is chemically distinct from the traditional central nervous system stimulants, has a relatively benign safety profile, and also has a low potential for abuse. Moreover, modafinil has a long half-life which permits once-daily dosing in most patients. Modafinil has been shown to be effective in reducing the EDS associated with narcolepsy and may have application in other diseases or syndromes where EDS or fatigue is a common symptom. This study evaluated the use of modafinil for the treatment of EDS in patients with OSA who were compliant with CPAP therapy.

Methods: Fourteen patients (12 men and 2 women) with previously diagnosed OSA and persistent EDS were included in the study medication phase of the trial. The patients ranged in age from 36 to 64 years (mean 51 years). At entry into the study, CPAP treatment was initiated. The mean respiratory disturbance index (RDI) prior to CPAP treatment was 49.9 (range 15 to 127). In order to continue into the study medication phase of the trial, patients were required to have used CPAP for at least 2 months, have an RDI <10, but still have persistent EDS (ie, an Epworth Sleepiness Scale [ESS] score >10). During the CPAP lead-in treatment phase, CPAP effectiveness was monitored for 2 nights using a Resmed Autoset T device followed by a 21-day assessment period to determine compliance with CPAP treatment. Compliance was defined as use of CPAP for >4 hours per night for >=70% of the study nights (Resmed Elite 5). All patients then had an overnight polysomnogram (PSG) while they were using CPAP at the prescribed pressure. This was followed by a Multiple Sleep Latency Test (MSLT) the next day. PSG data were used to confirm that patients had been treated at the appropriate CPAP pressure and MSLT results (mean 5.0 minutes, range 1.3 to 7.7 minutes) confirmed the presence of EDS. The patients then continued their regular CPAP treatment and also were placed on 200-mg daily doses of modafinil for 1 week and 400-mg daily doses of modafinil the following week. At that time, the physician and the patient selected the optimum dose for continuing treatment. Efficacy measures included the ESS and baseline and the ESS and Clinical Global Impression of Change

(CGI-C) at time points throughout the study.

Results: The mean baseline ESS score was 14.0 (range 11 to 19). The mean ESS score during treatment with modafinil was 7.4 (range 0 to 13). All patients reported improvements in daytime sleepiness while receiving modafinil. CGI-C scores also were significantly improved in all patients. No cardiovascular side effects were reported, and there were no significant changes observed in blood pressure, pulse rate, or electrocardiogram recordings for any of the patients. Thirteen of 14 patients chose 400-mg daily doses of modafinil as the preferred dose and 1 patient chose 200-mg daily doses as the most effective dose.

Conclusions: Modafinil is effective as an adjunctive therapy for improving the symptoms of EDS in patients with OSA who are CPAP compliant.

Research supported by Cephalon, Inc., West Chester, PA

1021.K3

Intermittent Use of Zolpidem for the Treatment of Primary Insomnia

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Introduction: Intermittent use of hypnotic medication is often recommended for the treatment of chronic insomnia. Presumably this recommendation is made because of concerns about potential tolerance and/or abuse with nightly use. Efficacy and undesirable effects of intermittent hypnotic use for chronic insomnia have not been adequately investigated. Cluydts, et al[1] compared two weeks of nightly use of zolpidem 10 mg (Z10), to two weeks of five nights use of Z10 (and two nights without any medication). They reported no differences in efficacy or adverse events between conditions. However, patients did not choose medication nights in the intermittent condition, no placebo (Pbo) group was included, and the two-week duration of the study meant that 10 nights of Z10 were compared to 14 nights. The present study compared the efficacy of Z10 versus Pbo when each were taken between 3 and 5 nights per week, on nights selected by the subjects, for a period of 8 weeks.

Methods: DSM-IV primary insomniacs were randomly assigned to either Z10 (N=81) or Pbo (N=81) in a double-blind, parallel group design. Subjective sleep data were collected for 10 consecutive weeks using daily morning sleep questionnaires. Patient global impression (PGI)and investigator global impression (CGI) measures were completed after every two weeks of randomized treatment. After one week of baseline (with no pill), patients took either Z10 or Pbo "as needed" for 8 weeks with the restriction that they must take a pill 3 to 5 times/week. One week without pills followed discontinuation of treatment. Continuous and categorical variables were analyzed with ANOVA and the Cochran-Mantel-Haenszel Test, respectively.

Results: No demographic or baseline sleep variables differed between groups. The mean number of pills taken did not differ a) between groups at any time, nor b) as a function of duration of use (see below):

Group	Weeks 1+2	Weeks 3+4	Weeks 5+6	Weeks 7+8
Pbo	7.7	7.8	7.7	7.6
Z10	7.8	7.6	7.8	7.9

Both the PGI and CGI of therapeutic effect revealed significant differences between groups in favor of Z10, at all time points measured ($p < 0.01$). When including all randomized nights, reported total sleep time (TST) was significantly greater for Z10 than Pbo during weeks 1+2 and 3+4 (both $p < 0.02$), and there was a trend ($p < 0.09$) for greater TST for Z10 during weeks 5+6 (see below).

Group	Bsln	Weeks 1+2	Weeks 3+4	Weeks 5+6	Weeks 7+8	Disc
Pbo	320.7	351.1	353.3	362.5	363.6	361.0
Z10	319.8	373.1	374.4	378.8	373.9	354.8

Comparing groups only on "pill nights" revealed significantly higher TST ($p < 0.001$ for each) and shorter sleep latency (SL; $p < 0.05$) with Z10 at all study periods during randomization. TST was significantly less for Z10 than Pbo on "no pill" nights only for weeks 1+2, but there was a trend in that direction at other study periods. SL was significantly greater for Z10 than Pbo on "no pill" nights during all weeks except weeks 3-4 ($p < 0.05$). There was no difference between "pill" and "no pill" nights in the Pbo condition. Baseline and discontinuation week TST (see below) and SL values did not differ between groups.

Group	Bsln	Weeks 1+2	Weeks 3+4	Weeks 5+6	Weeks 7+8	Disc
Pbo–pill	320.7	358.4	360.3	365.2	372.4	361.0
Pbo–no pill	320.7	342.3	353.0	360.1	356.1	361.0
Z10–pill	319.8	415.9	417.7	415.1	413.0	354.8
Z10–no pill	319.8	316.9	329.6	339.6	335.5	354.8

Comparison of TST on all Z10 nights without a pill which immediately followed a Z10 pill night showed no difference as compared to baseline, indicating no rebound insomnia.

Conclusions: Sleep questionnaires and global patient and investigator evaluations indicate significant benefit from intermittent use of Z10, as compared to Pbo, over the 8 weeks of treatment. There was no evidence of rebound insomnia. The number of nights per week on which a pill was taken did not increase during the study, which is inconsistent with a high abuse liability of hypnotics.

References:
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Research supported by Lorex Pharmaceuticals

1327.K3

Olanzapine as a Treatment for Insomnia

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Insomnia Research Foundation

Introduction: No one pharmacologic treatment intervention is currently recommended or FDA approved for Psychophysiological Insomnia with agitation. Most interventions supported by current sleep literature involve benzodiazepines and/or sedating antidepressants. However, clinical lore supports the use of sedating typical neuroleptics for the acute presentation, such as chlorpromazine or thioridizine. To our knowledge, there are no insomnia treatment references in the literature regarding the use of olanzapine, an atypical antipsychotic drug with potent H-1 blocking effects and minimal neurological side effects and risks.

Methods: Nine females, ages 34 - 67, presenting with long-standing

insomnia (Psychophysiological Insomnia: 307.42-0) of greater than six months duration. Each subject complained of a variety of sleep disruption symptoms including sleep onset difficulty, sleep maintenance difficulties and/or feeling unrefreshed upon awakening. No one complaint or pattern dominated the symptom picture. Each individual complained of significant distress concerning her decrement in daytime functioning. Additionally, each female exhibited marked agitation and complained of anxiety and tension, particularly as the time for sleep approached. Following nights of no sleep, these individuals reported extreme changes in mood and personality that could be reversed by a night of good quality and adequate amount of sleep. All subjects had been tried, by us or other physicians, on a variety of medications for sleep including most standard hypnotics, as well as medications for depression and/or anxiety. One subject had responded to thioridizine for sleep in the past and one subject had previously been on risperidone. None of the other subjects had previously been on any other typical or atypical antipsychotic drugs.All individuals were interviewed for sleep related symptoms and history, medical and psychiatric history, and lifestyle behaviors. Trials of medications traditionally used to treat insomnia were unsuccessful. Symptoms of agitation and tension remained predominant. Determination was made that psychological intervention for behavioral treatments had already been or would be unsuccessful due to significant agitation. Treatment with olanzapine was initiated with a dose of 5, 7.5, 10, 15 or 20 mg, depending on clinical judgement, taken approximately 30-60 minutes prior to the desired bedtime. Treatment doses were adjusted based on morning reports of the prior night's sleep. Although some individuals required a maximum dose of 15mg following the first night, doses of 7.5mg to 10mg were usually necessary to achieve a continuation of rapid sleep onset and minimal nocturnal awakenings. Any antidepressant or antianxiety medications that patients had required prior to the initiation of olanzapine were continued. After these individuals described sleeping well, doses of olanzapine were reduced as tolerated; however, all but one individual still required an ongoing dose of 2.5-7.5mg per night. Following successful dose adjustment, several of these individuals were referred for psychological treatment using cognitive therapy to address irrational thoughts concerning sleep and to learn behavioral techniques to treat future bouts of insomnia.

Results: Only one of the nine subjects reported daytime sedation the following day, and that individual had not complied with the prescribed medication administration. Eight of the nine showed a good response immediately. Five of the subjects were able to achieve adequate amount and quality of sleep on 5mg olanzapine. The other two sub ects required higher doses (7.5 and l5mg), One subject eventually did well on just the clonazepam she was previously taking, once her olanzapine was stopped. "Good sleep" was described as falling asleep quickly (subjective report) and experiencing uninterrupted sleep or 1-2 brief awakenings with a total sleep time of seven or more hours. Olanzapine treatment duration has ranged from six weeks to five months. Those individuals subsequently seen for psychological treatment are more ready to learn non-pharmacological methods to cope with future bouts of insomnia. The only persistent side effects have been increased hunger and weight gain; the maximum gain having been four pounds.

Conclusions: For those individuals suffering from severe Psychophysiological Insomnia with agitation, and for whom standard treatments have been unsuccessful, olanzapine may be the optimal treatment. Patients tend to respond immediately and enjoy continued benefit, while psychological and other phannacological interventions can be phased in. Side effects and risks pale in comparison to those of continued sleep deprivation, agitation and inability to function.

1054.K3

Behavioral Treatment for Sleep Maintenance Insomnia: The Trajectory of Change

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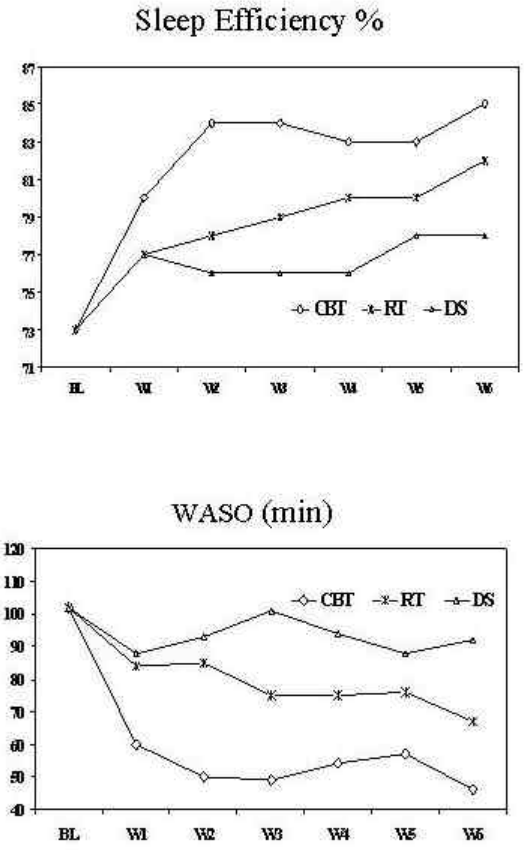
Introduction: Behavioral treatments for primary insomnia are both efficacious and durable.[1] Typically, the authors of behavioral treatment studies analyze data from the pre- and post-treatment timepoints but neglect analyzing the trajectory of change during treatment. In most cases behavioral treatment of insomnia occurs overs a 6 to 8-week period; however, little is known about the course of change during this 6-8 week period. The present study is designed to focus on the pattern of change during behavioral treatment of insomnia. Such information about the course of change will provide clinicians and their patients with accurate expectations regarding the outcome of behavioral treatment.

Table 1



Methods: Patients recruited to participate in this trial were middle-aged and older adults who presented with moderate to severe primary sleep-maintenance insomnia. Prospective subjects for this trial were first thoroughly screened via structured psychiatric and sleep interviews, one night of ambulatory polysomnography (APSG), medical examination, thyroid testing and sleep log monitoring. Once enrolled in the study, subjects completed baseline assessment including two weeks of sleep log monitoring, actigraphy, an overnight PSG study and several paper and pencil questionnaires. After completing this baseline assessment, patients were randomized to cognitive-behavioral therapy (CBT), relaxation therapy (RT) or placebo (PC). Subsequently, subjects received 6 weekly treatment sessions during which they were provided their respec-

tive treatments. CBT consisted of a combination of sleep education, stimulus control and sleep restriction. RT consisted of progressive muscle relaxation modeled on the Bernstein and Borkovec model of tensing and relaxing muscle groups. PC was a quasi-desensitization protocol described by Steinmark and Borkovec. During treatment, subjects completed daily sleep logs. Data for the present study were derived from these daily sleep logs. Since our laboratory has previously reported the pre- to post-treatment analysis for these data,[2] the present analysis will exclude the post-treatment and focus instead on the week-to-week differences among the three treatment conditions.

Results: The results presented here pertain to the 63 subjects (CBT=22, RT=17, PC=24) who had complete data for all timepoints. The mean age of these subjects (30 females; 33 males) was 54.8 yrs. (SD = 11.8 yrs.). Pre-treatment comparisons showed that the three treatment groups did not differ (p's > .05) in regard to their mean ages, gender compositions or baseline values on the various outcome measures. The treatment (CBT, RT, DS) by time (BL, Weeks 1 to 6) interactions in an ANCOVA (covarying for baseline) were significant for both SE% (F = 2.16, p = .03) and WASO (F = 2.54, p = .009). Post-hoc analyses indicate that for SE% CBT was significantly greater than DS beginning with Week 2 of treatment and continuing through Week 6. In addition, CBT was significantly greater than RT during Weeks 2, 3 and 6. Post-hoc analyses for WASO indicate that CBT was significantly greater than both DS and RT during each week of treatment.

Conclusions: These results indicate that cognitive-behavioral therapy for primary sleep-maintenance insomnia has a more rapid and larger treatment effect than either progressive muscle relaxation or placebo control. The differences between the conditions emerge during the first and second week of treatment and remain throughout the 6-week therapy.

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1184.K3

Predicting Clinically Significant Response to Cognitive Behavior Therapy (CBT) for Chronic Insomnia in General Medical Practice: Analayses or Outcome Data at 12 Months Post-Treatment

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Introduction: Meta-analyses support the clinical efficacy of CBT for chronic insomnia, but recent reviews (Edinger and Wohlegemuth, 1999; Morin et al, 1999) concur that predicting responders is problematic. Studies of potential moderators eg. age, duration of problem, history of hypnotic use, are inconclusive. However, (contra)indications are difficult to establish from efficacy studies which may 'dilute' the clinic-presenting population. This paper, therefore, reports further analyses from a large clinical effectiveness study (Espie et al 1999).

Methods: We wanted to predict durable outcome, therefore, subjects from our cohort (n = 139) who completed 12 month follow-up were included (n = 109; 78.4%) - two-thirds female, average age 52.1 years (sd. 16.2) with persistent insomnia (44% with over 10 year duration), and 56% taking hypnotic medication. Intervention comprised standard CBT methods (see Espie et al, 1999). A comprehensive range of predictor variables was considered against 6 dichotomous outcomes, representing achievement (or not) of 50% reduction, or reduction to sub-clinical level, in a sleep variable (see column and row; Table 1).

Table 1

	SOL 50%	SOL 30min	WASO 50%	WASO 30min	nWAKE5 0%	ENJOY 50%
Demographic						
sex	.680	.834	.884	.529	.262	.359
age	.189	.419	.493	**.022***	.470	.948
status	.586	.641	.502	.966	.838	**.043***
occupation	.642	.905	.608	.366	.932	.840
Sleep						
duration	.842	.252	.487	.610	.739	.200
drug	.725	.107	.399	.582	.306	.128
tiredness	.311	.608	.469	.790	**.070**	.131
severity	**.001*****	**.072**	**.007****	**.001*****	.368	.399
Psychopathology						
depression	**.071**	.969	**.035***	.150	**.061**	.844
state	.129	.698	**.044***	**.043***	.265	.920
trait	.240	.386	.179	**.062**	.170	.107
worry	.962	.417	.880	.154	.424	**.067**
Psychological						
SDQ FI	.930	.801	.363	.354	.759	.496
SDQ FII	.906	.715	.673	.353	.739	.436
SDQ FIII	.116	.675	.624	.209	.360	.138
SDQ FIV	.847	.944	**.073**	.743	.556	.177
DBAS FI	.578	.745	.529	.227	.170	**.057**
DBAS FII	**.014***	**.036***	.950	.339	.837	.338
DBAS FIII	.803	.975	.554	.260	.688	.329
Treatment						
credibility	.472	.607	.408	.679	.300	**.044***
therapist	.188	.664	.213	.209	.198	.140

Associations between clinical outcomes and pre-treatment characteristics (n =109). Tabulated data are p values from chi-square (categorical variables) or independent sample t-tests with significant values in bold typeface and with * p< .05 ** p < .01 *** p < .001
SDQ = Sleep Disturbance Questionnaire; *DBAS* = Dysfunctional Beliefs and Attitudes about Sleep

Table 2

	Log likelihood	Chi-square	df	Sig.	Predictors	Sig.	*R*	% correct responders	% correct non-responders
SOL >= 50% reduction	132.6	17.3	3	.0006	severity DBAS Factor II	.010 .061	.195 .106	55.6	74.2
SOL <= 30 minutes	133.7	13.1	3	.0044	DBAS Factor II severity	.010 .023	.183 .160	87.7	35.04
WASO >= 50% reduction	128.9	19.4	4	.0007	BDI SDQ Factor IV severity	.014 .032 .038	.175 -.139 .137	70.4	64.2
WASO <= 30 minutes	123.1	23.1	3	<.0001	severity STAI state	.001 .013	.274 .178	77.1	46.3
nWAKE >= 50% reduction	129.9	3.4	1	.0671	BDI	.068	.010	12.5	100.0
ENJOY >= 50% increase	95.1	11.7	3	.0085	PSWQ status credibility	.014 .076 .090	-.201 -.108 .094	16.7	94.3

Table 2 Predictors of clinically significant outcome for each of the sleep outcome measures (n = 109). Results represent logistic regression analyses of contributing variables ie. where p < .10 (following Hosmer and Lemeshow, 1989).
SOL = Sleep Onset Latency; WASO = Wake time After Sleep Onset; nWAKE = number of wakenings; ENJOY = rating of 'sleep enjoyment'; BDI = Beck Depression Inventory; PSWQ = Penn State Worry Questionnaire; *SDQ* = Sleep Disturbance Questionnaire; *DBAS* = Dysfunctional Beliefs and Attitudes about Sleep

Results: Variables were screened by examining bivariate relationships with outcome (Table 1), and significant sub-sets were entered in logistic regression models to determine combinations most accurately identify-

ing responders/ non-responders (Table 2). Insomnia severity and DBAS Factor II (beliefs about negative long-term consequences of insomnia) predicted half of responders and three-quarters of non-responders on the SOL >= 50% criterion, severity having the stronger impact. These variables also predicted SOL <= 30 minutes (88%), but identified fewer non-responders (35%). Three variables contributed to WASO >= 50% reduction. Symptoms of depression, SDQ Factor IV (lack of sleep readiness) and severity predicted 70% and 64% of responders and non-responders respectively. State anxiety and severity predicted WASO <= 30 minutes, identifying 77% of responders and half of non-responders. Symptoms of depression predicted 100% of non-responders on nWAKE, identifying only 13% of responders, and worry, civil status and treatment credibility predicted 94% of non-responders in ENJOY, failing to identify 85% of responders.

Conclusions: There is no evidence to contraindicate CBT for chronic insomnia in terms of demographic (eg. age) or clinical factors (eg. hypnotic use). Regression generally explained small amounts of variance. Severity of insomnia reflects a law of initial values; more severe problems have greater likelihood of proportionate reduction but less likelihood of low absolute outcomes. The direction of effect of psychological characteristics generally suggests greater levels of symptomatology relate to better outcome, but at least do not suggest poor response.

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1528.K3

Self-Reported Levels of Sleepiness Among Subjects with Insomnia

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Introduction: The Sleep-Wake Activity Inventory (SWAI) is a self-report questionnaire that contains two validated scales which measure excessive daytime sleepiness (EDS) and nocturnal sleep (NS). The EDS scale has been validated in the general population and in patients who complain of EDS, and can detect differential levels of sleepiness (Rosenthal et. al, 1993, Breslau et. al, 1997, Johnson et. al, 1999). The NS scale of the SWAI has been demonstrated to be predictive of disturbed nocturnal sleep in the same populations. The goals of the present study were to determine the prevalence of EDS among subjects with insomnia, and to determine if the EDS scale of the SWAI is associated with polysomnographic (PSG) characteristics.

Methods: Subjects were 62 (32M, 30F) consecutive individuals who had a complaint of insomnia in the context of a regular nocturnal sleep schedule. All subjects responded to advertisements for various research protocols. Subjects completed a medical screen by a physician to ensure their healthy and drug free status prior to their entry to the study. Subjects completed the SWAI before the 8-hour PSG recording. Subjects were grouped according to their scores on the EDS scale of the SWAI. Group 1 (n=14) had EDS-SWAI scores of <50, consistent with the level of daytime sleepiness in apnea patients. Group 2 (n=19) was derived from subjects with EDS-SWAI scores of >50<65, which is the most prevalent range of scores among asymptomatic subjects. Group 3 (n=29) was derived from subjects with scores of >65 on the EDS-SWAI, which is consistent with lowest levels of sleepiness, and may reflect a state of hyperarousal.

Results: There were 14 subjects with findings consistent with symptomatic EDS (22%). Consistent with differential levels of sleepiness, insomnia subjects manifested differential levels of disturbed nocturnal sleep (NS scale, p<.01). The PSG recording found significant differences in sleep propensity and continuity. The sleepy group (EDS-SWAI scores <50) had significantly shorter latencies to stage 1, stage 2, and persistent sleep than the alert group (EDS-SWAI>65, p<.05). The index of the number of awakenings during the night was significantly higher for those with EDS scores of >65 when compared with those with scores of >50<65(p<.05). The groups were comparable on all sleep stage parameters.

Table 1

	EDS-SWAI Scores		
	≤50	>50≤65	>65
NS-SWAI*	18 (6)	25 (5)	14 (4)
Sleep Efficiency	76 (11)	80 (9)	76 (11)
St 1%	20 (16)	22 (12)	21 (2)
St 2%	57 (14)	54 (11)	54 (13)
St 3 / 4%	7 (9)	6 (8)	7 (9)
St REM%	16 (6)	18 (7)	19 (5)
Lat to St 1+	15 (20)	20 (17)	36 (45)
Lat to St 2+	23 (25)	34 (25)	48 (44)
Lat to PS+	27 (26)	35 (31)	53 (43)
# Awakenings Index+	1.2 (.7)	0.9 (0.6)	1.3 (0.6)
* p<.01 + p<.05			

Conclusions: This study found a wide range of scores on the EDS scale of the SWAI. A small but yet significant prevalence of EDS was encountered among subjects with insomnia. These findings suggest that the EDS scale is sensitive in detecting polysomnographic differences in this population. Of particular interest is the group of subjects with EDS scores of >65. These subjects may experience a state of hyperalertness that has been previously entertained in the literature. The PSG findings for this group would certainly be supportive of this notion. Finally, both the EDS and NS scales of the SWAI seem to provide an insight into the subject's degree of homeostatic sleep need.

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1318.P

Developmental Changes in Brain Derived-Neurotrophic Factor mRNA Level After Sleep Deprivation

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Introduction: We reported previously an increase in brain-derived neu-

rotrophic factor (BDNF) mRNA level in multiple brain regions of adult Wistar rat following 6 hrs of sleep deprivation (SD).[1] Here, we aimed to characterize the development of this response. We hypothesized that it corresponds to other developmental changes in sleep behavior and sleep homeostatic regulation. Indeed, recent studies indicate that diurnal organization and homeostatic regulation of EEG slow-wave activity occurs between days 20 and 24 in post-natal Long-Evans rats pups.[2,3] Therefore, we examined BDNF cortical RNA levels in Long-Evans rat pups after SD versus control conditions at 3 developmental ages: P16, P20, and P24.

Figure 1

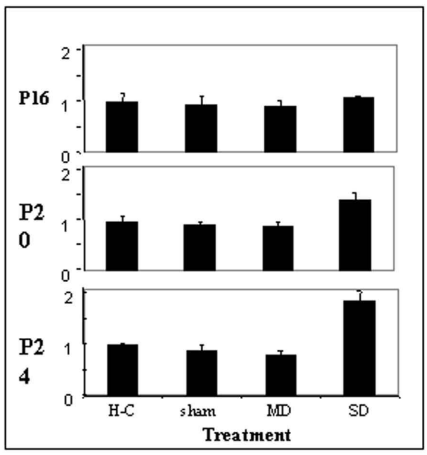

Figure 1. BDNF mRNA level increases after SD in P20 and P24 rats. Error bars represent SEM.

Methods: For each age, pups were randomly divided in 4 groups: home-cage, sham, maternal deprivation (MD) and SD. Ninety Long-Evans pups (age P9) were surgically prepared under Metophane anesthesia for EEG/EEG sleep recordings. Recordings were conducted on MD and SD animals for at least 12 hours of baseline and during the SD, if applicable. SD, performed by gentle handling, started at light onset (ZT0) and lasted 1.5 hrs, 2.5 hrs and 3.0 hrs for P16, P20, and P24, respectively. In agreement with earlier observations 3, we noted that P16 and P20 pups were resistant to further sleep deprivation after 1.5 and 2.5 hrs, respectively. Animals were sacrificed by decapitation immediately after SD. Brains were rapidly removed, dissected in numerous regions, and flash-frozen on dry-ice. Total RNA was isolated from the cortical tissue, separated on a 1.2% agarose-formaldehyde gel, and transferred to a Nylon membrane. Blots were hybridized to 32P random prime-labeled BDNF cDNA overnight at 42oC in Melton's buffer. Quantification was performed via phosphoimage analysis and Molecular Analyst v. 2.1 (BioRad). Statistical analyses were performed by ANOVA and student's t-test.

Results: We observed no change in BDNF mRNA level after 1.5 hrs of SD in P16 pups in comparison with the 3 control groups (H-C, sham and MD) (Figure 1; p=0.773). In contrast, 2.5 hrs of SD in P20 pups elicited a 44% increase in BDNF mRNA expression in comparison with controls (Figure 1; p=0.012), and 3 hrs of SD in P24 pups yielded an 85% increase in BDNF mRNA level (Figure 1; p=0.002).

Conclusions: Results from P20 and P24 pups were comparable to those observed in adult rats1. The lack of change in BDNF expression following SD at P16 may be attributable to the shortened SD time. Alternatively, these results may illustrate a developmental change in BDNF regulation in response to SD. Indeed, the occurrence of BDNF regulation with SD appears to correspond with developmental changes in other aspects of sleep behavior 2. This suggests that BDNF might be a component of sleep homeostatic regulation.

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1722.P

Mutation Screening of Hypocretin System Genes in Human Narcoleptics

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Introduction: Recent publications have implicated the neuropeptides hypocretin 1 and 2 (Hcrt) and one of their receptors (Hcrtr2) in the pathophysiology of narcolepsy. Canine narcolepsy has been shown to be caused by Hcrtr2 mutations in three breeds[1,2] and preprohypocretin knockout mice have abnormalities suggesting narcolepsy.[3] Nevertheless, the cause of narcolepsy in humans remains unknown. We used a sequence-based mutation screening strategy to investigate the role of this system in the etiology of human narcolepsy.

Methods: We sequenced exons and flanking intronic regions of the HCRT, HCRTR1 and HCRTR2 loci in 70 narcoleptics and 152 controls. We selected subjects with and without the HLA-DQB1*0602 allele and with and without a family history. All patients had cataplexy and MSLT abnormalities.

Results: We identified fifteen polymorphisms, including 9 amino acid substitutions. Further analysis indicated that most of these were not associated with narcolepsy. One case was caused by a mutation in the HCRT locus. This patient is HLA-DQB1*0602 negative, with severe cataplexy, daytime sleepiness, sleep paralysis and hypnagogic hallucinations. Twenty four hour polysomnography documented fragmented sleep/wake patterns and SOREMPs during sleep attacks. He first demonstrated cataplexy at 6 months of age. Most cases of human narcolepsy only appear during adolescence whereas narcolepsy in canines and mice begins before sexual maturity. Interestingly, spike-slow wave complexes and low frequency (3-4 Hz) discharges without associated clinical findings were observed in combination with REM sleep. These findings are reminiscent of pre-REM sleep spindling activity reported in the preprohypocretin knockout mice. The HCRT mutation is a leucine to arginine substitution in the hydrophobic core of the signal peptide, and was not observed in 270 control chromosomes. Signal peptide mutations produce a variety of genetic disorders, frequently display autosomal dominant transmission and have been proposed to cause cell death through accumulation of mutant polypeptides.

Conclusions: Our results demonstrate that hypocretin mutations in humans can produce fullblown narcolepsy. We are analyzing the effects of the mutation on the processing and secretion of preprohypocretin. Only one disease-causing mutation was found among 70 narcoleptic patients of various clinical and HLA status but many informative polymorphisms were observed. We conclude that these three loci are not significantly involved in predisposition to human narcolepsy, indicating genetic heterogeneity. Further studies will be needed to explore the

effects of these polymorphisms on disease expressivity, onset and drug response.

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1223.P

The Role of Orexin Receptor Type-1 (OX1R) in the Regulation of Sleep

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Introduction: Recently we reported that mice with a targeted disruption of the orexin gene (*orexin-/-*) exhibit a phenotype remarkably similar to human narcolepsy patients and *canarc-1* mutant dogs (Chemelli et al 1999). Interestingly, the narcoleptic phenotype of *canarc-1* mutant dog is caused by mutations in orexin receptor type-2 (*OX2R*) gene (Lin and Faraco et al, 1999). Comparison of phenotypes among *orexin-/-* mice, *OX2R-/-* mice and *canarc-1* mutant dogs shows that *OX2R-/-* mice and *canarc-1* mutant dogs have a similar, but less severe phenotype than *orexin-/-* mice. Similarities include i) direct transitions from wakefulness to REM sleep and ii) increased fragmentation of the sleep-wake cycle. These similarities suggest that orexin-OX2R interaction is crucial for the regulation of organized transitions between wakefulness, non-REM sleep and REM sleep. However, the severity of the disturbance in both frequency of sleep-onset REM and sleep fragmentation is much less in *OX2R-/-* mice than *orexin-/-* mice and the total REM sleep time in *orexin-/-* mice is much longer than in *OX2R-/-* mice. The differences in the phenotypes between *orexin-/-* mice and *OX2R-/-* mice can be explained by a modification of sleep homeostat via orexin receptor type-1 (OX1R) activation. Thus, we hypothesize that orexin-OX1R interaction is involved in the control of sleep homeostat.

Methods: By transfection of mouse embryonic stem (ES) cells and subsequent homologous recombination, we generated mice with a targeted disruption of exon 1 and 2 of the mouse *OX1R*. We examined *OX1R* expression in *OX1R-/-* mice by northern blot analysis of the brain. EEG/EMG recording and infrared videophotography of age-matched (14 weeks old), male mice are ongoing. An 8 mm CCD videocamera with infrared and digital time recording capabilities is used to document dark cycle behavior. Two weeks after the implantation of EEG/EMG electrodes, signals are recorded for three consecutive 24 hours. EEG/EMG records are scored visually in 20 second epochs of Awake, REM and non-REM sleep. Differences between vigilance state data for *OX1R-/-* mice and wild-type mice are analyzed by repeated measurements ANOVA.

Results: Heterozygous *OX1R+/–* mice are phenotypically normal. Ratio of genotypes of progeny of F1 heterozygote crosses at weaning is consistent with Mendelian inheritance, indicating that homozygosity does not cause significant embryonic/neonatal lethality. Gross anatomical and histological studies show no detectable structural abnormalities in the brains of *OX1R-/-* mice. Northern blot analysis confirms that the targeted *OX1R* allele is a null mutation. Results of EEG/EMG recordings and infrared videophotography will be presented.

Conclusions: We generated *OX1R*-deficient mice. They will provide a valuable, new tool to understand the sleep homeostat and the role of the orexin system in sleep regulation.

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1799.K2

A Behavioral Paradigm that Elicits Narcoleptic Attacks in orexin Knockout Mice

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Introduction: Orexin-A and orexin-B, a pair of hypothalamic neuropeptides, are endogenous ligands for two G protein-coupled receptors (OX1R and OX2R) expressed throughout the central nervous system. By behavioral and electroencephalographic criteria, *orexin* knockout mice exhibit a phenotype strikingly similar to human narcolepsy patients, as well as *canarc-1* mutant dogs.[1] Narcoleptic dogs have been used to understand the neurochemical control of cataplexy. Canine cataplexy is triggered by emotional stimuli such as presentation of appetitive food to trained dogs (food elicited cataplexy test), a paradigm which has been used to study the effect of pharmacologic agents on the control of cataplexy. To study the neurochemistry of narcolepsy in *orexin* knockout mice, we have undertaken development of a behavioral bioassay for mouse narcolepsy based on emotional triggers specific to mice. Previous behavioral analysis of knockout mice has demonstrated inconsistent episode frequency over several experimental sessions. To facilitate pharmacologic studies, however, experimental paradigms must elicit consistent numbers of narcoleptic attacks over repeated sessions. To achieve this goal, experimental paradigms based on the food elicited cataplexy test and a restricted feeding schedule (food shift) are being tested.

Methods: Scoring of narcoleptic attacks by mice in plexiglass-covered cages using nighttime infrared video photography is as reported.[1] In the food shift paradigm, normal chow is only available for the first three hours of the dark cycle. For the food elicited cataplexy test, knockout mice maintained on the food shift paradigm are removed from their home cages and trained to dig up and consume appetitive food (pieces of Fruit Loops cereal buried in bedding material) for ten minutes before the dark cycle on seven consecutive days.

Results: *orexin* knockout mice maintained on the food shift paradigm are forced to consolidate arousal during the first three hours of the dark cycle in order to consume enough calories for survival. Indeed, normal sleep is almost completely absent during this period. Importantly, attack frequency during this period is increased over levels prior to the food shift, and analysis over several filming sessions reveals that attack fre-

quency remains relatively stable. By contrast, knockout mice trained in the food elicited cataplexy test revealed no attacks over the entire training period despite improved performance at finding and consuming the cereal.

Conclusions: Behavioral studies of *orexin* knockout mice suggest that attacks are elicited by arousal during a restricted feeding schedule. A food elicited cataplexy test similar to that used in narcoleptic dogs, however, does not elicit attacks in mice. The food shift paradigm should allow greater understanding of emotional triggers of narcoleptic attacks in mice as well as the development of a behavioral bioassay for use in pharmacalogic studies of *orexin* knockout mice.

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1075.P

A Genetic Study of the Epworth Sleepiness Scale in 1608 Male-Male Twin Pairs from the NAS-NRC World War II Twin Registry

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Introduction: Excessive daytime sleepiness is common among the elderly and often considered an indicator of various medical and neurological conditions. The genetic determinants, however, of individual differences in daytime sleepiness, especially among the elderly, are poorly understood. The objective of the present study was to investigate the contribution of genetic and environmental influences to daytime sleepiness and excessive daytime sleepiness in a large population-based cohort of male-male twin pairs.

Methods: Responses to the 8-item Epworth Sleepiness Scale (ESS), a validated screening instrument for daytime sleepiness, were obtained from both twins of 1608 male-male twin pairs from the NAS-NRC World War II Twin Registry. The sample consisted of 840 monozygotic (MZ) and 768 dizygotic (DZ) twin pairs, ages 69 to 82 years old when surveyed for daytime sleepiness. For each zygosity group, intraclass twin correlations and concordance rates were calculated for the full ESS scale and for high scores (ESS > 11) indicative of excessive daytime sleepiness. The observed variance-covariance matrices in each zygosity were subjected to structural equation modeling, which allowed for the estimation of the proportion of genetic and environmental components of variance.

Results: The average ESS score (± SD) for this sample of twins was 7.1 ± 3.9, range 0 to 24. More than half of the twins (65%-67%) reported a moderate to high chance of falling asleep while lying down to rest in the afternoon; however less than 3% admitted that this would occur while sitting and talking to someone or while stopped for a few minutes in traffic. In this sample age was not significantly associated with daytime sleepiness; however, obesity, assessed by BMI, waist or neck circumference, was significantly and positively associated with high ESS scores. Approximately 54% of twins in this sample reported snoring loudly or disruptively during sleep. Mean ESS score in snorers was 7.5 (SD = 4.0), whereas in non-snorers it was 6.7 (SD = 3.8, $P < 0.01$). Twin-pair similarity on ESS scores, regardless of zygosity, was statistically significant ($P = 0.001$). Corresponding intraclass correlations were 0.39 in MZ pairs and 0.21 in DZ pairs, respectively. Structural equation modeling indicated that a model with additive genetic influences and nonshared environmental influences best explained the observed twin-pair similarities on ESS scores. Additive genetic effects accounted for 38% of the total phenotypic variance (95% confidence interval of 33% to 44%) in ESS scores, whereas individual nonshared environmental influences explained the remaining 62% of the phenotypic variance. The analysis of twin concordance for extreme scores (ESS > 11) found proband concordance rates of 38% and 26%, respectively, in MZ twins and DZ twins (both $P < 0.01$). Fitting a structural genetic model to twin-pair similarity on extreme scores, we estimated the heritability of excessive daytime sleepiness to be 40% (95% confidence interval 11% to 50%).

Conclusions: These data are the first to demonstrate a significant heritability for scores on the Epworth Sleepiness Scale and determine twin-pair concordance rates for excessive daytime sleepiness. Further investigation of the genetic determinants of daytime sleepiness in the elderly is warranted.

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1316.P

The Contribution of Obesity to Genetic Variation in Daytime Sleepiness: A Bivariate Genetic Analysis in World War II Male Twins from the NAS-NRC Twin Registry

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Introduction: Daytime sleepiness is a common complaint associated with sleep apnea; however, sleepiness is also associated with aging and a variety of disease-specific and environmental factors including, but not limited to, habitual sleep schedules and duration, levels of social and occupational physical activity, and caffeine intake. Given that many diseases associated with sleepiness, including sleep apnea and obesity are at least in part under genetic control, we undertook an analysis to determine the extent to which the heritability of sleepiness is determined by genes influencing measures of body habitus and obesity.

Methods: Responses to the 8-item Epworth Sleepiness Scale (ESS) and self-reports of height, weight, and waist and neck circumferences were obtained from both twins of 1608 male-male twin pairs from the NAS-NRC World War II Twin Registry. The sample consisted of 840 monozygotic (MZ) and 768 dizygotic (DZ) twin pairs ages 69 to 82 years old. Subjects' self-reports of height and weight were used to calculate the body mass index (BMI) as a measure of overall obesity. Genetic analyses using structural equation models were used to test the following two hypotheses: (1) a significant genetic association between obesity and ESS scores exists; (2) there are, however, genes influencing daytime sleepiness above and beyond those influencing obesity.

Results: Independent analyses of ESS scores and obesity measures revealed that twin similarities on these measures can be explained solely by additive genetic and nonshared environmental factors. The estimated heritability for ESS scores was 38%, while the heritabilities of BMI, waist, and neck circumference were 54%, 52%, and 45%, respectively. There was no evidence that twin resemblance on ESS scores or obesity measures was influenced by environmental factors shared between twin brothers. For the sample as a whole, the phenotypic correlation between obesity and sleepiness was modest but statistically significant ($r = 0.10$ to 0.12, $P = 0.001$). Fitting bivariate genetic models to the joint distribution of ESS scores and obesity measures revealed that genetic effects influencing obesity only partly explain individual differ-

ences in sleepiness. A modest, but significant genetic correlation between BMI and ESS ($r = 0.25$, $P < 0.001$) was found, suggesting that 25% of the additive genetic variance was shared by BMI and ESS scores. There was no evidence, however, for a similar sharing of environmental influences. Replicating the bivariate genetic modeling with other measures of obesity (e.g., waist or neck circumference), similar findings emerged.

Conclusions: These data suggest a modest genetic overlap between obesity and daytime sleepiness as measured by the Epworth Sleepiness Scale. We found, however, that the vast majority of the estimated genetic variance in ESS scores could not be accounted for by individual differences in obesity measures. Whether physiologic measurements of sleep apnea may enhance interpretation of the sources of genetic variance in sleepiness remains to be determined.

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1694.A

Alterations in the Sleep Paterns in Beta-Amyloid Precursor Protein Transgenic Mice

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Introduction: Alzheimer's Disease (AD) is the most prevalent form of age-related neurodegenerative disorder. The pathogenesis of this neurodegenerative disease remains unclear. However, the disease is characterized by synaptic loss and neuronal death in some brain areas, with the presence of extracellular amyloid plaques (Selkoe, 1991). Transgenic mice overexpressing a mutant amyloid precursor protein (PDAPP) exhibit age-dependent neuropathology similar to that reported in AD (Games et al., 1995). To further characterize the behavioral and physiological profile of this mouse model of AD, we recorded and compared the sleep/wake cycle and circadian rhythmicity in both PDAPP transgenic mice and their nontransgenic littermates

Methods: Adult (5-7 month old) PDAPP transgenic mice and nontransgenic littermates were housed individually, with ad libitum access to food and water and maintained on a normal 12-hr light cycle (on 06:00 hr, off 18:00 hr). Mice were anesthetized with 1.0 % halothane and implanted for chronic sleep recordings. One week after surgery, mice were habituated to the recording conditions for at least 24 hours. Once the habituation period was completed, mice were recorded for 24 h beginning in the dark onset. Sleep recordings were visually scored and three stages were determined: wakefulness (W), slow-wave sleep (SWS), and rapid eye movement (REM) sleep. Statistical analysis was carried out using a Student's t test.

Results: Our results demonstrate that PDAPP transgenic mice spent significantly less time in SWS during the dark phase and spent more time in SWS during the light phase ($p < 0.05$ and $p < 0.01$, respectively; compared to nontransgenic mice). In addition, PDAPP transgenic mice showed a significant reduction in REM sleep during the last three hours of the dark phase ($p < 0.01$), compared to nontransgenic mice. The alteration in REM sleep was due to a significant decrease in the number of REM episodes ($p < 0.01$). On the other hand, the PDAPP transgenic mice spent significantly more time in W during the last three hours of dark and less time during the second three hours period of light ($p < 0.05$ and $p < 0.01$, respectively).

Conclusions: These results show that the most significant alterations in the sleep/wake cycle of PDAPP transgenic mice were observed during the dark phase period. Thus, it is likely that mice overexpressing the amyloid precursor protein could have alterations in the circadian mechanisms regulating sleep. Moreover, the significant decrease in the number of episodes of REM sleep observed in PDAPP transgenic mice support the hypothesis that mechanisms that trigger REM sleep are altered in Alzheimer's disease (Hassainia et al., 1997). Finally, our results suggest that PDAPP transgenic mice provide a useful animal model to study the alterations in the sleep/wake cycle observed during AD.

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1666.A

Effects of Microinjection of Orexin-A into the Preoptic Area on Sleep-Wakefulness in Rats

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Introduction: Orexins (Hypocretins) are hypothalamic neuropeptides (Orexins A and B) implicated in the regulation of several physiological functions such as feeding and sleep-wakefulness (Hagan et al, 1999). Mutations of the Orexin-2 receptor have been linked to the etiology of narcolepsy in the canine model (Lin et al, 1999). Orexin-containing neurons localized in the peri-fornical hypothalamus project to multiple areas involved in sleep /arousal regulation but have strong projections to the preoptic area (Peyron et al., 1998). Since the preoptic area has been implicated in control of sleep and body temperature, the possible effects of Orexin - A microinjection into preoptic area on sleep-wakefulness and body temperature were studied.

Methods: Four male Sprague-Dawley rats were chronically implanted with bilateral guide cannulae aimed at preoptic area, EEG and EMG electrodes, and a thermocouple for temperature measurement. Three days after recovery from surgery and following 8 hours habituation to the recording chamber, each rat was injected with 0.2 µl (~ 0.7 µgm) of Orexin A (1mM) or 0.2 µl saline vehicle and recorded for five hours, with two days between treatments. All injections were made in the light phase (ZT5). The records were visually scored for awake, light slow wave sleep (SWS1), deep slow wave sleep (SWS 2) and REM.

Results: Orexin-A microinjection into preoptic area caused, during the first hour, a significant increase in the percentage of awake (Orexin:88.35 ± 11.55 %; Saline: 30.95 ± 4.15%; $p < 0.0001$), and a decline in sleep percentages, including SWS 2 (Orexin:3.4 ± 3.4 %;Saline :36.6 ± 3.7%; $p < 0.0001$) and REM (Orexin:0.3 ± 0.3% ;Saline:6.5 ± 3.2%; $p < 0.05$). SWS 1 was suppressed for 30 minutes (Orexin:8.0 ± 7.8 %; Saline: 24.2 ± 1.0%; $p < 0.009$). Orexin A and saline vehicle microinjections induced equivalent fevers lasting 5 hours.

Conclusions: These findings support a hypothesis that wake-promoting and REM-inhibiting effects of Orexin A are mediated, at least in part, in the preoptic area. The sleep-inhibiting effects of Orexin-A were not related to changes in body temperature. The preoptic area may mediate the wake-promoting effects of Orexin-A observed after ICV application (Hagan et al, 1999). As the preoptic area has potent sleep-promoting effects, this area may be important in the generation of symptoms such as sleepiness that characterize the narcoleptic dog.

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1777.A

The effects of insulin on sleep in rats

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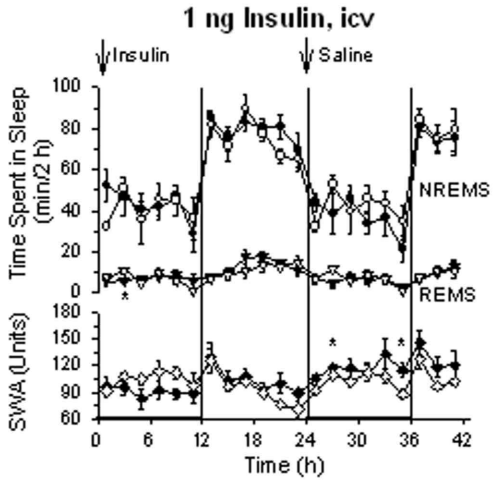
Introduction: Several gastrointestinal hormones are implicated in sleep regulation. For example, systemic injection of cholecystokinin and bombesin promotes sleep (reviewed in Kapas et al., 1993). Insulin, a pancreatic hormone, has been reported to suppress REMS and increase NREMS in the first few hours after intracerebroventricular (icv) injection (Sangiah et al., 1982; Danguir and Nicolaidis, 1984). The insulin preparations used in earlier studies in rats were purified beef-pork insulin preparations. Non species-specific proteins, however, may trigger immune responses. Any sleep change in response to the treatment may be due to the release of cytokines or other bioactive Immunomodulators. The aim of the present study was to test the effects of rat insulin on the sleep in rats.

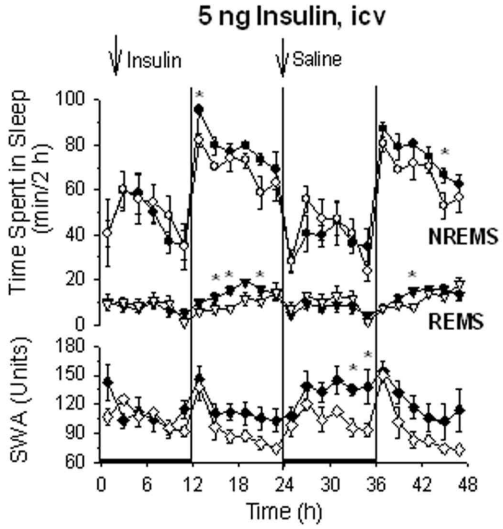
Methods: Adult male Sprague-Dawley rats were implanted with EEG and electromyographic electrodes. On the baseline day, the rats were injected with 5 µ l saline icv. On the test day 1 (n = 5) or 5 ng (n = 5) purified rat insulin (Linco Research Inc., St. Charles, Mo.) was given icv. On the following, recovery, day saline was injected again. All injections were done at dark onset.

Figure 1



Results: After the injection of 1 ng of insulin, there was a tendency to increased NREMS in the first two hours and a significant decrease in REMS in the second two hours. Slow–wave activity (SWA) of the EEG, which is often regarded as an indicator of NREMS intensity, was elevated during the recovery day after the insulin treatment. Five ng insulin elicited long-lasting increases in both REMS and NREMS. The effects became significant after a latency of ~12 h and were confined to the light periods of the test and recovery days. NREMS and REMS were increased by 51 ± 20 (~13%) and 30 ± 10 min (~60%), respectively, during the light period of the test day. SWA was increased from h 13 after insulin injection.Figure Legend: The effect of insulin on sleep and SWA in rats. Open symbols: baseline day. Solid symbols: insulin day. Solid bars: dark periods. Asterisks: $p < 0.05$.

Figure 2



Conclusions: Our results indicate that insulin promotes both NREMS and REMS in rats as well as NREMS intensity. We hypothesize that insulin, release from the pancreas in response to feeding, may act directly on the brain to induce sleep, especially after eating.

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1398.A

Prepro-hypocretin (Prepro-orexin) Levels are Unaffected by Short-Term Sleep Deprivation in Rats and Mice

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Introduction: Two lines of evidence have implicated the hypocretin/orexin ligand-receptor system in narcolepsy: identification of the canine mutation as a deletion in the hypocretin-2 receptor and the occurrence of cataplectic attacks and sleep-onset REM periods in prepro-orexin (prepro-hypocretin) null mutant mice. These mice also exhib-

it increased levels of REM and NREM sleep, short latency REM periods and decreased sleep bout lengths. In the rat, intracerebroventricular injection of orexin-A early in the light period increases wakefulness and reduces REM, suggesting that this system may be involved in the normal regulation of sleep and wakefulness. We therefore measured prepro-hypocretin (hcrt) mRNA levels in mouse and rat hypothalamus after short-term sleep deprivation (SD) and 2-4h after recovery sleep.

Methods: Adult male Wistar rats and C57BL/6 mice were implanted with EEG/EMG electrodes for sleep recording. Recordings were conducted for at least 48h of baseline, during 6h of SD and during recovery sleep. Twenty rats were randomly divided in 4 groups: (1) 6h SD from light onset (ZT0-ZT6); (2) control rats for the SD group; (3) 6h SD (ZT0-ZT6) followed by 2h of recovery (R) sleep (ZT6-ZT8); (4) control rats for the R group. Rats were sacrificed by decapitation at ZT6 for Groups 1 and 2 and at ZT8 for Groups 3 and 4. The experimental design for mice was similar except that n=7 per group and Groups 3 and 4 were sacrificed at ZT10, allowing 4h recovery sleep. Brains were rapidly removed, dissected into multiple regions and frozen on dry ice. Total RNA was isolated from each cortex and hypothalamus. Northern blots were prepared and hybridized to [32P] random prime-labeled cDNAs for c-fos, hcrt and beta-actin. RNA expression was quantified by phosphorimage analysis as ratios relative to beta-actin. mRNA levels were also quantified using the Taqman real-time fluorescence detection method. After first-strand cDNA synthesis from each sample, "target" cDNAs (cFos or hcrt) and a reference cDNA (G3PDH) were PCR-amplified simultaneously using an oligonucleotide probe with a 5' fluorescent reporter dye (6FAM for the targets and VIC for G3PDH) and a 3' quencher dye (TAMRA). Target cDNA and G3PDH amounts were determined in each sample and normalized to G3PDH.

Results: In both rats and mice, 6h SD resulted in a significant increase in total sleep time and EEG delta activity during the recovery period. ANOVA revealed a significant variation in c-fos mRNA levels in rat cortex ($p<0.0001$; $F=40.167$, $df=3,12$); post hoc tests revealed that the SD group had a 3-fold elevation of c-fos relative to each of the other groups ($p<0.001$). In rat hypothalamus, c-fos mRNA expression was also significantly increased by SD ($p=0.0018$; $t=4.22$; $df=10$). In contrast, hcrt expression in the hypothalamus was unchanged by SD or by recovery sleep ($p=0.33$; $F=1.26$; $df=3, 14$).In mouse cortex, ANOVA also revealed a significant variation in c-fos mRNA among the four groups ($p=0.013$; $F=5.466$, $df=3.12$); post-hoc tests revealed that the SD group had a 2-fold elevation of c-fos relative to each of the other groups ($p<0.01$). However, neither SD nor 4h recovery sleep affected hcrt expression in mouse hypothalamus. Taqman analysis also failed to find any significant change in hcrt expression in mouse hypothalamus ($p=0.90$; $F=0.20$; $df=3,23$).

Conclusions: We find no evidence in either rat or mouse hypothalamus that hcrt mRNA levels are modulated by short-term SD. If the hcrt system is involved in normal regulation of sleep and wakefulness, longer periods of SD may be necessary to affect hcrt mRNA levels or changes may occur at the protein rather than mRNA level. Alternatively, this system may be involved in another function that counterbalances any SD-induced changes in hcrt levels.

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1210.A

Adenosine Modulation of Intrinsic Delta Rhythms in the Isolated Whole Hippocampus of Mouse

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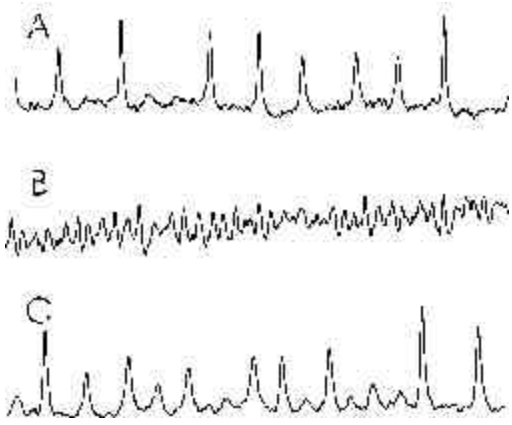
Introduction: Adenosine has been implicated in the control of sleep. Infusion of adenosine, and its agonists have been shown to increase delta EEG slow rhythms. However whether this effect is the result of adenosine action on "sleep control centers" or rather on local neuronal networks is unknown. In-vivo, slow delta rhythms are observed in the rat hippocampus with their highest amplitudes occurring during SWS. Utilizing our recently discovered isolated whole hippocampal in-vitro preparation, which spontaneously oscillates in the delta frequency range we examined the effects of adenosine receptor antagonists on this delta rhythm.

Methods: Hippocampi were isolated from mice (C57BL) and maintained in standard in vitro conditions for electrophysiological assessments. Simultaneous extracellular and patch clamp recordings were used to monitor rhythmic field potentials, and single cell activities from individual pyramidal neurons and GABAergic interneurons. Adenosine receptor antagonist 8-(p-Sulfophenyl)theophylline (8-PST) was applied through bath perfusion. Data were continuously collected, digitized, and frequency spectrum analyses were conducted offline via using Origin software.

Figure 1. Extracellular recordings in isolated hippocampal preparation, a) Intrinsic delta oscillation in control perfusion, b) 8-PST application induces theta oscillation, c) Recovery after wash, Scale Y=0.05mV, X=0.5s



Results: Our preliminary experiments indicate that application of the water soluble adenosine antagonist (8-PST), at concentrations preferential for the adenosine A1 subtype receptor (25 micromolar), resulted in 1)enhanced evoked synaptic responses, and 2)desynchronization of the slow delta rhythms with a concurrent induction of theta rhythm. Prolonged application of 8-PST was associated with large spontaneous bursting discharges. These effects were thoroughly reversible with wash.

Conclusions: The results indicate that endogenous adenosine is involved in the generation and maintenance of delta frequency rhythms in the local neuronal network of the mouse hippocampus. Thus, this provides the first evidence that adenosine is involved in the control of delta rhythmicity at the local neuronal level.

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1762.G

Infant Sleep and Temperament: Is there a Predictive or Concurrent Relationship?

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Introduction: The relationship between infants' sleep patterns and mother-reported temperament ratings has been the topic of many investigations (e.g., Halpern et al 1994; Keener et al 1988). These studies have reported small to moderate correlations between some temperament dimensions and some sleep-related variables and have analyzed relatively small samples of infants. The object of the current analysis was to examine the relationship between sleep and temperament in a larger sample of infants studied longitudinally.

Methods: The sleep patterns of 82 infants (41 males) were recorded for two consecutive nights at five ages across the first year of life using videosomnography. The tapes were coded for sleep-wake states using an established protocol and the following variables were determined: Longest Sleep Period (LSP), Total Sleep Time (TST), Number of Night Awakenings (NAWK), and the percentages of time spent Out of Crib (OOC) and Awake in the Crib (AW). Ratings of each child's Self-Soothing Status and Sleepaid Use were also determined for each night. Temperament was assessed at 3- and 12-months using the Infant Behavior Questionnaire (IBQ, Rothbart, 1981). The IBQ measures six dimensions of temperament: activity level, smiling and laughter, distress and latency to approach stimuli, distress to limitations, soothability, and duration of orienting. Pearson correlation coefficients were computed between LSP, TST, NAWK, OOC, and AW and each temperament dimension at 3 and 12-months. Correlations were also computed between the sleep variables at 1-month and temperament dimensions at 3- and 12-months. Finally, independent samples t-tests were computed to determine if the temperament dimensions differed based on the infants' self-soothing status or sleepaid use.

Results: No consistent patterns of correlations were found between sleep variables and temperament dimensions at 3- and 12-months; different relationships were observed at the two ages. At three months, OOC percent was positively associated with Distress to Limitations ($r = .28$, $p = .01$) and TST was negatively associated with Activity Level ($r = -.23$, $p = .04$). Distress was also related to Self-Soothing Status, with self-soothing infants rated lower than non-self-soothing infants ($M = 2.94$ & $M = 3.64$, respectively, $t = 2.37$, $p = .03$). At 12-months, AW percent was positively associated with Duration of Orienting ($r = .24$, $p = .04$) and NAWK was negatively associated with Soothability ($r = -.34$, $p = .00$). Also, Activity was related to Sleepaid Use, with sleepaid-users rated higher than non-sleepaid-users ($M = 4.23$ & $M = 3.82$, respectively, $t = -2.21$, $p = .03$). Two predictive relationships were found between sleep variables at 1-month and temperament dimensions at 3-months. Both TST and LSP at 1-month were negatively associated with Distress at 3-months ($rs = -.33$ & $-.38$, respectively, $p = .00$).

Conclusions: Consistent with previous research, this analysis revealed some moderate correlations between sleep and temperament. The negative relationships between LSP and TST at 1-month and Distress to Limitations at 3-months are particularly compelling. Infants who have more mature sleep patterns at 1-month tend to be rated by their mothers as exhibiting less distress to limitations at 3-months. A similar relationship does not hold for distress ratings at 12-months. The temperament ratings, however, were only moderately correlated between 3- and 12-months, so this result is not overly surprising. Perhaps most intriguing is the relationship found between self-soothing status and distress at 3-months. Self-soothers were rated significantly lower on distress to limitations than non-self-soothers.

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1165.G

Effect of Supplemental Oxygen on Sleep Architecture and Cardiorespiratory Events in Premature Infants

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Introduction: Although the effect of supplemental oxygen (SupOx) on oxygenation, apnea and bradycardic events and sleep architecture in premature infants has been previously investigated, there is very limited information on this issue. Improved oxygenation with SupOx decreased apnea incidence and respiratory periodicity in pre-term infants (Weintraub et al. 1992). In addition, higher oxygen saturations increased sleep efficiency but did not influence REM sleep duration or arousal index in infants with bronchopulmonary dysplasia (Fitzgerald et al. 1998).

Methods: We conducted a polysomnographic evaluation of 10 premature infants born at 30.6+3.0 [SD] wks postconceptional age (PCA) and studied at 39.0+5.8 PCA, who were free of any adverse events including cardiorespiratory monitor alarms in the nursery for at least 1 week prior to the study. All infants were considered as ready for discharge from the nursery while breathing room air (RA) by their caretakers. The studies were performed on RA for 4 hrs, and then SupOx was initiated via nasal canula at 0.25 l/min for an additional 4 hour period. The standard infant montage was employed which allowed for the assessment of body position, left and right EOG, 3 channel EEG, chin EMG, pulse oximetry and pulse waveform, thoracic and abdominal inductance plethysmography, nasal airflow, end-tidal pCO2, transcutaneous pO2 and pCO2. Sleep scoring was performed using standard criteria for the scoring of states of sleep and wakefulness in newborn infants (Andre et al. 1971). For periods corresponding to RA and SupOx, the time spent in active (AS), quiet (QS), or undetermined sleep states expressed in %TST (total sleep time), and sleep efficiency were analyzed. For cardiorespiratory data, respiratory disturbance index (RDI), periodic breathing (%TST), number of bradycardic, oxyhemoglobin saturation (SaO2), and end-tidal pCO2 were examined.

Results: QS density was increased during SupOx (38.9+9.9% vs. 32.9+9.1%TST in RA, $p<0.005$). However, this was associated with a reciprocal decrease in AS density (53.1+9.0 % vs. 58.0+9.2 %TST in RA; $p<0.01$). No differences in sleep efficiency occurred (70.9+10.8% SupOx vs. 68.5+5.8% RA, p-NS). SupOx elicited significant decreases in RDI (4.2+2.2 events/hr vs. 11.7+7.9 events/hour in RA , $p<0.002$), a

decrease in the percentage time spent in periodic breathing (4.8+3.7% vs. 14.7+11.8% in RA, p<0.005) and improved overall SaO2 (98.7+1.4% vs. 95.4+2.3% in RA, p<0.01). A trend towards decreased frequency of bradycardic events (2.0+2.3 events vs. 4.7+3.7 events in RA, p>0.05) was also present. No changes in alveolar ventilation, as derived from end-tidal pCO2 were detected during SupOx (36.2+5.9 mmHg vs. 36.2+5.8 mmHg inRA, p-NS).

Conclusions: Asymptomatic pre-term infants exhibit frequent and potentially clinically adverse cardiorespiratory events when assessed in the sleep laboratory. Administration of supplemental oxygen to these infants will lead to increases in the overall duration and percent TST spent in QS with reciprocal changes in AS. In addition, improvements in respiratory stability without any adverse effect on alveolar ventilation occur with low flow SupOx. Thus, more liberal use of SupOx in a priori healthy pre-term infants may lead to enhanced cardiorespiratory stability, and prevention of ALTE and SIDS in this vulnerable population.

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1397.G

An Association Between Attention Deficit Disorder and Obstructive Sleep Apnea in Children

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Introduction: The relationship between sleep and pediatric behavioral and learning disorders is complex. Children with attention deficit and hyperactivity disorder (ADHD) have increased number of awakenings that disrupt their night's sleep (Kaplan, 1987). In that study, parents also perceived that their children were generally poor sleepers. Chervin, in 1997, found that children with ADHD experienced an increased incidence of habitual snoring, which suggested a sleep-related breathing disorder (SRBD). Studies have not examined the presence of obstructive sleep apnea syndrome (OSAS) in this population as diagnosed by polysomnography. We hypothesize that a correlation exists between children with OSAS and ADHD.

Methods: The study was a retrospective review of all children who underwent polysomnographies for snoring in our pediatric sleep laboratory from July 1996 through January 1999. Criteria for inclusion was age greater than five years. Exclusion criteria were as follows: neurological disorders, psychiatric diagnoses (other than ADHD), chronic respiratory diseases, and concomitant sleep disorders. Physiologic sleep parameters examined included the following: total sleep time, sleep efficiency, sleep latency, REM latency, total number of awakenings, total arousals, and subjective degree of snoring. Insurance status was divided into private insurance versus medicaid. Statistical evaluation utilized the student t test, and p <0.05 was considered significant.

Results: A total of 184 completed polysomnographies were evaluated and 86 studies were selected for inclusion. Groups were divided into obstructive sleep apnea syndrome (OSAS) and non-OSAS (NOSA) groups (eg. primary snoring or normal). A total of 40 children were identified in the OSAS group and 46 in the NOSA group. In the NOSA group, 22 were male as compared with 28 males in the OSAS group. Mean age of the NOSA group was 8.86 ± 3.06 years and OSAS group was 10.11 ± 3.50 years. In those children diagnosed with OSAS, five of 40 were diagnosed with ADHD versus one of 46 in the NOSA group (p< 0.05). There was no statistically significant difference in other sleep parameters or insurance status.

Conclusions: Our findings suggest that there is an association between OSAS and ADHD. Our polysomnography study compliments Chervin and colleagues' parent survey, and partially explains their correlation between sleep-related breathing disorders and inattention levels in their ADHD population. However, there are no data or prospective studies that determine whether OSAS contributes to the presence or severity of ADHD, or if children with ADHD are at increased the risk for OSAS. A number of studies have revealed behavioral and growth abnormalities in children with OSAS, which improved after adenotonsillectomy. This suggests that OSAS could worsen the severity of ADHD. Follow-up of these children after adenotonsillectomy may provide insight into the relationship between OSAS and ADHD. Given these results, a larger, prospective, multicenter study examining ADHD and OSAS is recommended.

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1652.G

Risk Factors, Symptomatology, and Polysomnography in Obese and Overweight Children and Adolescents with Obstructive Sleep Apnea Syndrome (OSAS)

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Introduction: Although studies implicate obesity as a significant risk factor for OSAS in adults, a relative paucity of data exists regarding the association of obesity and OSAS in children.Estimates of increased risk for OSAS in obese children vary, from a 4 to 5-fold increase (Redline et al,1999)in a non-referral population to a 68% incidence of OSAS in children with an ideal body weight (IBW)>200% (Silvestri et al,1993). A range of correlations between the degree of obesity in children and polysomnographic (PSG) measures have also been reported. In order to further examine the relationship between obesity and OSAS in children, we compared putative risk factors, clinical symptoms, and PSG variables in 3 groups of children (obese, overweight, and average weight) meeting clinical and PSG criteria for the diagnosis of OSAS.

Methods: 114 children (mean age 7.9 S.D. 3.7 yrs,range 3.0 - 17.6) evaluated in a children's teaching hospital for OSAS were divided into 3 weight groups based on Body Mass Index(BMI): Obese (BMI>29,n=16),Overweight (BMI 26-29,n=19),and Average (BMI 16-25,n=79).The 3 groups were compared on the presence of OSAS risk

factors (demographic variables,upper and lower airway problems,family history of snoring),sleep-related symptoms of OSAS (snoring,etc) and disease severity-related PSG variables (Apnea-Hypopnea Index(AHI),O2 saturation, arousals)

Results: Both the Obese (mean age=10.1yrs) and Overweight (mean age=10.4)groups were significantly older($p<.001$) than the average group (mean age=7.3);there were no group differences in gender, SES,or race.There were also no differences in the prevalence of upper and lower airway disease symptoms among groups; however, the Obese and Overweight groups were more likely to have a history of adenotonsillectomy. The only group difference in OSAS symptoms was increased sleep hyperhidrosis in the Overweight group.There were no significant correlations between BMI and PSG variables;however, the mean AHI of the Overweight group (AHI=15.2,SD 17.4) was significantly greater than the other two groups (Obese AHI=8.3,SD 7.2;Average AHI=8.2 SD7.7,$p<.05$); a similar trend was found for nadir O2 saturation.

Conclusions: Our data suggests that a substantial percentage of children with OSAS are overweight (31% of the sample),but that disease severity does not correlate with BMI.The group age distribution also suggests that weight may become a relatively more important risk factor for OSAS starting in mid-childhood. Given the increasing numbers of obese and overweight children in the U.S.,and the fact that obesity in mid-childhood and adolescence is a significant predictor of obesity in adults, our results support targeting intensive weight interventions towards at-risk school-aged populations.

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1785.G

Sleep Disturbance in Infants of Substance Abusing Mothers

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Introduction: Sleep disturbances in infants and toddlers are commonly reported by parents. The present study investigated the sleep-cycle characteristics of infants with mothers who had a substance abuse history.

Methods: A total of twenty infants of mothers who were participating in a parent-infant residential treatment program for substance abusing mothers were enrolled in this study. They were followed longitudinally and were videotaped using our established time lapse video protocol (Anders & Sostek, 1976). Recordings were obtained on two consecutive nights at ages one, three, six, nine, and twelve months of age. Some subjects did not enter the study until age three months, and some did not complete the study to age twelve months. From the coded sleep data the following variables were derived: Active Sleep (AS) percent, Quiet Sleep (QS) percent, Awake (AW) percent, Out of Crib (OOC) percent, Longest Sleep Period (LSP), Total Sleep Time (TST), and Number of Awakenings (VARS). Comparisons to sleep/wake patterns of same age infants of non-substance abusing mothers were made for all sleep variables. All substance abusing mothers used substances during at least part of their pregnancy. All of the pregnancies were unplanned. Substance abusing mothers were unemployed, living on public assistance, and in a drug rehabilitation program during their participation in the study. Cessation of substance abuse and onset of treatment varied widely across the twenty mothers, with a few mothers not beginning treatment until after the birth of her infant.

Table 1. Means (SDs) of Sleep Variables for Hi-risk Sample

	1m	3m	6m	9m	12m
n	14	11	9	5	6
AW%	6.0 (3.1)	3.5 (2.4)	6.2 (3.5)	3.2 (2.9)	3.5 (3.1)
OOC%	25.1 (17.9)	7.6 (5.2)	13.4 (11.6)	8.8 (12.0)	3.4 (4.8)
QS%	26.4 (8.6)	40.3 (5.4)	42.9 (8.9)	46.9 (8.9)	51.7 (8.5)
AS%	61.4 (9.7)	53.5 (5.4)	47.1 (9.4)	46.3 (7.1)	44.4 (8.0)
LSP (min)	178.6 (93.8)	257.0 (123.4)	193.9 (81.3)	228.9 (131.6)	240.5 (73.8)
TST (min)	389.9 (115.3)	416.1 (95.5)	385.2 (107.9)	417.2 (191.4)	393.2 (129.9)
VARS	4.9 (3.0)	2.5 (1.4)	3.9 (2.4)	1.9 (1.9)	1.4 (1.5)

Results: There were no significant differences between the substance abusing and control groups in QS and AS across the first year of life. Both groups showed the expected rise in QS and decline in AS from one to 12 months. Also, both groups showed a marked decrease in OOC time from the beginning to the end of the year. However, hi-risk infants showed an upsurge in OOC at 6 months that was not displayed in the control infants. The LSP and TST scores of the hi-risk infants are noticeably less than the control subjects, especially in the second half of the first year. However, the only significant difference between the groups in LSP and TST occurred at 6 months ($t = -3.21$ & $t = -2.46$, respectively, $p < .05$). Additionally, we did not see a rise in LSP followed by a leveling off during the second half of the year in the hi-risk group that was observed in the control group. Although the number of awakenings at the end of the year in the hi-risk subjects was somewhat less than in our controls, the number of awakenings and percent awake seemed to follow similar trends over the year.

Table 2. Means (SDs) of Sleep Variables for Control Sample

	1m	3m	6m	9m	12m
n	81	81	80	79	77
AW%	5.5 (3.5)	4.6 (3.2)	5.6 (3.7)	5.0 (4.6)	5.1 (4.4)
OOC%	21.8 (15.9)	8.3 (9.3)	7.1 (11.0)	6.2 (9.5)	6.4 (10.1)
QS%	24.8 (8.8)	38.4 (6.8)	44.8 (8.2)	49.8 (8.1)	51.9 (6.8)
AS%	66.2 (9.3)	55.8 (6.1)	48.6 (7.1)	43.9 (7.2)	40.8 (8.7)
LSP (min)	183.3 (58.2)	279.8 (106.4)	293.5 (134.4)	285.8 (122.8)	287.2 (119.4)
TST (min)	347.4 (112.8)	443.5 (114.8)	480.6 (128.3)	469.7 (137.9)	483.2 (133.8)
VARS	4.2 (2.5)	2.7 (1.7)	2.9 (2.1)	2.7 (2.5)	2.5 (2.0)

Conclusions: This is the first video study of this subject population. The patterns of sleep/wake development are similar to what has been previously reported. There did appear to be differences between the two groups for LSP and TST, particularly during the second half of the first year. However, the sample size is small and attrition, which likely reflects a chaotic lifestyle, is high. Control subjects were not specifically matched. Further research is necessary.

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1182.G

Estimated Frequency of Obstructive Sleep-Related Breathing Disorders in General Pediatric Practices

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Introduction: Obstructive sleep-related breathing disorders (SRBDs) are common in children: obstructive sleep apnea is thought to affect between 0.7 and 3.0%,[1,2] and an unknown number have upper airway resistance syndrome. The frequency of SRBDs may be particularly high among children seen in pediatrician's offices, where SRBD risk factors — such as asthma, chronic nasal congestion, and hypertrophic tonsils - are especially common. We used a validated questionnaire to estimate what proportion of children seen at 2 general pediatrics clinics were likely to have SRBDs.

Methods: Surveys were administered at general pediatric practices that are university-owned but situated apart from the main medical campus and largely community-based. Subjects were 830 children (458 boys) between the ages of 2 and 13.9 years (mean ± s.d. = 6.7 ± 3.2) whose parents completed the Pediatric Sleep Questionnaire (PSQ) while waiting for an appointment. The PSQ contains a validated 22-item SRBD scale that includes questions about snoring, observed apneas, daytime sleepiness, daytime behavior, and other common symptoms.[3] Habitual snoring was defined as a positive response to one item that asks whether the child snores more than half the time while asleep. The overall SRBD score ranges from 0.0 to 1.0, and scores of 0.33 or higher were shown previously to identify polysomnographically-defined obstructive SRBDs with a sensitivity of 0.81 and a specificity of 0.87; among 54 subjects with SRBDs and 108 children at a pediatrics clinic (and conservatively assumed to have no SRBDs), the SRBD score correctly classified 85%.3 In the current study, data were grouped for analysis by gender and age [groups A, 2.0-4.9 years (N=315); B, 5.0-7.9 (N=231); C, 8.0-10.9 (N=172); D, 11.0-13.9 (N=112)].

Results: Habitual snoring was reported in 18.0 % (95% C.I. [15.3, 20.6]) of the total sample. Age groups and genders showed no significant differences. The mean SRBD score was 0.15 (95% C.I. 0.14 - 0.16). A positive SRBD score (0.33 or higher) was found in 11.4% (95% C.I. [9.28, 13.6]) of all the children; in 13.3% of boys and 9.1% of girls (chi square p = .06); and in 8.6, 13.9, 14.0, and 10.7 % of age groups A, B, C, and D, respectively (p = .17).

Conclusions: These findings suggest that obstructive SRBDs are highly prevalent among children seen in general pediatric practices. Although the PSQ may misclassify some children, the current study suggests that SRBDs are present among general pediatric patients at about 4 to 16 times the frequencies reported for obstructive sleep apnea alone in the general population. Specified age groups did not show statistically significant differences, but somewhat increased SRBD frequencies between the ages of 5.0 and 10.9 years could represent a delayed effect of tonsillar enlargement, relative to the pharynx, which is most prominent between 2 and 7 years of age.

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1350.K1

Echcocardiographic Changes in Children with Obstructive Sleep Apnea

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Introduction: Obstructive sleep apnea (OSA) is associated with a heightened sympathetic activity and a parallel increase in systemic blood pressure (BP) during and following the period of apnea. Since the elevation in BP cannot be explained by an increase in cardiac output, the likely reason for the elevation in BP is an increase in total peripheral resistance (TPR). We hypothesized that repetitive increase in TPR leads to remodeling and hypertrophy of the left ventricle (LV).

Table 1

Variables	A/HI< 5	A/HI> 5	*P value*
Number	6	10	
Age (years)	10.3 ± 4	9 ± 7	**NS**
WT (Kg)	41 ± 25	48 ± 37	**NS**
Ht cm	128 ± 1.7	124 ± 3.9	**NS**
BMI	22.8 ± 8.1	26 ± 7.2	**NS**
AHI	2.5 ± 1.3	22 ± 15	**0.006**
RV from 95th	(-) 12.9 ± 13	(-) 7.5± 31	**NS**
LV dimension From 95th	(-) 0.4 ± 6.	(-) 3 ± 16	**NS**
Septum from 95th*	(-) 28 ±12.	(-) 3 ± 21	**0.007**
Relative wall thickness*	0.27±.004	0.34±0.06	**0.04**
LV mass/HT$^{2.7}$*	30.6 ± 5.3	50 ± 23	**0.03**
LV mass/HT ^{3}*	28.4 ± 4.6	48.9± 26.5	**0.04**
Number of Subjects with LV mass/HT$^{2.7}$ > 95th	1	7	
LV mass/HT$^{2.7}$ 51gm/m^{27}	0	5	
Concentric hypertrophy	0	2	
Eccentric hypertrophy	1	5	
Normal geometry	5	3	

Methods: 16 children 2-17 years of age with OSA and no underlying cardiovascular disease underwent an echocardiography following an overnight polysomnography. The subjects were divided in two groups according to apnea/hypopnea index (AHI). None of the subjects had sustained daytime hypertension. Right and left ventricular dimensions were obtained from echocardiography. An index for each measurement was obtained by calculating the difference between the measured value and the 95th percentile for that measurement according to the subject's age. The LV mass was indexed to body size by dividing the LV mass by height exponent. Subjects were classified by the LV geometric patterns into those who had concentric hypertrophy, eccentric hypertrophy and normal geometry. Data were compared between groups using Student's t test

Results: The results of this study demonstrated significant differences between the two groups in septum thickness, relative wall thickness, and left ventricular mass index. The average LVmass/HT 2.7 in children with

AHI>5 reached a level of (50 gm/m2.7) which is close to the level of 51 gm/m2.7 that is considered a cutoff point beyond which there is 4.1-fold risk of cardiovascular morbidity in adults with hypertension. No difference was found between groups in right and left ventricular dimensions

Conclusions: This study demonstrates that children with moderate to severe degree of OSA develop hypertrophy of the left ventricle to a degree that increases the risk for future cardiovascular morbidity. Identification of the changes of the geometry of the LV could therefore represent early evidence of cardiovascular complications from OSA in children

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1347.D

Feelings Evoked by Dream Characters: How do these Compare to Feelings Evoked by their Waking Counterparts?

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Introduction: Feelings are evoked in us by people we know. We evoke feelings in people we know. In a dream both the dream characters and the emotions they evoke are created by the dreaming brain. In the case when a dream character was reported to have a waking counterpart, we investigated if the dream character differed from his/her waking counterpart in the feelings evoked to help answer the question: To what extent does the dreaming brain alter our feelings for characters known to us in waking life?

Methods: To do this we asked 35 subjects (17 men and 18 women students taking a course at the Harvard University Extension School) to record over a two-week period the feelings evoked in them by dream characters they believed represented a waking counterpart. The 35 subjects contributed 320 dream reports plus a log in which they recorded their feelings. In each case, the subjects were instructed to record whether these feelings were different from those expected from the dream characters' corresponding waking counterparts.

Results: Analysis of the data has shown that 609 out of 1205 or approximately 50% of the dream characters were known to the subjects. Of these known dream characters, subjects found that 60% of them were discernably different from their waking counterparts. And relative to all discernable differences betweeen dream characters and their waking counterparts, feelings accounted for 49% of these differences, behavior 33%, age and appearance 18% each.

Conclusions: The dreaming brain creates a dream character that often differs from its waking counterpart. Differences were found in appearance, behavior, age and feelings. We conclude that emotions like other attributes are not tightly linked to known characteristics of persons known in waking life. We believe this is due in part to the differential activity of, for example, the dorsal lateral prefrontal cortex and limbic and paralimbic brain areas (Maquet et aL, 1996; Braun et al., 1998; Kahn et al., 1997).

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1426.D

Happiness in Dreams: Associations with Waking Happiness, Skills, and Challenges

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Introduction: The hypothesis that dreams mirror waking cognition and emotions has generally been tested with negative or problematic emotions and events. We extend this work with a sample that includes many happy, skilled individuals. Following Csikszentmihalyi and LeFevre (1989) we also assess the effects and interactions of levels of waking skills and challenges.

Methods: 108 participants (M=36, F=72, mean age=29.5yrs, SD=16.4, range 14 - 78yrs) completed the Depression-Happiness Scale (Joseph and Lewis, 1998), two 10-point scales to answer the questions 'Considering all areas of your life, how challenged do you feel in your life?' and 'How skilled are you to meet these challenges?', rated their dream recall frequency, wrote down the last dream that they could recall (if any), and rated how they felt in the dream from 0 (unhappy) to 4 (happy). Following Winget and Kramer (1979, pp.43-46 and 52-53), dream reports were also independently blind rated for hedonic tone from 1 (very unpleasant) to 7 (very pleasant), and for level of challenge/threat from 0 (no challenge/threat) to 4 (extreme challenge/threat of imminent death or injury).

Table 1

	Dream		Waking			
	rcall	happ	happ	skill	chal	Age
Mean =	2.4	1.8	50.6	5.4	6.0	29.5
Dm rcall r=		.22*	.07	.01	-.05	-.16*
Dm happ r=	.22*		.19*	.29**	.01	-.36***

Results: Table 1 shows the means for variables, and their linear correlations with frequency of dream recall per week (n=108) and self-assessed dream happiness (n=91). A quadratic inverted-U function of waking happiness, (b0=-3.72, b1=0.216, b2=-.002) fitted better (R=.30) to dream happiness than the positive linear function alone, due to individuals with waking happiness >63 (n=11) having a mean dream happiness score of 1.4, against 1.9 for the (n=80) others. On stepwise regression dream happiness was found to be predicted by age (Beta = -.35, t=-3.67, p<.001) and the quadratic function of waking happiness (Beta = .29, t=3.01, p=.003), but not by gender, waking skills, or challenges. Under regression dream recall frequency was only predicted by dream happiness (Beta=.22, t=2.10, p=.038). If the sample was categorized into low/medium/high skills, and low/high challenges, dream happiness increased with level of skill (low skill, dream happiness M=.67; medium skill, M=1.7; high skill, M=2.2; F(2,85)=5.97, p=.004) but the two levels of challenge did not differ in dream happiness nor interact with level of skill. Independent blind ratings of each dream report for level of challenge/threat did not correlate significantly with waking challenges, whereas blind ratings of dream hedonic tone with waking happiness approached significance (r=.187, p=.053). (table should be placed here)*p<.05 **p<.005 ***p<.001

Conclusions: Happiness when awake is not associated with dream recall

frequency, but is significantly associated with happiness in dreams. The quadratic element to the latter needs replicating because of its implications for whether dreams mirror the full range of waking emotions, or are more responsive to negative emotions or challenges, although level of waking challenges was not reflected in the dreams here.

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1656.D

A Relationship Between Nightmare Content and Somatic Complaints in a Sleep Disordered Population: a Preliminary Study

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Introduction: It has been suggested that dreams and nightmares may be influenced by the biological state of the dreamer (Smith, 1984,1987). This study tested the hypothesis that somatic stimuli or concerns are incorporated into manifest nightmare content.

Table 1

Somatic Complaint	Related Dream	% with dream	X2=	P=
Heart Problems (n=4)	Pressure on Chest	75	.377	Ns
Heart Problems (n=4)	Heart Pounding	75	.458	Ns
Muscular Weakness (n=42)	Escaping/ Wanting to escape	62	.004	Ns
Muscular Weakness (n=42)	Not able to move	52	.523	Ns
Abnormal Blood Pressure (n=2)	Heart Pounding	100	1.428	Ns
Paralysis (n=9)	Not able to move	67	1.432	Ns
Numbness (n=21)	Not able to move	57	.866	Ns
Poor Health in general (n=13)	Dying/ being dead	23	.171	Ns
Excessive Perspiration (n=14)	Perspiring	86	7.40	.0065
Difficulty Breathing (n=17)	Choking/cannot breathe	47	6.58	.0103

Methods: These data were compiled from patient questionnaires completed by each patient seen at the Sleep Disorders Laboratory prior to overnight polysomnography (PSG). From a cohort of patients seen between 1995-1998, 124 subjects were selected. Inclusion criteria were: finding on an overnight study indicating obstructive sleep apnea or narcolepsy or periodic k-alpha/alpha EEG arousal disturbance or periodic leg movements during sleep. Exclusion criteria were: a diagnosis of an associated primary medical or mental disorder; medications known to affect dream mentation. Data were obtained from the Wahler Physical Symptoms Inventory (42 items) and the nightmare content section of the TWH Sleep-Wake questionnaire (37 items). On the Wahler 0-5 scale, scores of 0 (=never) to 2 (=once a month) were coded as symptom absent, whereas scores of 3 (=once a week) and higher were coded as symptoms present. On the Sleep-Wake Questionnaire 0-3 scale, a score of 0 (=never) was coded as dream absent, and scores of 1(=sometimes) and above were coded as present. Chi-square (x2) tests were performed to examine the association between: I) each somatic complaint and the related dream content item; II) each diagnostic category (based on PSG) and the related dream content items.

Results: I) Bad dreams more than 1/month were reported by 84.6% of the entire (N=105) sample. Of the ten symptom- dream pairs tested, only two proved to be significant (See Table below). II) Recurring dreams (X2=5.19, p=. 023) and dreams of paralysis (X2=3.93, p=. 047) were significantly associated with a diagnosis of narcolepsy.

Conclusions: This preliminary study revealed the following:I) There was a significant association: a) between complaints of excessive perspiration and dreams about perspiring; b) between reports of difficulty breathing while awake and dreams with feelings of choking and suffocation.II) Reports of recurring dreams and dreams of paralysis are significantly associated with a diagnosis of narcolepsy. Otherwise, there was, in this study, no reliable association between dream content and the diagnosis of primary sleep disorders.

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1187.D

REM Sleep Processes and Dream Content in Posttraumatic Stress Disorder

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Introduction: Posttraumatic stress disorder results from exposure to a severely stressful event such as combat exposure, sexual assault, physical and/or emotional damage from accidents or exposure to natural disasters. Intrusive recollections of the event during the day, as well as repetitive nightmares are characteristic symptoms of this disorder. The relationship between sleep states and PTSD manifestations such as recurring or disturbing dreams remains unclear. Both increased and decreased REM latencies have been reported. In severe cases, total sleep reduction with lower than normal amounts of both REM and NREM sleep have been observed. It has been hypothesized by several authors that the REM sleep which normally provides restorative activity for the individual is non-functional in PTSD patients. The present study was done to examine the dreams of females who were assessed to have moderate PTSD. However, unlike the subjects in some PTSD studies, the females were not severely depressed and did not have a history of substance abuse.

Methods: Subjects were 10 female freshman college students from Trent University. The participants were initially chosen using the PTSD Severity Scale (self report scale) and the Impact of Event Scale. All promising subjects were then screened on the Beck Depression Inventory and the Trent Sleep Questionnaire. Final participants were then given the Clinician Administered PTSD Scale for DSM-IV (CAPS-DX) to measure the severity of the PTSD. Five normal and five PTSD individuals were chosen to be in the study. Subjects all spent an acclimatization night in the sleep lab with standard EEG (C3/A2, C4/A1), horizontal EOG and EMG placements. The electrodes were attached to a paperless polygraph system and all records were scored using Rechtschaffen and Kales. On night two in the sleep lab, subjects were awakened after their second, third and fourth REM periods. Dreams were recorded on audio tape for later transcription. Dreams were analyzed using the content analysis system of Hall and Van de Castle.

Results: Dreams: The mean number of stressful characters present (characters present during the stressful event) was higher for the PTSD than for the normal subjects [$F(1,8) = 14.24$, $p<.005$]. PTSD participants also had a greater frequency of colours described in their dreams [$F(1,8) = 23.27$, $p<.001$] than did the controls. The same general results were found for achromatic colours. PTSD participants reported many more images of black, white or grey [$F(1,8) = 22.22$, $p<.001$]. Post hoc tests revealed that the number of achromatic colours of the second recorded dream were higher than those in the first or third dream as well as any of the control dreams ($p < .05$). Number of descriptive elements (size, age, density, temperature, etc.) was also higher for the PTSD vs. the control

participants [F(1,8) = 19.31, p < .002]. Post hoc analyses showed dream two of the PTSD subjects to be higher than any of the control dreams (p < .05). There were no differences between groups on number of negative emotions or environmental press. PTSD dreams were no more likely to be about the past, or to be more repetitive. Sleep: There were no differences between these groups in terms of any of the sleep stages, number of rapid eye movements (REMs) or latency to onset of any of the REM periods.

Conclusions: The dreams of participants exhibiting moderate levels of PTSD had more stressful characters relating to a traumatic event than did controls. PTSD dreams were more vivid in terms of both chromatic and achromatic colour and had more descriptive elements. Generally the dreams could be judged to be more vivid than the dreams of the controls. On the other hand, PTSD dreams were no more unpleasant, repetitive, or tended to occur more in the past than the dreams of control participants.

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1079.I

Constructing a Dream in the Laboratory

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Introduction: Our recent studies have been based on the view that the center of a dream is the Contextualizing Image (CI), which contextualizes (provides a picture-context for) the dominant emotion of the dreamer.[1] Studies using a reliable rating scale for the number and intensity of CIs (the CI score) have demonstrated that CI scores are higher in dreams than in daydreams, higher in reports obtained from REM than from non-REM sleep, sleep onset, or waking (see elsewhere in this volume), and higher after trauma than at other times.[2] If the CI is indeed what characterizes a dream most clearly, it might be possible to construct a dream, or something very dreamlike, in a waking subject under relaxed conditions. Indeed, waking material can at times be quite dreamlike: daydreams in some subjects receive dreamlikeness and bizarreness ratings approximately equal to those of dreams.[3]

Methods: Forty-eight college-student subjects in a classroom situation received an answer booklet with six blank pages. On the first blank page they were asked to write a detailed description of their most recent remembered daydream. On the second they were asked to write the daydream that stood out the most in their memory. For the third page they were asked to sit still with closed eyes and let a daydream develop for three minutes, then to write down a detailed description. For the fourth page they were given a relaxation procedure, were asked to experience an emotion close at hand and to intensify this emotion, to let a daydream develop while holding on to the emotion, and then write a detailed description. On the fifth page they were asked to write a detailed description of their most recent dream, and on the sixth a detailed description of a dream that stands out in memory. They were asked not to use words such as "dream" or "daydream" in their reports.The six descriptions produced by each subject (recent DD, memorable DD, lab DD, lab DD with emotion, recent D and memorable D) were rated on a blind basis for bizarreness and dreamlikeness by two scorers using eight point rating scales developed by Foulkes. Inter-rater reliabilities were acceptable for bizarreness in all six conditions (.79 ³ r ³ .62), but were somewhat lower for dreamlikeness, r's ranging from about .72 for most of the six conditions down to .14 for the lab DD with emotion. The scores from the two raters were averaged for further analysis.

Results: See table. On bizarreness the lab DD with emotion was not significantly different from the most recent dream (t(43) = 1.01), though it was significantly more bizarre the lab DD and most recent DD. On dreamlikeness, again the lab DD with emotion was as dreamlike as the most recent dream (t(43) = .51), and was significantly more dreamlike than the lab DD.

Table 1

Scale	*Condition*		
	lab DD	**recent DD**	**memorable DD**
Bizarreness	2.34 ± 1.84	2.43 ± 1.66	2.64 ± 1.87
Dreamlikeness	4.15 ± 1.72	4.41 ± 1.68	4.39 ± 1.60
Scale	*Condition*		
	lab DD w/ emo	**recent D**	**memorable D**
Bizarreness	3.00 ± 2.03	3.33 ± 2.16	4.39 ± 2.14
Dreamlikeness	4.66 ± 1.02	4.81 ± 1.72	5.49 ± 1.47

Conclusions: Overall, the results make it clear that the "lab DD with emotion" condition produced very dreamlike material, not distinguishable in our ratings from the most recent dream. Qualitative examination of the "lab DD with emotion" reports also demonstrates that very dreamlike material was produced. Thus, as suspected from much previous data, the state of sleep is not essential for dreamlike material to occur. Very dreamlike material can result when imagery develops in a subject experiencing strong emotion.

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1205.K2

Contribution of Sleep-onset REM Periods and Cataplexy to Sleep Latency in Patients with Narcolepsy

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Introduction: Narcolepsy is defined by the clinical presentation of excessive daytime sleepiness, often combined with other elements of the classical tetrad (cataplexy, sleep paralysis and hypnagogic hallucinations). Electrophysiologically, sleep-onset REM periods (SOREMPs) are characteristic. In 12 subjects with narcolepsy-cataplexy, Broughton and Aguirre (1987) found shorter sleep latencies on naps with REM sleep than on naps without REM sleep. We sought to confirm these findings in a larger group of narcoleptics and to determine whether similar findings are present in narcoleptics without cataplexy.

Methods: We reviewed baseline Multiple Sleep Latency Tests (MSLTs) from 1985 to October 1999 on patients with narcolepsy. All patients were free of psychoactive medications. After eliminating studies with incomplete data, a total of 166 subjects with 4 or 5 naps with at least one SOREMP were identified. For each individual we calculated the mean sleep latency for the naps that had a SOREMP and for those that did not.

An independent samples t-test was performed to compare the mean sleep latency of naps with a SOREMP and those without a SOREMP for each subject and for subjects with and without cataplexy. Univariate analysis of variance was also performed to assess predictors of a short sleep latency.

Results: The 166 subjects (87 females; 79 males) had an age range of 6-81 years. The subjects included 71 without cataplexy (42%), 93 with cataplexy (56%), and 5 with symptomatic narcolepsy (1 of whom had cataplexy). Thirty-one subjects had SOREMPs in all 4 naps (18.7%). For all subjects, the mean sleep latency for naps with SOREMPs was 2.57 ± 2.15 minutes (min) and for naps without SOREMPs was 3.33 ± 3.38 min (p= 0.002). Among subjects with cataplexy, the mean sleep latency was 2.25 ± 2.11 min for naps with SOREMPs and 2.88 ± 2.53 min for naps without SOREMPs (p = 0.081). Among subjects without cataplexy, the mean sleep latency was 2.98 ± 2.14 min for naps with SOREMPs and 3.91 ± 3.15 min for naps without SOREMPs (p = 0.018). Univariate analysis of variance showed that both the presence of a SOREMP (F = 7.37; p = 0.007) and the presence of cataplexy (F = 9.30; p = 0.002) were independent predictors of a shortened mean sleep latency.

Conclusions: We found a reduced sleep latency in naps with SOREMPs for subjects as a whole and for those without cataplexy. A similar trend was present for subjects with cataplexy. The presence of a SOREMP and the occurrence of cataplexy were independent predictors of short sleep latency. Our findings extend those of Broughton and Aguirre (1987) and are consistent with the concept that pressure for REM sleep contributes to episodes of severe sleepiness in narcoleptics. This pressure appears to contribute to sleepiness in narcoleptics without cataplexy as well as in those with cataplexy.

References:
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1627.L

REM Sleep Characteristics in Patients with Parkinson's Disease Associated or not with REM Sleep Behavior Disorder

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Introduction: REM sleep behavior disorder (RBD) has been associated with a variety of neurodegenerative diseases, especially with Parkinson's disease (PD). A longitudinal study has reported that up to 38% of patients with RBD developed PD at a mean interval 12.7 years following the onset of RBD (Schenck et al. 1996). The aim of the present study was to quantify REM sleep parameters in PD patients with and without RBD and to compare them to those of controls.

Methods: Thirteen PD patients (67.8 ± 11.7 yrs) and 13 control subjects (62.2 ± 7.6 yrs) were recorded for one night in the sleep laboratory. Five PD patients reported a clinical history suggestive of RBD while 8 PD patients reported having no specific sleep problems. The majority of PD patients (77%) of both groups were treated with a dopaminergic agent.The methods used to quantify phasic EMG activity, REM density and percentage of atonia have been described elsewhere (Lapierre and Montplaisir 1992).

Results: Both groups of PD patients (with and without RBD) had a lower number of REM periods than did controls. In addition, PD patients with RBD differentiated themselves from the 2 other groups by a lower percentage of REM sleep atonia and by a higher percentage of phasic EMG activity. Specifically, all PD patients with RBD had a percentage of atonia lower than 15%. However, two PD patients without RBD and 1 control subject had low percentages of REM atonia (66.7%, 77,2% and 73.3%). REM density and REM sleep duration was similar for the 3 groups.

Table 1

	Controls	PD - RBD	PD + RBD	Stats
Age	62.2 ± 7.6	66.3 ± 13.3	70.2 ± 9.4	NS
# REM periods	4.3 ± 1.1	2.8 ± 1.2	2.4 ± 1.5	.01[ab]
REM sleep dur	70.4 ± 18.0	51.7 ± 31.6	71.7 ± 33.4	NS
REM density	29.0 ± 9.3	27.7 ± 8.4	30.4 ± 17.7	NS
Phasic EMG	8.5 ± 4.4	9.8 ± 0.1	22.1 ± 11.2	.05[bc]
Atonia	94.2 ± 7.1	89.7 ± 12.0	6.5 ± 6.5	.0001[bc]

[a] Ctrl vs PD - RBD: [b] Ctrl vs PD + RBD: [c] PD - RBD vs PD + RBD.

Conclusions: In PD patients without RBD, only the number of REM periods is decreased. The other REM sleep parameters (atonia, phasic EMG, REM density) are normal. One may wonder if the individuals with a lowered percentage of atonia (2 PD patients without RBD and 1control subject) are at risk of developing RBD. Indeed, it has been reported that 25% of RBD patients have had prodromal symptoms (Schenck et al. 1993).

References:
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1091.L

Sleep Disturbance and Quality of Life in Cancer Patients

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Introduction: Existing estimates of the prevalence of sleep problems in cancer patients range from as low as 24% to as high as 95%, perhaps in part because of the use of invalidated and novel definitions of sleep problems. Furthermore, no research has related sleep problems to decrements in cancer patients' quality of life. The purpose of this study was to examine to prevalence of sleep problems in cancer patients using a validated self-report measure and to examine the association of sleep problems with aspects of quality of life in a heterogeneous set of cancer patients.

Methods: The study sample consisted of 128 adult, cancer outpatients (29 newly diagnosed, 52 receiving cancer treatment, 36 post-treatment). The sample characteristics are shown in Table 1. All patients completed a personal background form, the Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989), and a measure of eight aspects of quality of life as measured by the Medical Outcome

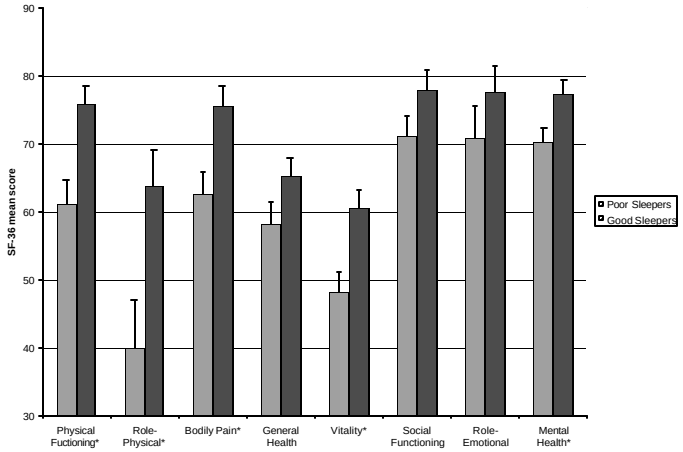
Studies – SF-36 (SF-36; Hays, R. D., Sherbourne, C. D., & Mazel, R. M., 1993).

Table 1

Demographic characteristics

		n	%
Gender			
	male	21	16.4
	female	106	82.8
Race			
	Caucasian		78.1
	minority	23	18.0
Marital Status			
	married	83	64.8
	non-married	44	34.4
Occupational Status			
	employed	52	40.6
	non-employed	65	50.1
		M	SD
Age		53.1	12.4
Years of Education		14.6	3.1

Figure 1



Results: Initial analysis of the PSQI revealed that all but 12 of the cancer patients had global PSQI scores above the cutoff score established by the scale originators in a noncancer sample. Therefore, a more conservative approach was used to differentiate poor sleepers from bad sleepers. Poor Sleepers were identified as those patients reporting Habitual Sleep Efficiency of less than 85% as defined by the PSQI. Forty-four percent (44.4%) of patients were identified as Poor Sleepers by this criterion. In order to examine the relationship between poor sleep and quality of life, Good Sleepers were compared to Poor Sleepers on the subscales of the SF-36. Table 2 shows that Bad Sleepers were significantly worse on the following SF-36 subscales as compared to Good Sleepers: Physical Functioning, Role-Physical, Bodily Pain, Vitality and Mental Health.

Conclusions: This study validates the notion that sleep disturbance is a prevalent problem for cancer patients, demonstrating that 44%?of patients had problematic sleep by a conservative and clinically accepted definition of sleep efficiency.?Furthermore, the study findings demonstrate that sleep disturbance is related to lower levels of quality of life in cancer patients.?Additional studies are needed using objective measures of sleep such as polysomnography to elucidate the characteristics of sleep disturbance in cancer patients and the causal relationship between disease, treatment, patient characteristics, quality of life, and sleep problems.?For example, it may be that physical pain and emotional health are both causes and consequences of sleep problems and effective intervention depends on accurate identification of the clinical syndrome producing the sleep disturbance.?Moreover, effective interventions validated in other populations need to be validated in cancer patients.

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1261.A

Parallels of Sleep Structure and Restoration of Cardiovascular Function During Sleep in Coronary Disease Patients

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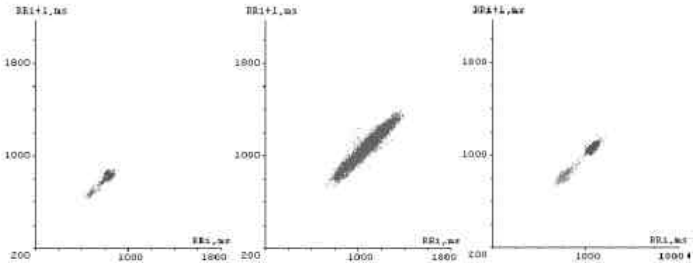
Introduction: Sleep and waking states exert profound influences on cardiac function, especially on the autonomic heart rate (HR) control, which is reflected by HR variability. Reduced HR variability is a powerful predictor of cardiac death in patients surviving after myocardial infarction. Sleep serves to restore physiological processes that are progressively degraded during prior wakefulness. A restoration of cardiovascular function depends on autonomic nervous system, hemodynamics and metabolic changes during sleep. A parasympathetic HR control is restored during continuity of sleep and correlates with maximal HR response to active orthostatic test which in healthy Ss, as was shown earlier, is increased in the morning time, as compared with the evening time. From the other hand, coronary artery disease can disturb sleep and process of restoration. The goal was to investigate the relationship between of modifications of HR variability and a quality of sleep.

Methods: All 303 coronary artery disease patients aged 28 to 85 years (mean 59.6 yr.) underwent convenient polysomnography using Alice-4 system and active orthostatic test (AOT) performed just before and after sleep. Maximal HR response to AOT was used as an index of parasympathetic control. HR variability was analyzed using Poincare plots that were constructed from RR intervals (RRn+1) versus the previous intervals (RRn), plotted as a function. The scatterplot length (L), representing HR responses, the width (W), reflecting HR variability, and the square (S), associated with total autonomic control, were calculated. The patients were distributed into 2 groups according the difference between maximal HR responses to AOT at morning-time and evening-time: (i) 227 pts demonstrating restoration of HR control; and (ii) 64 pts showing inability to restore. The mean age (59.1 & 61.2 yr., respectively), evidence of cardiac symptoms and heart failure in both groups did not differ significantly.

Results: CAD pts demonstrating an inability to restore cardiac function, as compared to pts showing a restoration, were characterized by a significantly reduced stage 3 (24.2 min., 6.9% & 30.6 min., 8.3%), stage 4 (5.9 min., 1.6% & 11.0 min., 2.8%) and REM sleep (39.1 min., 10.8% & 47.3 min., 12.4%, respectively) as well as by a non-significantly decreased TST (305 min. & 323 min., respectively). Stage 1 (37.9 min., 10.3% & 32.9 min., 8.0%) and stage 2 (190.1 min., 55.6% & 190.9 min., 51.8%, respectively) did not differ significantly.The scatterplot parameters L, W, and S, reflecting total HR variability, during sleep did not differ in both groups, although there was a significant increase in those characteristics after night sleep in patients demonstrating ability to restore autonomic HR control, as compared with the rest patients (L = 616 ms vs.492 ms; W = 71 ms vs. 58 ms; S = 44406 ms2 vs. 32214 ms2). An increased total HR variability at morning time reflects an increase of cardiovascular function restoration during sleep. It correlates with more

pronounced slow wave sleep and increased REM sleep. Figure demonstrates that total HR variability is mostly pronounced during sleep, although it is increased during morning-time, as compared with evening time. Because of that, HR response to AOT performed just before and just after sleep might be used for evaluation of restoration of cardiovascular function in sleep as well as an indicator of good quality sleep in CAD patients.

Figure 1. An example of Poincare plots constructed from RR intervals collected during sleep (medium) and AOT at evening-time (left) and at morning-time (right) in patient demonstrating a restoration of HR control.



Conclusions: An inability to restore cardiac function during sleep is associated with a reduction of slow wave sleep and REM one as well as with shorter total sleep time.

1233.L

Sleep Disturbances, Nocturia and Diabetes in African-American Community Dwelling Older Adults

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Introduction: Type 2 diabetes mellitus affects 14 million persons in the United States and is the fourth leading cause of death, 1 in 4 African Americans over age 65 has Type 2 diabetes. The symptoms of decreased energy and polyuria reported by poorly controlled diabetics are essentially the same as reports of excessive daytime sleepiness and nocturia that are characteristic of OSA. Increased diabetic retinopathy, neuropathy, and renal complications are associated with poor glucose control (HbA_{1c} > 7.0%). The primary aim of this study is to examine the association between sleep related breathing disturbances, nocturia, and HbA_{1c} levels (glucose control).

Methods: As part of a multi-phase study, subjects were recruited by either a random mailed questionnaire or at health fairs in the African-American community. The questionnaire solicited symptom reports reflective of poor sleep quality, OSA symptoms, nocturia, lower urinary tract symptoms (LUT), naps, and self-rated health (SRH). Responses to the sleep items are based on a five anchor Likert scale (range 1-5) with the highest value representing more frequent occurrence of a symptom. HbA_{1c} levels were determined either during the community screenings or during clinical interviews.

Results: The sample (n = 114) included a majority of women (58%), African Americans (76%), and obese persons (67% BMI > 30). The mean age was 64 years (range 50 - 90 years), and the sample had 41 persons (36%) with poor glucose control (HbA_{1c} > 7.0%). In the sample, there were no statistical differences in OSA symptoms, sleep quality, daytime sleepiness, frequency of nocturnal voiding, or LUT symptoms when comparing by age or gender. When comparing by ethnicity, African Americans had more OSA symptoms (p < .001), LUT symptoms (p < .001), daytime sleepiness (p =.04), and decreased SRH (p = .03). When comparing African Americans subjects (n = 87) by glucose control, subjects with an elevated HbA_{1c} > 7.0% had significantly more OSA symptoms (p <.01), more nocturia (p < .001), and decreased SRH (p =.03). In African Americans subjects with poor glucose control (HbA_{1c} > 7.0%) there were significant (p < .05) correlations between OSA and both daytime sleepiness (r = .60) and increased naps (r = .39), as well as between nocturia and naps (r=.41), nocturia and decreased sleep quality (r = .57), and nocturia and daytime sleepiness (r =.46).

Table 1

Characteristics of Sample: Gender, Ethnicity, and Glucose Control

	Male		Female		
Glucose Control	Good	Poor	Good	Poor	Total
African American	18	16	34	19	87
White	9	5	12	1	27
Total	27	21	46	20	114

Good - HbA_1c <7%; Poor - HbA_1c >7%

Table 2

OSA Symptoms & Nocturia by Glucose Control among African-American Subjects (n=87)

	HbA_{1C} < 7.0% (n = 52)		HbA_{1C} >7.0% (n = 35)	
	Mean	(SD)	Mean	(SD)
OSA **	2.0	0.91	2.5	0.75
Nocturia **	1.7	1.26	2.3	1.26
BMI **	30.2	5.46	31.0	6.56
SR Health *	2.6	0.74	2.3	0.67

Mann-Whitney U * p < .05 ** p < .01

Conclusions: These findings do not support traditional explanations for increased nocturnal voiding, which are prostatism and increased age. Although nocturia in poorly controlled Type 2 diabetes is assumed to be the result of glycosuria, nocturnal polyuria also occurs as the result of negative pressure breathing caused by OSA. Among older African American Type 2 diabetics, OSA was associated with increased nighttime sleep disturbances including poor sleep quality and nocturia, as well as increased daytime sleepiness and decreased self-rated health. Health care providers must be cognizant that Type 2 diabetes and OSA may coexist and potentially exacerbate each other.

1168.K5

State Dependent Excitability Changes of Spinal Flexor Reflex in Patients with RLS Secondary to Chronic Renal Failure

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Introduction: Periodic limb movement in sleep (PLMS) is a common dysfunction of motor control during sleep, occurring either in isolation or associated to a variety of neurological disorders including restless legs syndrome (RLS). Although the PLMS generators have not been established, their occurrence in patients with spinal cord injury and their clinical resemblance to the spinal cord flexor withdrawal reflex (FR) suggest that PLMD may originate in the circuitry that mediates the FR. Therefore, it has been described that primary RLS/PLMS patients had

significantly increased spinal cord excitability and this might be the evidence for an important role of enhanced spinal cord excitability in the pathophysiology of primary RLS.[1] The aim of this study is to see if the enhanced spinal cord excitability which is represented by a lower threshold and/or greater spatial spread of the FR is also true for the RLS/PLMS patients whose RLS are secondary to chronic renal failure (CRF).

Methods: Ten patients with RLS/PLMS secondary to CRF have been compared with matched controls according to the state dependent changes in FR excitability. All the patients met the diagnostic criteria for RLS and PLMS. They had CRF for 5.2+3.5 years and all described that RLS sympoms have started after CRF diagnosis. Ten normal, age and sex matched subjects were tested as controls. The electrophysiological testing of the FR was performed at wakefulness (9-10 p.m.) and during sleep (beginning of stage II, the first sleep cycle).

Results: As a result, the significant increase in FR excitability (regarding the number of muscles involved in the FR response and lover threshold) has been found in RLS/PLMS patients with CRF. This abnormality was also more prominent during sleep which was also true for the primary RLS

Conclusions: Our results suggest that similar neuronal pathways involve in primary and secondary RLS/PLMS patients. And they also support that secondary RLS/PLMD (secondary to CRF) and FR share common spinal mechanism.

References:
(1) Bara-Jimenez W, Hallett M. Increased spinal cord excitability in patients with restless legs syndrome (abstract). Mov Dis, 1998; 13[suppl 2]:294.

1535.K5

Neurophysiological Study of Corticomotor Pathway in Patients with Primary Restless Legs Syndrome (RLS)

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Introduction: RLS is a sensory-motor disorder characterised by unpleasant sensation in the legs and an urgent desire to move the limbs, mainly occurring in the night rest. The RLS prevalence in general population is estimated to be between 1% and 5%. and in the primary RLS it is described a positive family history. In RLS patients have been described Periodic Legs Movements in sleep and wake (PLMS-PLMW) and it is hypothesised that PLM result from a sleep-related dysinhibition of a descending central motor inhibitory pathways. Moreover, in primary RLS, modifications of the cortical excitability tested by TMS, are debated.

Methods: 15 patients with primary RLS, selected by International RLS Group study criteria, and 12 normal age-matched subjects were evaluated in the late afternoon. Physical examination, serologic tests and peripheral neurophysiologic evaluations were normal in all patients.SIT was performed according to Montplaisir criteria. TMS was done in Abductor Digiti Minimi (ADM) and Tibialis Anterior (TA) muscles by using the following parameters: Motor Evoked Potential (MEP) threshold, amplitude and latency at rest and with muscle activation; Silent Period (SP) threshold (Thr); MEP and SP recording at rest and during contraction, with increasing TMS intensities; Paired pulse TMS with short and long interstimulus intervals (ISIs); paired bilateral TMS with short and long ISIs; Peripheral SP.

Results: SIT discriminate patients with RLS from control subjects.Maximal amplitude of the CMAP and MEP, MEP/CMAP amplitude, F-waves latencies and peripheral SP duration were not different from the control group. Central Motor Conduction Time (CMCT) and Thresholds for MEP and SP were similar in patients and in controls. SP duration increased linearly with increasing stimulus intensities in both groups of muscles and was not significant difference between control subjects and patients. MEP recruitment curves recorded from the ADM muscles at rest and during voluntary muscle contraction were similar in both groups.Short ISI paired TMS resulted in significant increased inhibition and decreased facilitation in ADM muscles and, especially, in TA muscles of patients respect to the controls. Nevertheless Intracortical (corticocortical) Inhibition (ICI) and Intracortical Facilitation (ICF) maintained their typical trend even in patients muscles.Long interstimulus interval paired TMS resulted in normal motor cortex excitability bilaterally in both populations.Interhemisferic facilitation (IHF) and inhibition (IHI) after paired bilateral TMS with short interstimulus intervals was similar in both muscle groups.

Conclusions: In our study the conventional measures of motor pathways excitability were normal in all patients. Instead the modifications in short paired-pulse Intracortical (corticocortical) Inhibition (ICI) and Intracortical Facilitation (ICF) underlined the presence of altered excitability of central motor pathways, at different levels and particularly involving legs projections. Our data confirmed the impairment of cortico-subcortical motor structures in the pathogenesis of primary RLS, particularly involving motor inhibitory mechanisms.

1881.K5

Low Normal Ferritin Levels as a Marker of Patients with RLS who May Respond to Iron Therapy: A Re-Evaluation of the Normal Range of Ferritin

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Introduction: Restless Legs Syndrome is a commonly encountered disorder by most sleep specialists. Current treatments with medications elevating central dopamine level provide good results. Searching for an underlying etiology maybe be overlooked in light of the patients improvement. Literature describing anemia as an etiology is widely known and frequently a CBC is ordered on patients with RLS to screen for anemia. Several groups have previously reported ferritin levels below 50 ng/ml to be associated with RLS in some patients.[1,2] Normal Ferritin levels have been historically accepted as greater than 10 ng/ml. We assessed the value of obtaining Ferritin levels in addition to a Complete Blood Count (CBC) in patients presenting with RLS.

Methods: Ferritin levels and CBC's where drawn from sixteen nonconsecutive patients (ave. age 58 y/o, (ranging 23 – 79, 9male 7 female) identified with the Restless Legs Syndrome. Diagnosis of RLS was established by clinical history, and further confirmed by clinical improvement with treatment, consisting of either L-Dopa, Dopa agonists or Neurontin (in two patients). NPSG testing was performed on twelve of the sixteen patients and all twelve showed PLMS to further confirm the diagnosis.

Results: Of the sixteen patients, six (37.5%) had Ferritin levels less than 50 ng/ml and none had levels below 10 ng/ml. All of the patients had normal Hemoglobin and Hematocrit levels although three were low normal.

Conclusions: This data provides further support to existing reports that Ferritin levels may provide additional value in the evaluation and determining the treatment regimen in patients with RLS. Classic laboratory criteria for evaluating Ferritin levels, with less than 10 ng/dl, can not be

utilized. All of our patients had values greater than 10 ng/ml. Ferritin levels greater than 10 ng/dl satisfy metabolic requirements for hemoglobin synthesis but levels less than 50 ng/dl may be insufficient for normal dopamine metabolism in some patients.

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1472.B

Neuronal Networks Responsible for Paradoxical Sleep Onset and Maintenance in Rats: A New Hypothesis

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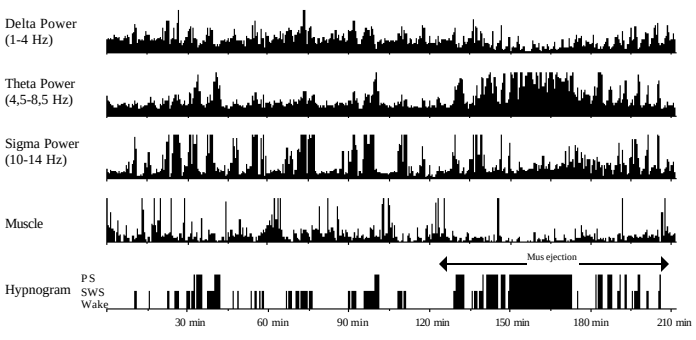
Introduction: Iontophoretic ejections of bicuculline (Bic) in the rat pontine dorsal subcoeruleus nucleus (SubCD) induce a long-lasting paradoxical sleep-like state (PS-like, Schmidt et al., this meeting). To determine the circuits responsible for this effect, the retrograde and anterograde tracer, cholera toxin B subunit (CTb) was ejected in the same site that Bic through another barrel of the micropipette. After CTb ejections in the SubCD (n= 9), numerous retrogradely-labeled neurons were distributed in the mesencephalic, pontine and medullary reticular nuclei as well as in the periaqueductal gray (PAG). On sections double-stained with CTb and choline acetyltransferase, only a few cholinergic neurons were retrogradely-labeled in the laterodorsal tegmental and pedunculopontine nuclei. These results suggest that the PAG and numerous reticular regions in addition to the SubCD and the cholinergic nuclei might play an important role in PS onset and maintenance. In agreement with this hypothesis, it has recently been shown in cats that pressure ejections of carbachol in the ventral rostral pontis oralis nucleus (Reinoso-Suarez et al.,[1] 1994) or muscimol (a GABAA agonist) in the ventrolateral PAG and the reticular formation ventral to it (vlPAG, Sastre et al.,[2] 1996) induced a strong PS hypersomnia. Following CTb injections in the SubCD, these regions contained many varicose fibers intermingled with retrogradely-labeled neurons indicating that they are reciprocally connected with the SubCD. From these results, we hypothesized that the vlPAG region might contain GABAergic neurons responsible for a tonic inhibition during wakefulness and slow waves sleep of the PS-executive neurons from the SubCD.

Methods: Six male rats were implanted for polygraphic recordings of cortical EEG, neck EMG, EOG and contention. Muscimol was iontophoretically administered (10mM, 100nA) into the vlPAG during 20min. To label the pathways involved, CTb was ejected in the effective sites through another barrel of the micropipette. In addition, Mus was ejected in two rats during 1h30 to induce Fos staining.

Figure 1



Results: A strong PS hypersomnia (n=11; PS: 38.3±4.8% versus 16.6±2.8min in control) was induced by the Mus ejection with a latency of 11.3±1.7min and a duration of 67.1±6.3min. On CTb-stained sections, anterogradely-labeled varicose fibers were intermingled with CTb retrogradely-labeled neurons in the SubCD, confirming the existence of a reciprocal connection between the vlPAG and the SubCD. On Fos-stained sections, numerous positive neurons were specifically observed in the ipsi-lateral SubCD.

Conclusions: From these results, we propose that the onset and maintenance of PS is controlled by an inhibitory projection from a population of GABAergic neurons localized in vlPAG to the SubCD and other reticular regions containing PS-executive neurons. In the future, we will try to determine the relationship between this new system and the monoaminergic and cholinergic neurons well known to be involved in PS control.

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1651.A

Activity of Periaqueductal Gray Neurons During Warming of the Preoptic/Anterior Hypothalamic Area

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Introduction: The midbrain periaqueductal gray (PAG) has extensive reciprocal connections with preoptic/anterior hypothalamic (POA) and basal forebrain regions involved in sleep-wake control. The PAG has been implicated in multiple physiological and behavioral functions, including respiration.[1] The onset of sleep is accompanied by respiratory changes. POA and PAG interactions could contribute to state-dependent modulation of respiratory control. The POA is also a critical thermosensing and thermointegrating region.[2] We hypothesize that warm-sensitive, sleep-active neurons in the POA[3] modulate the activity of PAG neurons. To test this hypothesis, we examined the responses of PAG neurons to local POA warming.

Methods: Sprague-Dawley rats (300-400g) were anesthetized with a katamine-zylazine mixture and surgically implanted with instrumentation to permit monitoring of the EEG and the electromyogram (EMG). In addition, multi-wire electrodes were directed at the lateral PAG cell columns. Unit recording electrodes consisted of ten, 25µ stainless steel wires attached to a microdrive that could be advanced in small increments. A stainless steel, water-perfused thermode was placed in the POA. A microthermocouple was implanted within 1 mm of the tip of the thermode to measure Tpoa. The thermode and PAG microwire bundle were placed on the same side of the brain. Leads from EEG, EMG and microwire electrodes was soldered to a small electrical connector, which was encased in dental acrylic and anchored to the skull. Electrophysiological recording began 5 days after surgery. Baseline neuronal activity was recorded during both waking and slow wave sleep

(SWS). Tpoa was increased 1-2°C by perfusing warm water through the thermode. The EEG, EMG, and unit activity were continually recorded during POA warming. Firing rates were determined before and after POA warming during both waking and SWS.

Results: Each recorded PAG cell was characterized by its spontaneous sleep-waking discharge profile, and its response to POA warming. Vigilance-related (wake-active or sleep-active) neurons were operationally defined as those demonstrating a minimum change in firing rate of 10% during SWS vs. wakefulness. Warming-responsive neurons were defined as those demonstrating a minimum change in firing rate of 10% during POA warming as compared to the pre-warming rate during the same vigilance state. Of 43 recorded PAG neurons, 29 (67%) were wake-active, 8 (19%) were sleep-active and 6 (14%) were vigilance-independent. During waking, 94% of the recorded PAG neurons responded to POA warming; 62% exhibited decreases in firing rate, while 32% exhibited increases in firing rate. During SWS, 84% of the recorded PAG neurons responded to POA warming; 55% exhibited decreases in firing rate, and 29% exhibited increases in firing rate.

Conclusions: These preliminary results suggest that a majority of lateral PAG neurons are wake-active and exhibit suppression of spontaneous discharge in response to POA warming during both wakefulness and SWS. It is well-documented that POA thermosensitive neurons play a key role in the modulation of vigilance[3]. These findings support the hypothesis that modulation of PAG neuronal activity by POA warm-sensitive, sleep-active neurons contributes to state-dependent changes in respiration.

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1515.A

5-HT2A Receptor-Like Immunoreactivity is Present in Cells and Cellular Processes Adjacent to Mesopontine Nitric Oxide Synthase-Containing Neurons

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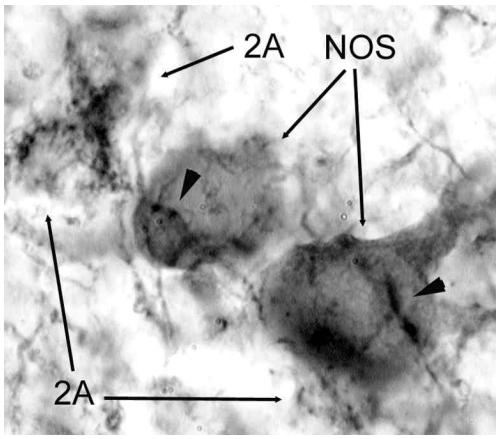
Introduction: Mesopontine acetylcholine (ACh) and nitric oxide synthase (NOS)-containing neurons are inhibited by serotonin (5-HT) acting on 5-HT1A receptors. 5-HT cell activity is maximal during wakefulness and minimal during REM sleep, whereas ACh cell activity is maximal during wakefulness and/or REM sleep and lowest during slow-wave sleep. The mechanisms contributing to these at least partially reciprocal activity patterns in mesopontine ACh and 5-HT neurons are not well understood. A subset of ACh cells may be inhibited by 5-HT,[1] however, some ACh cells may be excited by 5-HT acting on 5-HT2A receptors reported to be present in a majority of mesopontine ACh neurons.[2] The sleep-wake activity of individual ACh cells may depend on a combination of these two opposing effects of 5-HT. We investigated the expression of 5-HT2A receptors in the pedunculopontine (PPT) and laterodorsal tegmental (LDT) nuclei.

Methods: Free-floating sections from brainstems of Sprague-Dawley rats were successively incubated with antibodies against 5-HT2A receptors (Incstar, 1:750) and NOS (RBI, cat. # N-196, 1:3000). 5-HT2A receptor-like immunoreactivity was visualized using avidin-biotin-horseradish peroxidase staining with diaminobenzidine (DAB) and nickel intensification, yielding a black and granular reaction product. To visualize NOS, nickel was omitted, yielding a light brown and evenly distributed reaction product. PPT and LDT regions were inspected using 50x and 100x immersion objectives in both coronal (2 rats) and sagittal (one rat) sections.

Figure 1



Results: The distribution of NOS immunoreactivity was consistent with previous reports, and that for 5-HT2A receptors delineated regions labeled in earlier receptor binding and our immunohistochemical studies.[3] Within and around the PPT and LDT nuclei, small cells expressing 5-HT2A receptor-like immunoreactivity only were present adjacent to NOS-stained cells and tended to aggregate along the outlines of the two nuclei. A network of cellular processes, presumably dendrites of 5-HT2A receptor-expressing cells, often overlaid NOS-containing cells. In about 2/3 of PPT and LDT cells, NOS-staining was sufficiently light to determine that the cells did not contain black grains marking 5-HT2A receptors. Small cells expressing 5-HT2A receptors only were present among those neurons. The figure shows three small cells expressing 5-HT2A receptors only ("2A" arrows) located near two LDT cells expressing NOS only ("NOS" arrows), and 5-HT2A receptor-expressing processes (e.g., arrowheads) crossing over the two NOS-containing cells (100x oil).

Conclusions: The small 5-HT2A receptor-expressing cells and their processes located near and among cholinergic mesopontine neurons may represent local inhibitory or excitatory interneurons whose activation mediated by 5-HT2A receptors could lead to wakefulness-related reduction or increase, respectively, in the activity of mesopontine ACh neurons. Our study does not provide evidence for extensive co-localization of NOS and 5-HT2A receptors in mesopontine ACh neurons.

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1387.A

Different Populations of LDT-PPT Neurons Express c-fos During Carbachol-Induced Active Sleep

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Introduction: Neurons in the laterodorsal and pedunculo-pontine tegmental nuclei (LDT-PPT) are critically involved in the generation of active sleep (AS). For example, the number of neurons that express c-fos (a marker of neuronal activity) increase in the LDT/PPT in association with AS. However, we have reported that during carbachol-induced active sleep (AS-carbachol), LDT/PPT neurons that express c-fos are not cholinergic (Yamuy et al., 1998); therefore, we were interested in determining the neurotransmitter phenotype of these non-cholinergic neurons. As a first step, we determined if these c-fos-expressing neurons were GABAergic because such neurons are active in the LDT-PPT of the rat during the recovery of AS following sleep deprivation (Maloney et al., 1999); in addition, GABAergic neurons in the nucleus pontis oralis (NPO; Xi et al., 1999) are also involved in the control of sleep and waking states.

Methods: Three chronically-prepared cats were used as controls; two were maintained in quiet wakefulness for three hours and the other was undisturbed in its normal sleep-waking cycle for the same period of time. In other three animals, AS was induced by carbachol microinjection into the NPO (0.2 ml, 4 mg/ml; about 120 minutes of duration). Immediately thereafter, the cats were deeply anesthetized and perfused for immunocytochemistry. Antibodies against choline acetyltransferase (ChAT) were used to immunostain cholinergic neurons. Double immunostaining for Fos and GABA was performed in 14 microns-thick adjacent sections. ChAT+ Fos-, ChAT+ Fos+, GABA+ Fos+ and neurons single labeled for Fos were counted in the LDT/PPT at three levels (A 0.5-0, P 1-1.5, and P 2-2.5).

Results: The number of cholinergic neurons that expressed c-fos during AS-carbachol state was very low (0.31 % of the total ChAT+ cells). The number of GABA+ Fos+ neurons had a tendency to increase during AS-carbachol compared with control conditions (140.3 ± 43.1 vs 30 ± 8.5, $P = 0.06$). The population of LDT/PPT neurons that exhibited the largest increase in c-fos expression during AS-carbachol were neither GABA+ nor ChAT+ (285.7 ± 44.6 vs 44.0 ± 31.0, $P < 0.05$).

Conclusions: The present data reveal that a large number of GABAergic neurons are activated during AS-carbachol. In addition, non-cholinergic, non-GABAergic neurons in the LDT/PPT exhibited a large increase in c-fos expression during AS-carbachol compared with control condition. Because glutamatergic neurons of the LDT/PPT have been implicated in the generation of atonia during AS, we propose that this as yet unidentified population of neurons may be, at least in part, glutamatergic.

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1305.A

Subcellular Location of GABA and its Relationship with Cholinergic Neurons in the Laterodorsal and Pedunculopontine Tegmental Nuclei in the Cat

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Introduction: The brainstem pedunculopontine (PPT) and laterodorsal tegmental (LDT) nuclei play a critical role in rapid eye movement (REM) sleep and wakefulness (Jones BE, 1991). These structures contain a large number of GABAergic and cholinergic neurons as well as other neuronal types (glutamatergic, peptidergic; Clements JR et al, 1990, Maloney K et al 1999) that have been implicated in the control of behavioral states. For example, recent data indicate that the interaction of cholinergic and GABAergic cells may be important in the processes of regulation of REM sleep (Maloney et al, 1999). In order to understand the relationship between cholinergic and GABAergic neurons in the LDT and PPT, we sought to determine the interconnectivity of choline acetyltransferase immunoreactive (ChAT-IR) and GABA-IR profiles by electron microscopic immunocytochemical techniques.

Methods: Adult cats were deeply anesthetized (Nembutal, 60 mg/kg) and perfused with 2% glutaraldehyde and 2% paraformaldehyde in PB. After treatment with 1% sodium borohydride, sections were processed for preembedding immunostaining for GABA or ChAT. The sections were then processed for electron microscopy. The ultrathin sections immunostained for GABA were directly studied with an electron microscope; the sections immunostained for ChAT were processed for GABA postembedding immunogold staining prior to electron microscopic examination.

Results: In pre-embedded sections immunostained for GABA, immunoreactivity was found in neuronal cell bodies, dendrites as well as in axon terminals in both the LDT and PPT. Most GABA-IR terminals formed symmetrical synapses with non-immunolabeled dendrites; very few of them contacted GABA-IR somas and dendrites. A large number of ChAT-IR somas, dendrites and terminals and GABA-IR terminals were found in sections pre-embedded immunostaining for ChAT combined with post-embedded immunogold staining for GABA. For ChAT-IR profiles, about 40% of somas, 50% of proximal dendrites and 60% of small- and middle-sized dendrites received GABA-IR terminals in both the LDT and PPT. Interestingly, co-localization of ChAT and GABA was found in axon terminals in the LDT and PPT. Indeed, about 30% of ChAT-IR terminals were also GABA-IR, whereas only 6-8% of GABA-IR terminals were ChAT-IR. Most of ChAT/GABA-IR terminals formed symmetrical synapses with non-immunolabeled dendrites; few of them contacted ChAT-IR dendrites.

Conclusions: These data confirm and extend the concept that cholinergic and GABAergic neurons coexist in the LDT and PPT. Quantitative analysis revealed that a large number of cholinergic profiles (approximately 50%) received GABAergic input. Most importantly, we found that ACh and GABA are co-localized in a subpopulation of axon terminals. This intriguing finding is likely to be important in understanding the complex synaptic mechanisms that modulate the activity of non-cholinergic and a portion of cholinergic neurons in the LDT and PPT during sleep and waking states.

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Research supported by USPHS grants MH43362, NS23426, NS09999, and HL60296.

1635.A

Anatomical and Physiological Correlates of the 5-HT3 Receptor within the Hypoglossal Nucleus

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Introduction: Serotonin (5-HT) may play an important role in the pathogenesis of obstructive sleep-disordered breathing. Identifying 5-HT receptor subtypes involved in sleep-disordered breathing may provide pharmacotherapeutics for this highly prevalent disorder. Recent studies have shown that 5-HT3 drugs alter central sleep apnea frequency in the rat, and immunocytochemistry studies have shown 5-HT3 receptor immunoreactivity in close approximation to hypoglossal motoneurons. Therefore, 5-HT3 receptors may play a role in serotoninergic excitation of hypoglossal motoneurons.

Methods: To evaluate this potential role for the 5-HT3 receptor effects within the hypoglossal motor nuclei, we have performed acute microinjection trials in rats of selective 5-HT3 drugs across a wide range of concentrations for a selective agonist and two antagonists.

Results: Baseline hypoglossal activity and 5-HT excitation of hypoglossal motoneurons are not impacted upon by 5-HT3 drug injections. To determine if 5-HT3 receptors are produced by hypoglossal motoneurons, rather than adjacent to motoneurons, we performed in-situ hybridization for 5-HT3 receptors 5 weeks after unilateral hypoglossal nerve transections. Qualitatively, there is a marked reduction in 5-HT3 mRNA on the ipsilateral side of nerve transection.

Conclusions: Together, these data suggest that although hypoglossal motoneurons produce the 5-HT3 receptor, these receptors do not modulate hypoglossal motoneuronal activity in the hypoglossal nucleus of the rat. We hypothesize, therefore, that 5-HT3 receptors produced by hypoglossal motoneurons act distally.

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1639.A

Glycine-Immunoreactive Premotor Hypoglossal Interneurons in the Medulla of Cats

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Introduction: Hypoglossal motoneurons are important for various normal motor functions of the tongue. In addition, an abnormal function of the protruder (genioglossus) tongue muscles has been suggested to be involved in pharyngeal occlusion during the obstructive sleep apnea syndrome. Neuroanatomical studies have indicated that premotor hypoglossal interneurons that are activated during active sleep (AS) are located within the ventromedial medulla (Fung et al., 1999), in the same area that promotes the suppression of somatic motoneurons during AS. This area also contains pretrigeminal interneurons which are activated during AS (Morales et al., 1999). In the present study, we sought to determine the location of the glycinergic premotor hypoglossal interneurons and compare their distribution with that of AS-activated (as indicated by their c-fos expression) glycinergic neurons.

Methods: In chronic cats under halothane anesthesia, the hypoglossal nucleus was located based upon its extracellular field potential response to antidromic stimulation of the intramuscular fibers of the genioglossus nerve. Cholera toxin subunit B (CTb) was then injected into the hypoglossal nucleus by iontophoresis. Following a recovery period of 10 to 14 days, carbachol was microinjected into the nucleus pontis oralis (P2 L2 H-4.5) of head-restrained, unanesthetized cats to elicit a prolonged period of AS (approximately 90 min.). Under deep Nembutal anesthesia, each animal was then perfused for double immunostaining for glycine and either CTb or Fos protein. Coronal sections of the brainstem were cut at a thickness of 14 microns. One series of tissue sections were first reacted for CTb and then incubated in antiserum raised against glycine-conjugated proteins (Chemicon, Temecula, CA). Another series of sections were immunostained for Fos followed by the glycine-conjugated proteins.

Results: The first immunostained series revealed that double-labeled glycinergic interneurons contained black CTb granules within a homogenous, brown-stained cytoplasm, compared to the AS-activated glycinergic neurons (from the second immunostained series) that contained black nuclei within a brown cytoplasm. Whereas single-labeled glycinergic neurons were observed throughout ponto-medullary levels, double-labeled glycinergic CTb-containing interneurons were present mainly ipsilaterally in the ventral medulla (i.e., the ventral gigantocellular and magnocellular nuclei). These interneurons were medium-sized with soma diameters between 18 and 45 microns. Other c-fos-expressing glycinergic neurons were present bilaterally in the same medullary area.

Conclusions: Our results indicate that glycinergic premotor hypoglossal interneurons coexist with AS-activated glycinergic neurons within the "inhibitory region of Magoun and Rhines". These findings suggest that these glycinergic premotor interneurons are likely candidates for mediating the motor inhibition of hypoglossal motoneurons during AS.

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1845.E

Risk of Fatal Occupational Injury by Time of Day

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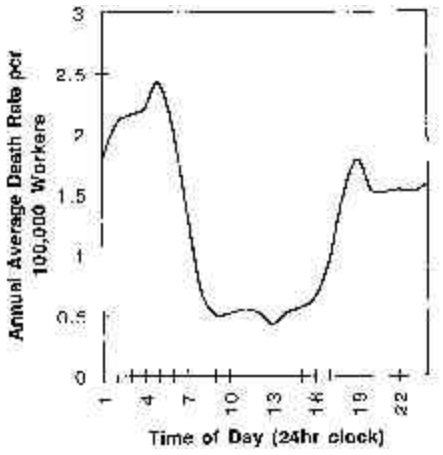
Introduction: Sleep and circadian rhythm physiology suggest a roughly sinusoidal curve of human performance across a 24-hour period with the nadir occur-ring in the early morning hours.[1-3] We hypothesized a reflection of this curve in data from 90,523 occupational fatalities in the

United States from 1980-1994.

Methods: Occupational fatality data were collected from the National Institute for Occupational Safety and Health (NIOSH) National Traumatic Occupational Fatalities surveillance system. For inclusion, the decedents must have been 16 years or older, had an external cause of death (ICD classification), and have been injured at work. A total of 74,735 fatalities met the criteria and were also recorded by time of day (by the hour).Data were also collected and analyzed from the United States Bureau of Labor Statistics, Division of Labor Force Statistics. The total number of people working at each hour of the day had to be calculated from start and stop times listed in the May 1985, 1991, and 1997 supplements to the Current Population Surveys (conducted by the Bureau of the Census for the Bureau of Labor Statistics).Annual average death rates per 100,000 civilian workers, by time of day, were calculated ([annual average number of fatalities each hour / annual average number of people working each hour] x 100,000) and graphically constructed.

Results: The fatal occupational injury death rate (DR) by time of day is depicted in the graph shown here. A roughly sinusoidal pattern is demonstrated. Relatively low risk of death occurs during the traditional daytime working hours of 9am to 5pm, with moderate risk and high risk occurring during swing shift and night shift hours respectively. The highest DR (2.42) occurs in the early morning hours (5am). The risk of death from an occupational injury is 3.32 times greater during the early morning hours (avg DR=1.96 from 1lpm-7am) than it is during traditional daytime working hours (avg DR=0.59 from 9am-5pm).

Figure 1. Risk of Fatal Occupational Injury by Time of Day (1980-1994)



Conclusions: Risk of death from an occupational injury is significantly greater in the early morning hours than it is during traditional daytime work hours. Many possible explanations exist for this finding. However, we suspect a significant degree of sleep/circadian rhythm effects in view of the parallels between this death rate curve and the human performance curve predicted by previous sleep/circadian rhythm physiology research(1-3).The accuracy of these results may be limited by several factors (e.g., death certificates only capture approximately 81% of fatal occupational injuries, the number of people working at each hour of the day are estimates). Our results suggest public health benefits from recording and analyzing accident/injury data with more precision and incorporating specific time of day.

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1030.E

An Attempt to Phase Shift Human Circadian Rhythms with Extraocular Light

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Introduction: Most invertebrate and vertebrate species have non-retinal, i.e. extraocular, photoreceptors for the entrainment of circadian rhythms. It is generally believed that mammals are the exception to this rule, and that the only way light can reach the circadian system is through the eyes. A recent study by Campbell & Murphy (1998) shocked the circadian scientific community by showing that bright light applied behind the knees could phase-shift human circadian rhythms. We used the same light apparatus in an attempt to produce phase shifts, but with a different design. Our protocol was more relevant to shift-work and jet-lag because subjects stayed awake all night and then went to sleep later in the day. We investigated whether the extraocular light could help phase delay circadian rhythms and thus facilitate circadian adaptation to the delayed sleep schedule.

Methods: Normal, healthy, young adults (n=16) participated. There were 3 baseline days with 8-hr sleep/dark (S/D) episodes at a normal time. Subjects were required to remain in bed, in the dark during these and all subsequent S/D episodes. After baseline there was a one-day phase assessment in which saliva samples were collected and later analyzed for melatonin. The dim light melatonin onset (DLMO) served as a phase marker. During the next 2 nights, subjects remained awake in dim light (10-20 lux) and were exposed to 3 hrs of either a) medium intensity (about 1000 lux) ocular light from light boxes (n=6), b) bright (about 13,000 lux) blue extraocular light from fiber optic pads attached behind the knees (n=7) or c) pads attached, no experimental light (n=3). The fiber optic pads do not emit heat, and in the control group the pads were attached, but unknown to the subjects were not turned on. After each night the subjects went to bed in the morning; the 8-hr S/D episodes were delayed 8 hrs from baseline. The 3-hr light pulses were applied at a time designed to facilitate the delay of circadian rhythms to the 8-hr delay of S/D: either 2:00-5:00 or 3:00-6:00 for a 23:00-7:00 or 0:00-8:00 baseline sleep schedule, respectively. A final phase assessment followed the second daytime S/D episode.

Results: The DLMOs of the control subjects delayed as expected, range -0.9 to -2.9 hrs, mean (SD) = -1.9 (1.0) hrs. The phase delays in the ocular light group ranged from -1.3 to -5.0 hrs, mean (SD) = -2.9 (1.7) hrs. The phase shifts in the extraocular group ranged from +0.1 to -1.8 hrs, mean (SD) = -1.0 (0.8) hrs. Thus, the medium intensity ocular light facilitated phase delays in some subjects, but the bright extraocular light did not appear to have an effect.

Conclusions: Extraocular light did not produce phase delays in this protocol. One limitation of this study is the small sample sizes. Perhaps if we had tested more subjects with extraocular light, a few would have delayed more than the controls. There are many differences between the protocol of Campbell & Murphy and ours that could account for the larger phase shifts, relative to controls, observed in their study with extraocular light. One difference is that our protocol included an 8-hr delay of S/D, whereas theirs had no specific shift of S/D. Another difference is that our subjects were somewhat sleep deprived when the extraocular light was applied, whereas their subjects were probably sleep satiated

because they were allowed to sleep from midnight to noon each day. Sleep deprivation can attenuate light-induced phase shifts (Mistlberger et al, 1997). Other differences are that for many of their trials subjects were awakened, moved from the dark into dim light (<20 lux), and moved from bed to a sitting position in order to receive the extraocular light. In our subjects there was no change in sleep state (they were awake), no change in ocular light intensity (they were in 10-20 lux), and no change in posture (they were reclined in sofa chairs) when the fiber optic pads were attached. It appears that certain conditions must prevail in order for extraocular light to exert a phase-shifting effect. Further research is necessary to determine under what conditions extraocular light might affect the human circadian system.

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(2) Mistlberger RE, Landry GL, Marchant EG: Sleep deprivation can attenuate light-induced phase shifts of circadian rhythms in hamsters. Neurosci Lett 1997, 238:5-8.

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1812.E

Melatonin Secretory Dynamics in Healthy Elderly: Evidence of Changes in Both Secretory Pulse Amplitude and Frequency

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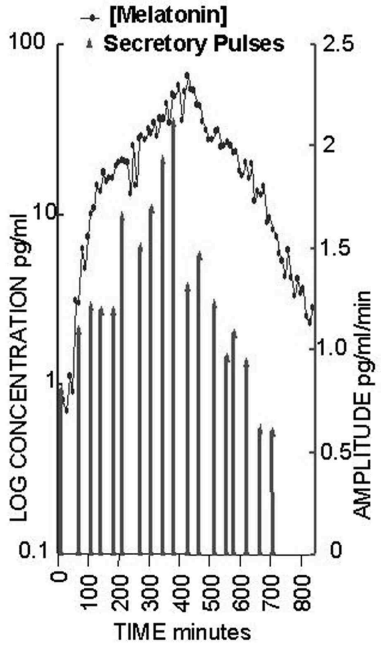
Introduction: While the secretion of the neurohormone melatonin is frequently observed to decline as people age, little is known about the actual changes in secretory kinetics that underlie this decrease in pineal gland activity. Preliminary work presented by our group[1] found that variations in pulse amplitude, but not frequency accounted for differences in nocturnal melatonin levels. We present here an expansion of our original data set of seven subjects to a larger set of twenty-one healthy individuals aged 65 and older.

Methods: Normal healthy subjects over age 65 (n=21) were carefully screened for medical or psychiatric conditions that could interfere with sleep. Subjects were excluded if they took CNS medications or beta-noradrenergic blockers. Subjects spent two nights of acclimation prior to the (third) actual study night. Blood was sampled every 10-minutes from 18:00-08:00 h. Lights-out was from 22:00-07:00 h. Subjects were free to go about their daily activities between study nights. Plasma melatonin was assayed by a RIA. The detection limit was 0.3 pg/ml. The intra-assay coefficient of variation was between 6.7 and 9.8%. The inter-assay coefficient of variation was between 7.2 and 16.3%. Elimination kinetics were calculated using a two-compartment model based on the observed biexponential clearance of melatonin. The half-lives, chosen from the literature as nominal values were first half-life 2.1 minutes, second 31.0 minutes, and fractional amplitude of the second half-life component 0.31. We employed a waveform independent deconvolution procedure that made no assumptions of secretory patterns. Such calculations allow for any combination of basal and/or pulsatile secretion.

Results: All subjects showed the classic nighttime rise of plasma melatonin. Mean nocturnal levels varied between 1.0 and 46.5 pg/ml, with peak values ranging from 3 to 110 pg/ml. Distinct secretory bursts accounted for 96-100% of the nocturnal rise observed in all subjects. A difference in both the pulse amplitude (0.34-4.0 pg/ml-min) and frequency of pulses (0.9-1.3 bursts/hour) correlated to nocturnal plasma levels between individuals. There were no significant correlations between plasma levels and subjects in the half-duration of bursts or the inter-burst interval.

Figure 1. Melatonin Concentration and Secretory Pulses



Conclusions: Despite a wide range of nocturnal melatonin concentrations between our elderly subjects, all subjects exhibited pulsatile secretory kinetics. We conclude that decreases in both pulse amplitude and frequency gives rise to the diminished melatonin secretion associated with aging.

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1421.C

Soporific Effects of Early Morning Melatonin Administration

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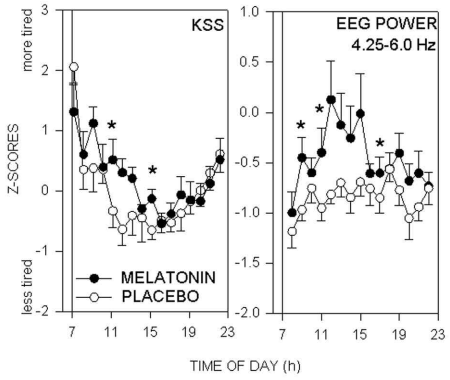
Introduction: Sleepiness increases with the duration of time awake and is dependent on circadian phase. Melatonin (MEL) administration during midday or evening acts as a soporific, increasing sleepiness and theta/alpha frequencies in the waking EEG, an objective measure of subjectively rated sleepiness (Cajochen et al 1997). Here we report the acute soporific effects of a single MEL administration immediately after waking.

Methods: We carried out a double-blind randomized-order placebo-controlled constant routine protocol (supine in bed for 58 hours, sleep 23-07h) in 9 healthy young men (age 24±1y, sem). MEL administration (5mg) was at 07h. During the daytime, beside scheduled tasks, subjects were administered Karolinska sleepiness scales (KSS, (Åkerstedt et al

1979) at 30-min intervals and waking EEGs at hourly intervals (3' eyes open, 2' eyes closed). Power spectra of the C3-A2 derivation were calculated for 4s epochs after visual inspection for artifacts. EEG power in the frequency range of 1.0 to 25 Hz for eyes open was z-transformed within each subject. KSS values were averaged over 1h intervals and also z-transformed within each subject.

Results: Subjective sleepiness (KSS) and EEG power in various frequency bins exhibit prominent change with elapsed time awake. Melatonin administration increased subjective sleepiness (2-way rANOVA 07-12h; 'time': $p<0.0001$, 'drug': ns, 'time*drug': $p<0.0286$) and EEG power specifically in the theta range (4.25-6.0 Hz; 2-way rANOVA 08-12h, 'time': $p<0.0348$, 'drug': $p<0.0307$, 'time*drug': ns) (see figure). However, only 6 out of 9 subjects showed clear acute soporific effects of MEL (theta frequency band; >30% of the average effect). Further analysis revealed that 5 of these subjects had been administered MEL during the second block of the experiment (after placebo in the first block). The 4 subjects who had received MEL on the first morning of the first block of the study showed no significant change in subjective sleepiness and in the theta range, but rather, a decrease in alpha power (8-10Hz). In addition, these two subgroups differed by chance in their circadian phase position (as measured by baseline dim light melatonin onset: N=5, DLMO=22:39±6'; N=4, DLMO=22:00±15'; $p<0.05$).

Figure 1



Conclusions: Morning MEL administration induced an increase in theta activity and sleepiness similar to the soporific effects that have previously found for MEL given later in the day (Cajochen et al 1997), even though subjects were still sleepy after awakening (possible masking effect). However, the response to morning MEL intake may be more sensitive to environmental circumstances, in this case, the higher arousal state on the first day of an experiment, and/or phase position, than MEL administration at later times of day.

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(2) Cajochen C, Kräuchi K, Wirz-Justice A: The acute soporific action of daytime melatonin administration: effects on the EEG during wakefulness and subjective alertness. Journal of Biological Rhythms 1997;12:636-643.

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1264.A

Morning Melatonin Administration and Heart Rate Variability in Healthy Young Men During 58 Hours Constant Bedrest

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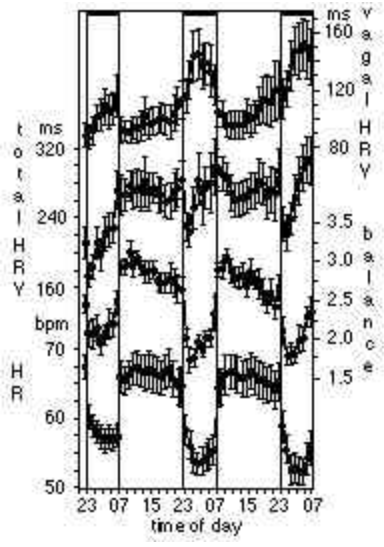
Introduction: Analysis of heart rate variability (HRV) is a dynamic non-invasive technique to quantify autonomic control of heart rate. Only few studies have controlled for posture effects on HRV by using constant bed rest during sleep and wake. Vagal nerve activity appears mainly circadian modulated, whereas sympathetic activity is rather sleep dependent (Burgess et al. 1997). The aims of this study were to show whether HRV (1) is changed after melatonin administration (5mg p.o. at 7 a.m.); (2) shows a circadian and nocturnal sleep modulation; and (3) is systematically changed during 58 hours constant bedrest.

Methods: We carried out a double-blind randomized-order placebo-controlled study. Nine healthy young men [age: 24y ±1 (sem), BMI: 23.5 ±0.7] entered the laboratory twice at 20h and remained supine in bed for the next 58 hours. Sleep was scheduled between 23-07h (lights off). A constant routine protocol (<8 lux) was carried out during the wake period. Thermometry (rectal and skin temperatures) and heart rate (inter beat interval, IBI) were continuously recorded. Both waking- and sleep-EEG were registered. HRV was analysed by histogram analysis of Poincaré plots (Kamen et al. 1996). Within succeding 15'-bins, the interdecile range of [(IBIt - IBIt-1)/sqrt 2]was calculated as a measure of vagal nervous activity (vagal HRV), total HRV was estimated by the interdecile range of IBIt, and the sympathovagal-balance (balance) was calculated by the quotient of total HRV / vagal HRV. The results (mean ± sem) are depicted in 1 hourly mean bins (Figure).

Figure 1



Results: (1) After melatonin administration neither HR nor the diverse HRV-measures were significantly changed, therefore, for further analyses both sessions were combined. (2) During the wake period, HR, total HRV and the balance showed highest values, vagal HRV the lowest (particularly early in the morning). At the beginning of nocturnal sleep, HR, total HRV and the balance immediately decreased, however, vagal HRV increased following a delay of 2 hours. (3) During the nocturnal sleep periods HR and the balance significantly decreased from night 1 to 3, whereas vagal HRV and total HRV increased. No differences were found between the wake period of day 1 and 2. Across the 58-hour protocol the

time course of vagal HRV and HR was inversely correlated (r = -0.79±0.16, p<0.0001).

Conclusions: (1) Morning melatonin administration does not affect HR nor HRV. (2) Under basal resting conditions the time course of HR is mainly under vagal nervous control. However, at lights off, HR declines by a decrease in sympathetic nervous activity even without any postural changes. (3) Long-term adaptation to constant bedrest seems to be mainly under vagal control.

References:
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1178.A

Sleep Propensity Following Melatonin & Zopiclone Administration is Related to Changes in Thermoregulation

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Introduction: The sleep promoting effects of the sedative-hypnotics, melatonin and temazepam, have been associated with a decline in core body temperature (Tc).[1] More recently, peripheral heat loss has been proposed to be the best physiological predictor for the rapid onset of sleep.[2] On the basis of these findings, it has been suggested that the thermoregulatory system may, in some way, form part of a physiological trigger for sleep onset. In order to determine whether changes in thermoregulation are a general feature of sleepiness, we compared the effects of melatonin and a cyclopyrrolone (zopiclone) on sleep propensity, Tc, foot temperature (Tf) and heart rate (HR).

Methods: Melatonin (5mg), zopiclone (7.5mg) and placebo were administered at 1400h to 12 healthy young adults (7m, 5f; 20.3 ± 0.6 years) in a double blind, cross-over design. Subjects were supine from 0800-2030h and rectal (Tc) and Tf were recorded continuously. From 1100-2000h, hourly multiple sleep onset latency (SOL) tests of a 20 min duration were conducted and HR was recorded.

Results: Compared with placebo, both melatonin and zopiclone significantly reduced SOL to stage 1 (SOL1) (-2.55 ± 0.85 min -2.3 ± 0.88 min, respectively). Melatonin and zopiclone also decreased Tc (0.27 ± 0.026 C & 0.20 ± 0.037 C) and increased Tf (1.37 ± 0.32 C & 0.78 ± 0.42 C). Moreover, a similar association between SOL1 and Tc was found for both treatments (0.39 & 0.38). Both melatonin and zopiclone also demonstrated a relationship between SOL1 and Tf (-0.28 & -0.45). Melatonin alone significantly reduced HR (-3.39 ± 1.47 b/min).

Conclusions: SOL1 was significantly reduced following the administration of both melatonin and zopiclone. More importantly, this reduction in SOL1 was associated with a concomitant reduction in Tc, thus highlighting the possibility that a decrease in Tc may be involved in the sleep-promoting effects of sedative-hypnotics.Moreover, melatonin and zopiclone also increased heat loss. Indeed, for zopiclone heat loss (Tf) was more closely related to SOL1 compared to Tc. While this finding supports the suggestion that heat loss is more salient than Tc when predicting SOL, the relationship between thermoregulation and sleep promotion appears more complex for melatonin.In addition to increasing heat loss, melatonin also reduced HR, an indicator of decreased heat production. Thus, SOL1 may have been associated more closely with Tc compared to heat loss because changes in heat production contributed to the overall thermoregulatory effect.In conclusion, the results of this study suggest that a thermoregulatory mechanism may be involved in the sleep promoting effects of sedative-hypnotics. While an increase in heat loss appears to be important in predicting SOL, the strength of this association may be dependent on the presence of a decrease in heat production.

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(2) Krauchi K, Cajochen C, Werth E, Wirz-Justice, A: Warm feet promote the rapid onset of sleep. Nature, 1999, 401: 36-37.

Research supported by National Health and Medical Research Council and Australian Research Council

1702.K2

Hypocretin Levels in Narcoleptic (Hypocretin Receptor-2 Mutated) and Control Dobermans

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Introduction: The phenotype of human and canine narcolepsy is similar and includes cataplexy, short sleep latency, and fragmented sleep. Our group recently discovered that mutations in the hypocretin receptor-2 gene cause narcolepsy in Dobermans and Labradors.[1] This report was followed by the observation that preprohypocretin knock-out mice display narcolepsy-like symptoms.[2] These findings suggest that deficits in either the hypocretin ligand or its receptor-2 mediated transmission are involved in generating narcolepsy. In this study, we measured the blood and cerebrospinal fluid (CSF) levels of hypocretins in narcoleptic and asymptomatic dogs to determine whether hypocretin production/secretion is altered in receptor-2 mutated narcoleptic animals.

Methods: Thirty three genetically narcoleptic (1.42± 0.30 years) and 20 asymptomatic (11 heterozygous and 9 control; 1.63 ± 0.25 years) Dobermans were used. Thirteen of the narcoleptic (N) and 11 of the heterozygous (Hz) dogs were born in backcross (HzxN) litters. Cisternal CSF taps were carried out between 9:00 a.m. and 2:00 p.m, and samples immediately frozen. In 7 dogs, hypocretin levels were also measured in the plasma; blood was drawn in Vacutainer tubes containing EDTA (1.8mg/ml) and aprotinin (0.6TIU/ml blood) and placed on ice. Peptides were extracted from CSF or plasma using a reversed phase SEP-PAK C-18 column, and were then measured using radioimmunoassay (RIA) kits (Phoenix Pharmaceuticals, Mountain View, CA; Peninsula Laboratories, San Carlos, CA).

Results: Hypocretin-1 and hypocretin-2 levels were undetectable in plasma (<6pg/ml, measured from 20ml of plasma). CSF hypocretin-2 levels were low and were only detectable in large CSF volumes (greater than or equal to 5 ml) in both narcoleptics and controls (about 8pg/ml). Hypocretin-1 levels were higher and reliably measured in 1ml of CSF (detection limit: 24 pg/ml). CSF hypocretin-1 levels were similar in narcoleptic (273.5 ± 5.75 pg/ml) and asymptomatic (260.0 ± 5.51 pg/ml) dogs. Additionally, there was no difference in hypocretin-1 levels between homozygous (257.3 ± 9.5 pg/ml) and heterozygous (261.6 ± 8.7 pg/ml) dogs born in the same backcross litter. Hypocretin-1 levels did not differ between males (264.5 ± 5.4 pg/ml) and females (272.8 ± 6.6 pg/ml), and were not correlated with age (age range of 0.36-9.56 years).

Conclusions: Although hypocretin production has been reported to occur peripherally in the gut,[3] hypocretin levels were undetectable in plasma using currently available RIAs. This result led us to explore

whether hypocretin levels were detectable in CSF. Hypocretin-1 but not hypocretin-2 were found at appreciable levels. This incongruity may reflect a difference in processing, or secretion or a faster turnover/instability for hypocretin-2. The finding that hypocretin-1 levels do not differ in narcoleptic versus asymtomatic animals suggests that hypocretin-1 production is not up or down-regulated in the presence of one or two copies of the mutated hypocretin-2 receptor. Additionally, the normal levels of hypocretins found in affected dogs is consistent with results showing that there is no destruction of hypocretin-containing neurons in narcoleptic Dobermans (Okura et al, in this issue). The finding that hypocretin-containing neurons and ligand production are essentially normal in Hcrtr2 mutated animals also indirectly demonstrates that receptor-1 mediated transmission is intact in narcoleptic canines. Receptor-2 mediated effects may thus be more critical for the expression of the narcolepsy phenotype.

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1452.K2

The Functional Variant of the Catechol-O-Metyltransferase (COMT) Gene Is Associated with Disease Severity in Narcolepsy

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Introduction: The susceptibility to narcolepsy is tightly associated with a specific HLA antigen (DQB1*0602). Also non-HLA genes can confer susceptibility as was shown by the recent cloning of the canine narcolepsy gene (orexin receptor 2) and the positive association found between narcolepsy and the MAO-A and the TNF-alpha. Since several lines of evidence have established a critical role of the monoaminergic system in the pathophysiology of narcolepsy, we sought for association between a COMT polymorphism and human narcolepsy. Since this polymorphism is functionally relevant (LL genotype corresponds to 3-4 times less activity of the enzyme as compared to HH genotype) we have also sought for COMT genotype effects on disease severity.

Methods: Ninety-seven Caucasian narcoleptics (38 females and 59 males, all from French extraction and 90 DQB1*0602 positive and 7 DQB1*0602 negative) and 121 ethnically but not DR2 matched normal controls (49 females and 72 males) were studied. COMT genotypes were determined by restriction fragment length polymorphism (RFLP) analysis from DNA extracted from peripheral blood by an investigator unaware of phenotype. The polymorphism is generated by a G to A substitution encoding a valine or methionine at codon 158. The target sequence was PCR amplified and the product was digested by the restriction enzyme NlaIII and electrophoresed in a 10% polyacrylamide gel to detect the digested (Met158 or L) vs. uncut fragments (Val158 or H). Clinical observations and PSG recordings were used in narcoleptics to establish correlations with COMT genotypes.

Results: Although there was no evidence of an association between either the genotype or the allele frequencies of the COMT gene in narcoleptics the genotype distribution was different between male and female narcoleptics (chi2 = 5.85, df 2, p = 0.05, Table 1). This difference resulted from a higher number of male narcoleptics with the LH genotype (LL vs. LH, $p < 0.03$, Fisher's exact test, Two-sided; odds ratio = 3.5, 95% CI = 1.2-10.2). Analysis of clinical and PSG recordings based on sex and COMT genotype yielded striking results. Independent of sex, the COMT genotype significantly affected the presence or absence of sleep paralysis (chi2 = 11.84, df 2, $p < 0.003$), sleep latency at night (ANOVA, $F2,65 = 3.4$, $p < 0.04$), and the number of SOREMPs during the MSLT (ANOVA, $F2,72 = 5.5$, $p < 0.007$). More interestingly, 2-way ANOVA on mean sleep latencies during the MSLT showed a significant sex and COMT genotype interaction ($F2,72 = 3.5$, $p < 0.04$). The MSLT scores in Table 2 clearly show that female narcoleptics with LL or LH genotype have an MSLT score twice longer than females with HH genotype while the opposite is true for males.

Table 1. COMT Genotypes in Narcoleptic and Control Subjects

	LL	LH	HH
Narcoleptic			
Female	12	13	13
Male	9	34	16
Control			
Female	10	26	13
Male	9	39	24

Table 2. Mean Sleep Latencies (min) During MSLT and COMT Genotypes in Narcoleptics

	LL	LH	HH
Female	6.0 ± 1.2 (n=9)	5.9 ± 1.1 (n=10)	3.0 ± 0.5 (n=10)
Male	4.1 ± 1.0 (n=6)	4.5 ± 0.5 (n=28)	5.6 ± 0.9 (n=10)

Conclusions: COMT is the key enzyme in the dopaminergic and noradrenergic neurotransmission supposed to present multiple alterations in narcolepsy. The present results suggest, for the first time, a sexual dimorphism in COMT activity in human narcolepsy, the mechanism of which remains to be defined. We also show that significant differences in disease severity (mostly related to excessive daytime sleepiness) are associated with the COMT genotype confirming as has been well-documented in the canine narcolepsy, that an abnormality in the dopaminergic/noradrenergic transmission is critically involved in the pathophysiology of narcolepsy.

1447.K2

Lack of Association Between the Monoamine Oxidase-A (MAO-A) Gene and Narcolepsy

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Introduction: Recently, based on abnormal REM sleep symptoms suggestive of narcolepsy in Norrie disease, Koch et al.[1] have studied markers in the Norrie disease region on chromosome X of 28 narcoleptic subjects and found evidence for a significant association with an intronic variable number tandem repeat (VNTR) marker of the monoamine oxidase-A gene (MAO-A). This finding may be of interest since a monoamine defect has long been recognized in narcolepsy. Thus we have sought to replicate this finding in a larger population of narcoleptics.

Methods: Ninety-eight Caucasian narcoleptics (39 females and 59 males, all from French extraction, 91 DQB1*0602 positive and 7 DQB1*0602 negative) and 130 ethnically but not DR2 matched normal

controls (51 females and 79 males) were studied. In addition, in 36 narcolepsy cases mothers and in some also fathers were studied in order to test for homogeneity of transmission disequilibrium between male and female probands and comparing transmission of alleles from heterozygous mothers. MAO-A genotypes were determined at 2 polymorphic sites: a T to G substitution at codon 297/exon 8, which results in a Fnu4H1 restriction fragment length polymorphism (RFLP), and the intron 1 VNTR reported by Koch et al..[1] The target sequences were PCR amplified and the products were either digested by the restriction enzyme Fnu4H1 and electrophoresed in a 2% agarose gel to detect the digested (H) vs. uncut fragments (L), or electrophoresed in a sequencing gel to detect the size of the VNTR (grouped as Short or Long). Clinical observations and PSG recordings were used in narcoleptics to establish correlations with the RFLP polymorphism since this polymorphism has been associated with high MAO-A activity in vitro.

Results: The table shows the allele distribution of the 2 markers for narcoleptic and control subjects. There was no evidence for an association between the allele frequencies of the MAO-A gene and narcolepsy. Moreover, analysis of the inheritance of the MAO-A variants in 36 narcoleptics and their mothers failed to indicate any preferential transmission pattern. In addition, among 10 heterozygous mothers, 5 transmitted one variant and 5 the other, suggesting a complete homogeneity of allele transmission. We have also analyzed the genotype frequencies for the MAO-A RFLP in females and did not find any significant difference between groups (chi2=1.91, $p > 0.3$). Analysis of clinical and PSG recordings showed a significant effect of sex and MAO-A variants on the amount of wake after sleep onset (ANOVA, $F1,65 = 10.5$, $p < 0.002$ for sex; and $F2,65 = 4.0$, $p < 0.03$ for MAO-A).

Table 1

	Total		*Female*		*Male*	
MAO-A RFLP	**H**	**L**	**H**	**L**	**H**	**L**
Narcoleptic	34	103	18	60	16	43
Control	61	120	33	69	28	51
	χ^2=2.94, p > 0.08		χ^2=1.87, p > 0.1		χ^2=1.08, p > 0.2	
MAO-A VNTR	**Short**	**Long**	**Short**	**Long**	**Short**	**Long**
Narcoleptic	30	86	16	52	14	34
Control	43	104	24	64	19	40
	χ^2=0.37, p > 0.5		χ^2=0.28, p > 0.5		χ^2=0.11, p > 0.7	

Conclusions: Based on the present analysis in a French narcoleptic population, we failed to demonstrate any allele or genotype association with the MAO-A variants. MAO-A accounts for 80-100% of MAO activity, which is under strong genetic control and is principally involved in the metabolic degradation of 5-HT. Among many clinical and laboratory data used in the present study, only the amount of wake after sleep onset was found to be affected by a functional MAO-A gene variant, suggesting a minor role for the serotonergic as compared to dopaminergic/noradrenergic transmission in the pathophysiology of narcolepsy (see Dauvilliers et al. this issue).

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1766.K2

Sulpiride, a D2/D3 antagonist, reduces cataplexy, but not REM sleep in the canine narcolepsy model

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Introduction: Cataplexy is pathognomonic for narcolepsy. This symptom is often classified as a dissociated REM sleep event together with hypogogic hallucinations and sleep paralysis. These symptoms are typically treated with antidepressant therapy which strongly reduces REM sleep. Recent experiments have shown that the mechanisms generating cataplexy are not identical to those generating REM sleep. REM cyclicity occurs with a clear 30-minute cyclicity in both narcoleptic and control animals; in contrast, cataplexy can be elicited anytime with emotional stimulation, and no 30-minute cyclicity is observed.[1] Based on this finding, we hypothesize that compounds acting more specifically on cataplexy, but not on physiological REM sleep could be developed. Previous pharmacological studies have demonstrated that dopaminergic neurons in the ventral tegmental area (VTA) and substantia nigra (SN) do not significantly reduce their firing rate during REM sleep; on the other hand, D2/D3 agonists administered systemically or locally into midbrain dopaminergic (VTA and SN) or diencephalic dopaminergic nuclei significantly enhance canine cataplexy.[2,3] It is therefore possible that the modulation of dopaminergic neurons in the midbrain and diencephalon is more specifically related to the regulation of cataplexy than REM sleep. In this study, we evaluated the effects of sulpiride, one of the most commonly used D2/D3 antagonists in clinical practice, on canine cataplexy.

Methods: We administrated sulpiride acutely and chronically to narcoleptic dogs, and evaluated its effects on cataplexy and sleep. Six genetically narcoleptic Dobermans were included for cataplexy testing studies and 3 narcoleptic Dobermans with chronically-implanted EEG, EOG, and EMG electrodes were used for polygraphic recordings. The effects on cataplexy were evaluated by the food-elicited cataplexy test (FECT). Six-hour daytime polygraphic sleep recordings were performed, beginning 2 hours after oral administration of sulpiride. In order to pharmacologically characterize the anticataplectic effect of sulpiride, we also examined if a pretreatment with this compound antagonizes the cataplexy-inducing effects of D2/D3 agonists (quinpirole 6 µg/kg, i.v. and 7OH-DPAT 6 µg/kg i.v.).

Results: Oral administration of sulpiride (300 or 600 mg per dog, p.o.) significantly reduced cataplexy in adose-dependent manner. Pretreatment with sulpiride (300 or 600 mg, p.o. administered 4 hours prior to the injection of D2/D3 agonists) blocked the cataplexy-aggravating effects of quinpirole and 7-OH-DPAT, suggesting that anticataplectic effects of sulpiride are mediated by blockade of dopamine autoreceptors. Six-hr polygraphic recording (2-8 hour after drug administration) demonstrated that a single oral administration of sulpiride (300 and 600 mg, p.o.) did not significantly modify the amount of REM sleep in narcoleptic animals. In order to assess the possible clinical application of D2/D3 antagonists for the treatment of human cataplexy, the effects of two week-chronic administration of sulpiride were also evaluated with systematic side effect monitoring. The chronic administration of sulpiride significantly reduced cataplexy, while the amount of REM sleep was not significantly modified. Interestingly, chronic administration tended to improve the sleep fragmentation; the mean duration of drowsy, light sleep and deep sleep was significantly increased.

Conclusions: The differential effects of sulpiride on cataplexy versus REM sleep is unique and further supports our hypothesis that cataplexy is modulated in a manner distinct from REM sleep. Sulpiride (and other D2/3 antagonists) may also prove to be a promising novel treatment in human narcolepsy.

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1319.L

Absence of Nystagmus During REM Sleep in 8 Patients with Vestibular Neuritis

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Introduction: Saccades, including the fast phase of nystagmus disappear during drowsiness and non REM sleep. The purpose of this study was to investigate spontaneous nystagmus in vestibular neuritis during REM sleep.

Methods: Eight patients with vestibular neuritis (VN) presenting with spontaneous nystagmus during the wake state and 8 controls underwent at least one night of polysomnography. Right and left horizontal saccades were counted separately during 3-5 minute samples of wake before sleep onset, wake after the night sleep period, the first REM episode and the last REM episode of the sleep cycle.

Results: Controls and patients with VN were similar in age and sex. All patients with VN showed significantly more saccades to the side contralateral vs. ipsilateral to their vestibular lesion in the wake state, which reflects their spontaneous nystagmus (wake before sleep: 0.96±0.49/s vs. 0.26±0.25/s; wake after sleep period: 0.79±0.33/s. vs. 0.3±0.3/s.; p=0.017). During REM sleep, the patients showed no difference in saccade direction. No difference in saccade direction was observed in controls during wake state or REM sleep.

Conclusions: Our results demonstrate, that nystagmus resulting from unilateral VN is not present during REM sleep. In conclusion, mechanisms controlling nystagmus associated with VN in the wake state are different from mechanisms involved in REM sleep. (results are given in mean±SD).

1204.L

Bright Light Therapy for Sleep-Activity Disruption in Alzheimer's Disease

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Introduction: Disturbances in sleep-activity rhythm and agitated behaviors are common in Alzheimer's disease (AD). While the etiology of these symptoms is not well understood, a complex interaction of genetic, neurodegenerative and environmental factors is hypothesized. Sleep-activity (circadian) rhythm disruption and low light exposure are common in institutionalized AD patients (Ancoli-Israel et al 1997). Bright light exposure has been reported to improve these problems (Mishima 1994; Van Someren et al 1997). The purpose of this study is to test the effectiveness of bright light therapy in reducing sleep-activity disruption in institutionalized patients with Alzheimer's disease (AD).

Methods: In this 12-week randomized clinical trial, subjects (n = 26 to date, mean age = 86 years, SD = 5 yrs) are randomly assigned to receive either one hour of bright outdoor light (9:30-10:30am) or usual indoor light for 10 weeks. Sleep-activity rhythm is assessed by actigraphy for 1 week at baseline, during weeks 3, 7, and 10 of the intervention phase, and 1 week after completion of the intervention.

Results: Preliminary analysis of actigraphy data indicates that subjects who received the bright light intervention improved their nighttime sleep efficiency slightly (71%, SD = 14% at baseline; 73%, SD = 15% at 10 wks) compared to subjects who did not (69% at baseline and at 10 wks). Mann-Whitney tests were also performed on the actigraphy data and while these results did not reach statistical significance, the mean ranks for nighttime sleep efficiency and total nighttime activity were in the direction of improvement for the experimental group (see Figures 1 and 2).

Figure 1. Nighttime Sleep Efficiency

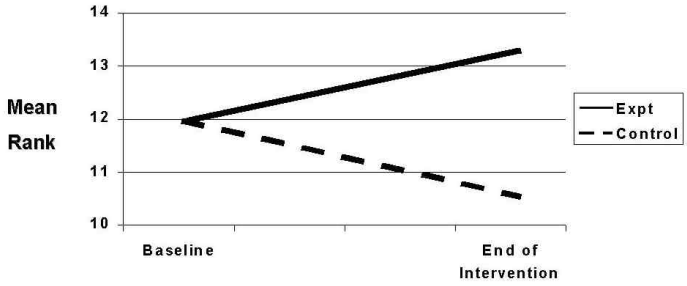
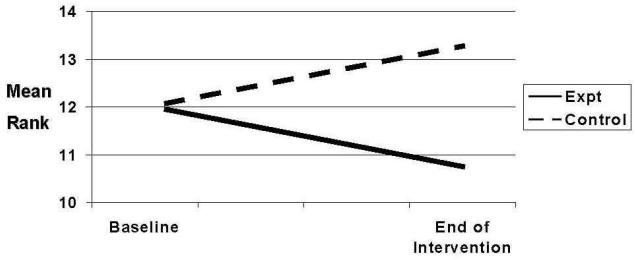


Figure 2. Nighttime Total Activity Score



Conclusions: While statistically significant improvement in sleep-activity rhythm may be demonstrated with larger numbers (target n = 64), the trend toward improved nighttime sleep efficiency and decreased nighttime total activity in those exposed to bright light is encouraging.

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1860.L

Role of CAP and of EEG Sychrony in the Activation of Primary Generalized Epilepsy During the First Two Sleep Cycles

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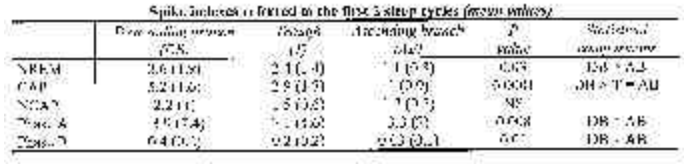
Introduction: The cyclic alternating pattern (CAP) is an EEG phenomenon of NREM sleep characterized by a periodic arousability. Each cycle of CAP is composed of a phase A (greater arousal level) and a phase B (lesser arousal level). The absence of CAP (non-CAP) reflects a condition of stable arousal. It is during CAP that a number of epileptic events occurring in NREM sleep are seen with the highest frequency. In primary generalized epilepsy (PGE), the majority of interictal EEG

abnormalities are associated with a CAP sequence and are triggered by an A phase. In a previous study we demonstrated that the increase of generalized spike-wave paroxysms was apparent during CAP in all NREM stages , but no evaluation was carried out on their position within the sleep cycle (SC). Conventionally, a SC is composed of three units : a descending branch sloping from the more superficial to the deeper NREM stages ; a central trough of deep sleep ; an ascending branch where lighter NREM stages precede the onset of REM sleep. To assess the impact of sleep depth on interictal discharges in PGE, we analyzed the distribution of CAP sequences and of EEG paroxysms in the descending branches, in the troughs and in ascending branches of the first two SCs, which offer a complete representation of all NREM stages.

Methods: The study was carried out on attended laboratory-recorded polysomnograms in subjects with an active form of PGE. Nocturnal investigation was accomplished on 18 subjects, but only in 6 of them did the first two SCs meet the inclusion requirements (SCs uninterrupted by intervening wakefulness and containing all stages linked in a regular succession of a descending branch, a trough and an ascending branch). Diurnal EEG showed paroxysmal discharges consisting of generalized spike-and-waves, a regular background rhythm and no focal abnormality. The age range of the 6 patients (2 males and 4 females) was between 10 and 25 years (17.4 ± 5.9). Patients were under mono- or polytherapy, with the exclusion of benzodiazepines and barbiturates in the previous 6 months. Neurological and neuroradiological investigation was normal. The frequency of EEG paroxysms was measured in terms of spike-index (SI : number of discharges per minute of sleep).

Results: Within the first two SCs, activation of EEG paroxysms was greater during NREM sleep (SI: 2.8) compared to REM sleep (SI: 0.8), during CAP (SI : 3.4) compared to non-CAP (SI:1.9) and during phase A (SI: 8.7) compared to phase B (SI : 0.3). Activation was highest in the descending branches and lowest in the ascending limbs of both SCs. The troughs presented intermediate values of activation between the ones expressed by the descending (high) and ascending branches (low). In both SCs, the Sl quantified during the A phases of CAP was 3-fold higher compared to the values expressed throughout the entire units (SI in NREM sleep).

Table 1



Conclusions: Within the first two SCs, generalized epileptic discharges are mostly activated during the progressive enhancement of slow wave activity (descending branch), in contrast to the shallow role played by the demolition of EEG synchrony (ascending branch). Regardless of the position within the SC, the A phases of CAP offer a particularly favorable background for the onset of EEG paroxysms.

1069.L

Effects of Vagus Nerve Stimulation on Sleep-Onset REM Periods and Daytime Alertness in Epilepsy Patients

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Introduction: Vagus nerve stimulation (VNS) is an FDA-approved adjunctive treatment for partial epilepsy. Vagal efferents to the parabrachial nucleus send projections to both noradrenergic and cholinergic brainstem regions and to the thalamus (reviewed in Fernández-Guardiola et al, 1999). Stimulation of these regions may result in seizure suppression, perhaps through cortical activation, although the specific antiepileptic mechanisms of VNS are unknown. In recent reports, locus coeruleus lesions suppressed the seizure-attenuating effects of VNS in rats (Krahl et al, 1998), and VNS delayed amygdaloid kindling and enhanced PGO wave density during rapid eye movement (REM) sleep in cats (Fernández-Guardiola et al, 1999). To test the hypothesis that VNS increases daytime alertness, we performed sleep studies in six epilepsy patients before and during treatment with VNS.

Methods: Prior to VNS initiation, six adult subjects with refractory partial epilepsy underwent baseline polysomnograms (PSGs) followed by Multiple Sleep Latency Tests (MSLTs). Three months after VNS was initiated, treatment PSGs and MSLTs were performed. Subjects were maintained on stable doses of antiepileptic medication. Stimulation intensities during treatment studies ranged from 0.75 mA to 2.75 mA, with a stimulation frequency of 30 Hz, a pulse width of 500 ms, an on-time of 30 seconds, and an off-time of 5 minutes. Studies were scored by a registered polysomnography technologist (MM) blinded to the subjects and study condition (baseline vs. treatment). The first author, a board-certified clinical neurophysiologist, reviewed each study to confirm sleep latency and sleep-onset REM periods (SOREMs).

Table 1. MSLT and VNS Parameters in Six Treated Subjects

Baseline MSL (minutes)	SOREMs on Baseline MSLT/naps	Treatmt MSL (minutes)	SOREMs on Treatmt MSLT/naps	Ambiguous SOREMs on Treatmt MSLT
6.3	0/4	13.7	2/4	0
7.2	0/4	3.7	2/5	0
1.2	0/4	12.3	1/4	1
1	0/4	1.3	0/4	1
8.7	0/4	16.6	0/4	0
16	0/4	10.1	0/4	0
6.7 (mean)	0/24* (total)	9.6 (mean)	5/25* (total)	2 (total)

*p < 0.03, Fisher exact test

Results: The SOREMs occurred on five of 25 treatment naps as compared to none of 24 baseline naps ($p < 0.03$; Fisher exact test). Two additional treatment naps showed ambiguous REM periods (rapid eye movements with preservation of sleep spindles and chin EMG tone). Four of six subjects had SOREMs or ambiguous SOREMs. After treatment with VNS, mean sleep latency (MSL) increased in three subjects, two of whom had SOREMs. Although the MSL after treatment increased in the six subjects combined, this increase was not statistically significant ($p > 0.1$; paired samples t-test). The REM latency and percentage of REM sleep were not statistically different between baseline and treatment PSGs ($p > 0.1$; paired samples t-test). All subjects improved in seizure frequency, seizure severity, or both during treatment with VNS.

Conclusions: Daytime REM sleep, as measured by SOREMs on MSLT, was enhanced by VNS. This finding is consistent with the activation of cholinergic regions. These SOREMs were associated with increased sleep latency in two subjects, suggesting that VNS may simultaneously activate cholinergic and noradrenergic regions. Stimulation of one or both of these neurochemical systems, which modulate cortical activation, may mediate the antiepileptic effects of VNS in humans. This possibility awaits future experimental investigation.

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1570.C

Plasma Norepinephrine During 66 hr of Sustained Low-Dose Caffeine Intake and 88 hr of Sleep Deprivation

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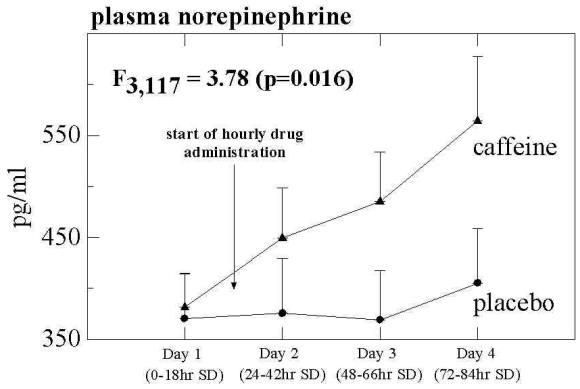
Introduction: Previous studies have been contradictory regarding the effects of sleep deprivation (SD) on norepinephrine (NE) secretion in humans.[1,2] Similarly, previous studies have reported that caffeine has either no effect or increases NE concentrations in humans.[3] To clarify these results we performed a randomized, double-blind experiment consisting of two levels of 88-hr sleep deprivation crossed with a placebo-controlled trial of sustained low-dose caffeine.

Methods: Following extensive screening and caffeine withdrawal 2 weeks prior to the study, n=41 healthy, male adults (M=28yr, range=21-47) lived in temporal isolation for 10 days, during which time their plasma levels of NE and caffeine were monitored through an IV catheter for days 3-8. The first 3 days were baseline sleep/wake cycles. During the next 3.67 days (88 hr) the subjects were randomly assigned to either total sleep deprivation (TSD) or partial sleep deprivation (PSD = 2hr nap per 12hr for 88hr). The final 3 days were recovery sleep/wake cycles. Subjects were randomized to either hourly placebo (n=20) or hourly caffeine (n=21; 0.3mg/kg/hr) administration throughout the final 66hr of the 88hr period. The first pill was taken 22hr after the beginning of the deprivation period. Subjects were blindly administered the same pill (placebo or caffeine) every hour of the remaining 66hr (except for the mid-nap hour for PSD subjects). Blood was collected for NE sampling every 6hr beginning at 2230hr on day 3 of baseline and ending at 1930hr on day 1 of recovery. Samples were spun and stored at -75°C until assayed blind to condition using Catecholamine-RIA(125I). Data were analyzed across the 88hr SD period using mixed-model ANOVA with p values corrected for sphericity.

Results: Plasma NE levels increased significantly across all 4 conditions (TSD+placebo; TSD+caffeine; PSD+placebo; PSD+caffeine) during the 88hr SD period ($F[3,111]=8.65$, $p=0.0001$), but the effect was most evident in the caffeine conditions ($F[9,111]=1.94$, $p=0.057$). This was confirmed by ANOVA's within each condition (Fs < 1 for both TSD and PSD placebo conditions; $F[3,21]=6.61$, $p=0.026$, for TSD+caffeine; $F[3,36]=3.77$, $p=0.029$ for PSD+caffeine). Given that the effects of SD+caffeine were much larger than those of SD+placebo (with no difference between TSD and PSD), subjects were pooled into two groups: those that received caffeine (n = 21) and those that received placebo (n = 20) regardless of SD. The 88hr-deprivation period was separated into 4 intervals: Day 1 from 0730-0130 (0-18hr SD); Day 2 from 0730-0130 (24-42hr SD); Day 3 from 0730-0130 (48-66hr SD); and Day 4 from 0730-1930 (72-84hr SD). A mixed-model ANOVA revealed the increases in NE across SD in the caffeine condition ($F[3,117]=3.78$, $p=0.016$). The results are shown in Figure 1 below.

Figure 1



Conclusions: Sustained (0.3mg/kg/hr for 66hr) low-dose caffeine administration elevated plasma NE levels regardless of the severity of sleep loss (88hr TSD vs PSD). In contrast, sleep loss alone (with placebo) had little effect on NE levels. Heart rate and blood pressure data are being analyzed to determine other effects of caffeine on autonomic nervous system (ANS). These data will be further complemented by analyses of plasma cortisol levels and caffeine pharmacokinetics. Other abstracts from this project report the effects of caffeine and sleep loss on neurobehavioral functions, nap PSGs, and subjects' perceptions of what they were receiving (caffeine vs. placebo). This may help us to understand why caffeine activates the ANS much more so than severe sleep deprivation alone.

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Research supported by AFOSR grant F49620-1-0388, and the IEPRF.

1604.C

Effects of 66h of Sustained Low-Dose Caffeine on Prophylactic Naps During 88h of Continuous Operations

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Introduction: Prophylactic naps have been demonstrated to be an effective countermeasure for preventing neurobehavioral impairment during continuous operations.[1] Caffeine has also been proven to be an effective wake-promoting therapeutic.[2] Combining naps and caffeine may provide an optimal strategy for maintaining neurobehavioral functions during continuous operations. However, it is not known what effects the sustained use of caffeine might have on nap duration and PSG during continuous operations. Although caffeine would be expected to increase sleep latency (SL) and reduce total sleep time (TST) and slow wave sleep (SWS) during naps, these effects might be mitigated by the escalating homeostatic drive for sleep engendered by sleep restriction. Therefore an experiment was conducted to determine how sustained

low-dose caffeine use affected nap PSG and EEG power spectra during 2h nap opportunities taken every 12h throughout 88h of continuous performance demands.

Methods: A total of n=28 healthy, young male adults (M=29y, range 21-47) participated in a 10-day laboratory double-blind, randomized, placebo-controlled experiment on the effects of sustained low-dose caffeine (0.3mg/kg/hr for 66h). After one adaptation night, subjects had two baseline days with bedtimes from 23:30 until 07:30. They then underwent 88h of quasi-continuous performance demands in which the only sleep opportunities were 7 naps scheduled every twelve hours at 14:45-16:45 and 02:45-04:45. Thus, subjects were permitted no more than 4h sleep per day throughout the 88h period, and were tested on a 30-min computerized assessment battery every 2h (except during naps). Subjects took a pill (0.3mg/kg caffeine or placebo) every hour (except when sleeping), for a total period of 66h: n=15 subjects were randomized to caffeine for all 66h, and n=13 to placebo. Hourly pill administration began 9h before the 3rd nap. PSG was recorded during each nap and scored visually (30s epochs) blind to drug condition using conventional criteria. Data from naps 3 through 7 (during caffeine/placebo administration) were analyzed using a mixed-model ANOVA. Naps 1 and 2 (predrug) were analyzed separately by the same procedure to determine potential baseline differences. Nap EEG power spectra are still being analyzed.

Results: Naps 1 and 2 showed no significant between-group differences ($F[1,26] < 2$). Across naps 3 through 7 (caffeine vs. placebo), there were significant within-subjects effects; subjects had more TST, more SWS, and less WASO, as sleep loss progressed (all $F[4,104] > 7.9$; all $P < 0.005$). There were also significant main effects between groups, with the caffeine group having an average (across naps) of 10min longer sleep latency (P=0.006), 13.4min less TST (P=0.01), and 5.4min less REM sleep (P=0.044) than the placebo group (all $F[1,26] > 4.49$). Only the amount of SWS showed a condition by time interaction ($F[4,104] = 2.87$, P=0.043), being reduced in nap 3 by 8.4min (P=0.081) and in nap 4 by 12.2min (P=0.036) in the caffeine condition relative to the placebo condition (naps 3 and 4 were the first two nap opportunities during the 66h of pill administration).

Conclusions: Sustained low-dose caffeine administration increased SL and decreased the amount of TST, REM, and SWS in naps. This suggests that caffeine disruption of nap sleep continued even in the face of escalating homeostatic sleep drive. SWS deficits from hourly caffeine in naps 3 and 4 were associated with the rising slope of the plasma caffeine pharmacokinetic curve. Sleep EEG power spectral analyses will provide a quantitative estimate of the effects of caffeine on nap slow wave activity (SWA), the putative marker of the homeostatic drive for sleep. These effects of sustained low-dose caffeine on nap sleep are currently being evaluated relative to the effects of caffeine and naps on performance, mood, and endocrine responses throughout the sustained operations trial.

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1696.I

Sustained Low-Dose Caffeine Administration Reduces Sleep Inertia After Nap Sleep During 88h Extended Wakefulness

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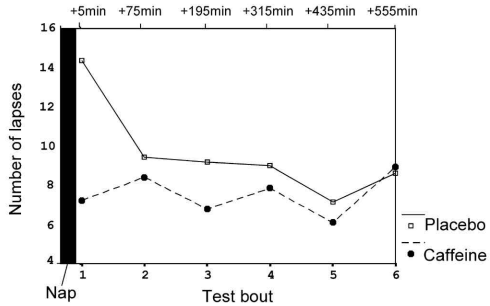
Introduction: Sleep inertia, the feeling of grogginess usually experienced after awakening from sleep, has been reported to be associated with vigilance performance impairment.[1] In this randomized, double-blind, placebo-controlled study of extended wakefulness with brief naps at regular intervals, we investigated the potential that sustained low-dose caffeine may have to attenuate the vigilance-reducing effect of sleep inertia.

Methods: A total of n=28 healthy adult males (mean age 29y, range 21y-47y) participated in a 10-day study of sustained low-dose caffeine (0.3mg/kg/h) under controlled laboratory conditions. After one adaptation day and two baseline days with bedtimes from 23:30 until 07:30, subjects underwent 88h (i.e., 3.7 days) of extended wakefulness with naps scheduled every 12h from 14:45 until 16:45 and from 02:45 until 04:45. Starting at 08:00 in the first hour of extended wakefulness, and then every 2h except during naps, subjects were tested on a 30min computerized neurobehavioral assessment battery. Performance testing also occurred 5min after each nap. The test battery included a 10min psychomotor vigilance task (PVT-192;[2]), which yielded the number of performance lapses (reaction times longer than 500ms) as outcome variable. Subjects were randomized to receive either a caffeine (n=15) or placebo (n=13) pill every hour, starting 22h into the 88h extended wakefulness period (i.e., 45min after the second nap). Performance lapses were analyzed for the six test bouts following each of naps 3, 4, 5 and 6 (i.e., across four uninterrupted 10h periods of wakefulness during caffeine/placebo administration). Given that naps 3 and 5 occurred during the day and naps 4 and 6 during the night, that is, at opposite circadian phases, the data were analyzed with analysis of variance (ANOVA) in a mixed-model design of two days of sleep restriction by two circadian phases by six test bouts vs. condition.

Figure 1



Results: A significant main effect for days of sleep restriction was found ($F[1,26]=14.9$; P=0.001), revealing that performance lapses increased over days of extended wakefulness irrespective of caffeine/placebo condition. Furthermore, a significant main effect of circadian phase was observed ($F[1,26]=17.5$; $P<0.001$), as performance lapses occurred more often during the night than during the day regardless of condition. Finally, there were a significant main effect of test bout ($F[5,130]=4.80$; P=0.001) and a significant interaction of test bout by condition ($F[5,130]=4.46$; P=0.002). As shown in the Figure, performance lapses

were relatively stable across test bouts after each nap for the caffeine condition, but for the placebo condition there were twice as many performance lapses in the test bout immediately after each nap relative to all other test bouts. Post-hoc t-tests revealed a significant difference between the two conditions only for the test bout immediately following the naps (t[110]=2.5; P<0.001).

Conclusions: The 88h of extended wakefulness induced performance decrements, with evidence of substantial circadian modulation, in subjects receiving placebo and caffeine alike. Furthermore, the placebo group showed a clear effect of sleep inertia, with PVT performance lapses occurring twice as often immediately following the naps compared to other neurobehavioral performance test times. In this study, the dominant effect of sustained low-dose caffeine was an elimination of the additional vigilance lapses associated with sleep inertia. This result may explain why a cup of coffee in the morning is so popular throughout society. Caffeine also affected nap sleep architecture, as presented in a separate abstract (MacAdam et al.). Future investigation of the simultaneous caffeine-induced changes in nap sleep architecture and the magnitude of sleep inertia may provide insight into the nature and cause of sleep inertia.

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1547.C

The Alerting Effect of 4 Mg of Dexamethasone on a Sleep Deprived Population

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Introduction: Research investigating the effects of gluccocorticoids on sleep has yielded contradicting results. For the most part, dexamethasone has been found to produce negligible effects on nocturnal sleep. However, our group has reported consistent alerting effects on the MSLT following the nocturnal administration of 1, 2 and 8 mgs of dexamethasone. These alerting effects occurred despite the absence of immediate effects on the 8-hour PSG recording post drug administration. The purpose of this study was to determine if the absence of these effects was due to the lack of PSG sensitivity versus the MSLT, or to a time-locked nature of the alerting effects of Dex.

Methods: Thirteen healthy male subjects (mean age= 26.9 + 7.3) were screened to assure they maintained regular sleep schedules and had no acute stressors. All subjects underwent medical and toxicology screens to prove their medical and drug free status. Subjects were given a structured psychiatric interview (SCIDS DSM-IV) and were determined to be free of any psychiatric diagnosis. All subjects completed polysomnographic screening to document that they had a sleep efficiency of > 88%, MSLT of > 8 min, and no evidence of any sleep disorder. Eligible subjects were given placebo (Dex 0) or 4 mg of dexamethasone (Dex 4) in a double blind procedure. Dex was administered at 22:30 hrs. A modified MSLT was started at 23:00 hrs with the remaining tests done at 1:00, 3:00, 4:30, 5:30, 7:30, 9:30, 11:30, 13:30, 15:30, 17:30 and 19:30 hrs. For each test, if sleep occurred within the 20 min nap opportunity, subjects were allowed to sleep for 15 min. If sleep was not manifested, the nap was terminated. Subjects were monitored to assure wakefulness throughout the day. Serum cortisol levels were evaluated at 8:00 hrs to document HPA axis suppression following the administration of dexamethasone. All subjects receiving Dex 4 showed suppression of the HPA axis.

Results: The data were submitted to a two-factor repeated measures ANOVA to characterize the effects of Dex on the MSLT. The results showed a significant main effect of drug on the MSLT. Overall, a significantly longer (p<.05) latency to sleep for those subjects receiving Dex 4 was documented when compared to the placebo group (8.6+3.1 vs. 4.9+2.8 min). There was also a main effect of nap (p<.01). Increasing levels of sleepiness through the night were apparent from 23:00 through 7:30 hrs (11.9 +6.1 vs. 1.85 +2.4 min, p<.00) with relatively improved alertness on the 9:30, 11:30, and 13:30 naps (4.8 +5.6, 7.0 +7.0, and 5.7 +6.7 min respectively). A definite improvement was observed on the naps at 17:30 and 19:30 hrs (11.5 +7.0 and 13.4 +7.33 min). Most interesting, a significant drug by nap interaction was documented (p<.01). The latencies to sleep for both groups were comparable for 23:00 through 7:30 hrs (p>.10). However, they differed for naps 9:30 through 17:30 hrs (p<.01) with those subjects receiving dexamethasone having longer latencies on each of those naps. Relevant to these findings is the lack of a comparable effect on the amount slept or the sleep content of the nap opportunities.

Table 1

ALERTING EFFECT OF 4 MG OF DEXAMETHASONE ON A SLEEP DEPRIVED POPULATION

Nap	23:00	1:00	3:00	4:30	5:30	7:30
Placebo	9.3 +6.6	10.8 +7.6	5.3 +3.6	3.8 +3.4	2.2 +1.0	1.1 +1.0
Dex	14.2 +4.8	6.3 +7.8	6.0 +5.2	4.1 +4.4	2.8 +4.1	2.5 +3.0
p value	N/S	N/S	N/S	N/S	N/S	N/S
Nap	9:30	11:30	13:30	15:30	17:30	19:30
Placebo	1.3 ±.9	2.3 ±2.8	1.8 ±1.6	4.3 ±7.1	7.5 ±7.0	9.9 ±8.5
Dex	7.8 ±6.3	11.1 ±7.0	9.1 ±7.8	10.3 ±6.1	14.9 ±5.4	16.3 ±5.0
p value	<.00	<.01	<.03	<.02	<.04	N/S

Conclusions: The results of this study further characterize the altering effects of dexamethasone. Interestingly, the effects were manifested only 11 hrs after the administration of the drug and did not affect the sleep content of the naps once sleep was manifested. These results uphold the findings of our past research involving Dex and suggest that Dex is exerting alerting effects during the day in a time-locked fashion without altering the physiology of sleep.

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1743.A

A CCK-A Receptor Antagonist Inhibits Sleep Responses to Feeding in Rats

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Introduction: Several lines of evidence indicate that there is an intricate relationship between feeding and sleep (Borbely, 1977). Excessive eating induced by cafeteria diet or refeeding after starvation increases sleep. In rats, several somnogenic gastrointestinal hormones are released after eating, and they may mediate the sleep-inducing effects of food. CCK is one of the most studied sleep-inducing gastrointestinal hormones. Systemic injection of CCK elicits NREMS increases (Kapas et al. 1988) acting on CCK-A receptors (Chang and Kapas 1997). The aim of the present experiments was to investigate the role of CCK in feeding-

induced sleep by using L-364,718, a selective CCK-A receptor antagonist.

Methods: The experimental protocol included 2 baseline days followed by 4 starvation days and consecutive 2 days of refeeding. Sleep was recorded on the baseline and refeeding days. Control rats (n = 8) were treated with saline (2 ml/kg, ip) throughout the entire experimental period. The experimental group (n = 8) was injected with saline during baseline and starvation days, and a CCK-A receptor antagonist (L-364,718, 500 mg/kg, ip) on the refeeding days. All recording sessions were conducted from dark onset to dark onset. All injections were done at light onset. Food was given ad libitum during baseline and refeeding days, and water was available all the time.

Figure 1

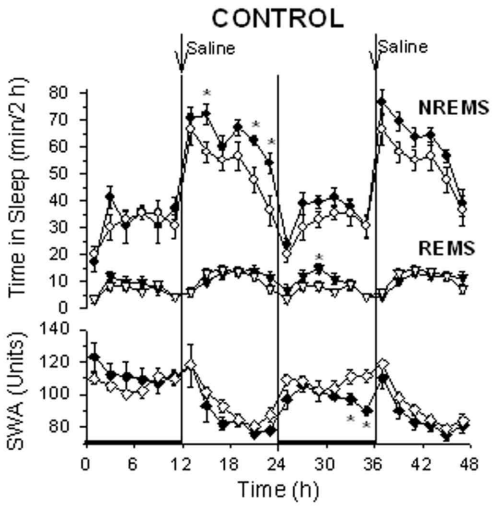
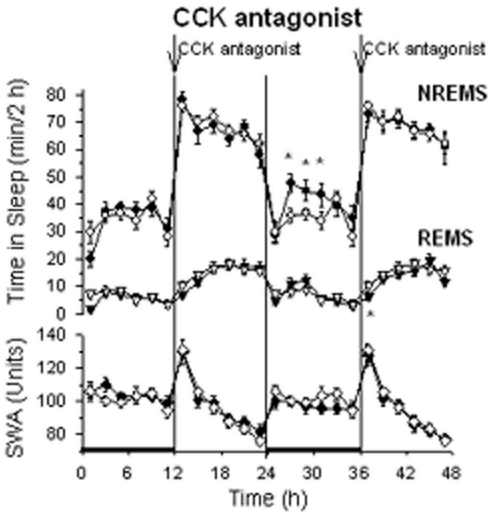


Figure 2



Results: During the light period of the first refeeding day, control rats showed statistically significant increase in the amount of time spent in NREMS as compared to baseline (ANOVA, $p < 0.05$). During the second refeeding day, increase in REMS (ANOVA, $p < 0.05$) and decrease in SWA (ANOVA, $p < 0.05$) during dark period were observed. The effects of refeeding on NREMS during the light period were completely abolished by CCK antagonist treatment. Statistically significant increase in amount of time spent in NREMS (ANOVA, $p < 0.05$) during dark phase and a decrease in NREMS (ANOVA, $p < 0.05$) during light phase on the second refeeding day were observed in CCK antagonist treated rats. Figure Legend: The effect of refeeding on the sleep of control and CCK antagonist-treated rats. Open symbols: Baseline day. Solid symbols: refeeding days. Solid bars: Dark periods. Asterisks: $p < 0.05$. Time '0': the time of returning the food on the refeeding day.

Conclusions: The results suggest that CCK plays an important role in sleep responses to feeding. The effects of CCK are mediated, at least in part, by CCK-A receptors.

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1225.A

REM Sleep Induction in the Rat by Independent Actions of Adenosine A1 and A2a Receptors

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Introduction: Microinjection of the adenosine agonist cyclohexaladenosine (CHA) (10^{-5} M/60 nl) into the medial pontine reticular formation (mPRF) of the rat produces a long lasting increase in REM sleep (Marks and Birabil, 1998). Microinjection of the adenylyl cyclase inhibitor SQ22,536 produces similar effects on REM sleep (paper submitted), and A1 adenosine receptors are coupled to the inhibition of this enzyme. This led us to hypothesize that A1 receptors mediate adenosine effects in the brainstem. It has been shown, however, that ligands, such as VIP, which bind to receptors coupled to the activation rather than inhibition of adenylyl cyclase, also induce REM sleep when injected into rat mPRF(Bourgin et al., 1999). The REM sleep-inducing effect of VIP is blocked by atropine, a muscarinic antagonist, while the effect of CHA (10^{-5} M) is only initially affected by atropine. This indicates that at least two independent mechanisms underlie ligand induced increases in REM sleep. One mechanism may require interaction with the cholinergic system and one not. Here, we report on the dose-response relationship of adenosine agonists selective for A1 receptors that are coupled to adenylyl cyclase inhibition and A2a receptors coupled to adenylyl cyclase activation, and the sensitivity of their effects to atropine.

Methods: Under anesthesia, Long-Evans Hooded rats were surgically prepared for chronic sleep recording and additionally implanted with bilaterally symmetric guide cannulae aimed at medial sites in the caudal, oral pontine reticular formation. Injections were made unilaterally in 60 nl volumes within one hour after lights-on. At least seven days transpired between injections. The adenosine agonists used were CHA (10^{-7} -10^{-5} M), which has more than two orders of magnitude greater affinity for A1 over A2a receptors, and CGS 21680 (CGS) (10^{-8} -10^{-4} M), which has more than two orders of magnitude greater affinity for A2a over A1 receptors. Each animal received four saline vehicle injections as control. Eight-hour, electrographic recordings were conventionally scored in 15 sec. epochs as wake, slow wave or REM sleep. Each animal also received a series of three, paired-consecutive injections of atropine ($4x10^{-4}$ M) followed by the lowest effective dose of CHA, CGS or saline as control. The lowest effective dose has the highest probability of act-

ing with receptor-subtype selectivity.

Results: The A2a receptor agonist, CGS, was one order of magnitude more potent than the A1 receptor agonist, CHA, in inducing REM sleep increases. A significant difference in effect occurred at the 10^{-7} M concentration at which CGS persistently increased REM sleep and CHA was ineffective. Preinjection of atropine blocked CGS increases in REM sleep at all sites. CHA effects on REM sleep were reduced when preceded by atropine only at the sites at which atropine/saline reduced REM sleep. Thus, preinjection of atropine at a dose that does not affect REM sleep results in antagonism of CGS, but not CHA, to increase REM sleep.

Conclusions: If only one adenosine receptor-subtype were mediating the effects of agonists to increase REM sleep, the increased potency of CGS over CHA would indicate mediation by A2a receptors. The differential sensitivity of these ligands to antagonism by atropine, however, favors the conclusion that both A1 and A2a receptor subtypes subserve agonist-induced REM sleep and that they do so by independent mechanisms. The A2a-mediated effects require an interaction with the cholinergic system, whereas the A1-mediated effects do not and may act through inhibition of adenylyl cyclase. Whether activation of A2a receptors also results in adenylyl cyclase inhibition, perhaps indirectly through a presynaptic increase in release of acetylcholine, is currently being considered.

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1706.A

Basal Forebrain Unit Recordings in Response to Neurotensin Perfusion in Freely Moving Cats

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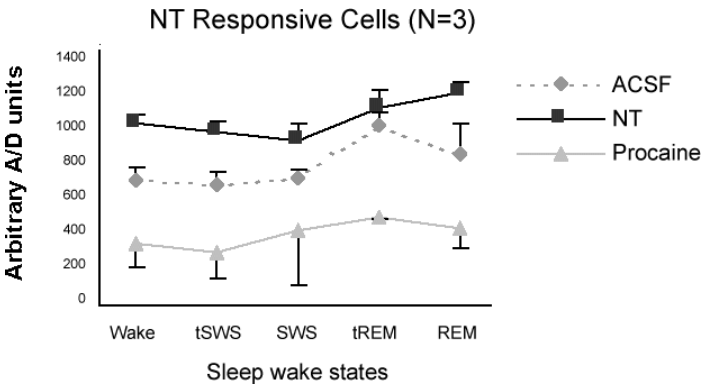
Introduction: Considerable evidence has shown that basal forebrain cholinergic neurons play a major role in the modulation of cortical activity in association with behavioral state. Cholinergic neurons are in turn modulated by multiple neurotransmitters, including neurotensin (NT). NT is especially interesting as a possible cholinergic cell identifier, since in vitro data indicate that it does not excite non-cholinergic neurons but does selectively excite cholinergic neurons, inducing a rhythmic bursting discharge.[1] Moreover, in urethane-anesthetized rats, recent preliminary data indicate that NT induced rhythmic discharge of the immunohistochemically confirmed cholinergic neurons (juxtacellular labeling + ChAT) recorded in the magnocellular preoptic area (MCPO) and substantia innominata (SI).[2] With respect to effect on state control, Cape et al.[3] found that microinjections of NT into the basal forebrain of naturally sleeping-waking rats elicits an increase in theta EEG activity in association with gamma activity and also causes a transition to REM sleep without a normal transition to slow wave sleep (SWS). Thus, these data strongly support: 1) the selective nature of the NT affect on MCPO and SI ChAT+ cells, and hence its utility in identifying cholinergic neurons; and 2) NT activation and production of rhythmic activity from these putatively cholinergic cells, which we will label as cholinergic_{NT}. The present study was designed to provide a direct test of NT activation of basal forebrain neurons behaviorally identified as wake-active in freely moving cats.

Methods: A male adult cat was anesthetized for implantation of chronic sleep recording electrodes. A mechanical microdrive with two cannulaes, one for the microwires and one for a microdialysis probe (CMA 11/probe, 0.24 mm diameter with 2 mm dialysis membrane) were targeted toward the basal forebrain with an array of guide cannulae to allow multiple descents of the probe/ microwire cannulae. After a week of recovery, recordings were begun. The microdrive was advanced in steps of 40 um, until resolvable single units (signal:noise = 2:1) were encountered. The probe was continuously perfused with artificial CSF (ACSF). Once an acceptable single unit was encountered, EEG, EGO, EMG PGO and the window discriminated single neuronal activity were recorded. The unit was recorded for 2 complete sleep-wake cycles. Once the profile of the unit was complete, marked by the onset of REM, NT (100 μM) was perfused for 30 minutes. Lastly, after approximately another 30 min, an anesthetic (10% procaine) was perfused until either modulation of the cell activity was evident, or 30 the end of minutes. The unit activity was continuously monitored to rule out artifacts. Sleep-wakefulness records of the cats were classified into the following five stages: wake, transition to SWS (tSWS), SWS, tREM and REM. FFT analysis was performed to measure voltage amplitude (square root of power) on the EEG, EMG and unit activity to subsequently examine a possible association between increased gamma (30-60 Hz) and decreased delta (1-3 Hz) amplitudes in the EEG with increased unit activity (each presented as arbitrary analog to digital (A/D) units using Stellate Systems EEG analysis software). The units thus far recorded were categorized as either increasing their total discharge rate, or not responding to NT (no cells decreased total rate of firing).

Results: Preliminary data showed that 10 cells responded to procaine, 3 of which were depolarized and activated by NT as evidenced by a mean increase in total activity of 50% (see figure) throughout the sleep wake cycle. This activation seemed to manifest in both the occurrence of tonic firing intermixed with short bouts of clusters of action potentials. These 3 units had discharge rates that were higher in wake and REM than in SWS. Regression analysis of gamma or delta EEG amplitude on unit discharge rate showed a positive slope for gamma, and a negative slope for delta (2 cells had R values > 0.70, and with $p < 0.0001$). Of the 7 cells that did not respond to NT, 3 have thus far been analyzed, of which only one showed higher discharge rates in wake and REM, similar to the units that responded to NT.

Figure 1



Conclusions: These data are consistent with previous electrophysiological in vitro and in vivo observations demonstrating NT-induced increases in discharge in ChAT BF cells. Lastly, these preliminary data are consistent with al large subgroup of Wake - REM active cells being

cholinergic$_{NT}$.

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1710.A

Increases in Inhibitory Amino Acids Release in the Hypoglossal Nucleus During Medial Medulla-Induced Muscle Tone Suppression: An in Vivo Dialysis Study

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Introduction: Reduction of muscle tone in sleep has been hypothesized to be mediated through pontomedullary activation. Chase and his colleagues have demonstrated that glycine is released onto motoneuron pools during REM sleep atonia. However, iontophoretic application of both glycine and GABA has been shown to decrease motoneuron excitability in anesthetized animals. We have found that the rostromedial medullary inhibitory system can be divided into a ventral glutamatergic region (nucleus magnocellularis; NMC) and a dorsal non-glutamatergic/non-cholinergic region (nuclei gigantocellularis; NGC and dorsal paragigantocellularis; dNPGC). Reticulospinal projections have been found originate, mainly from the NMC. Therefore, the mechanisms mediating muscle tone suppression elicited by NMC and NGC/dNPGC stimulation might utilize a different pathway. The goal of the present study was to evaluate this hypothesis using electrical stimulation and in vivo microdialysis techniques.

Methods: Experiments were performed on 4 male and 5 female decerebrate cats. Electromyograms (EMG) were recorded from occipitoscapularis, splenius and genioglossal muscles by bipolar electrodes. Three hundred msec trains with 100 Hz, 0.2 msec and 10-40 uA rectangular cathodal pulses were delivered through a stainless steel microelectrode (A-M Systems, 5710) once every 10 sec over a period of 5 min. Ten microliters of dialysate were collected from the hypoglossal nucleus during 5 minute pre-stimulation, stimulation and post-stimulation periods. The collecting polyethlene tubing was kept at 10 C and the samples stored at -80 C. Amino acid assay: The concentration of amino acid in the perfusate was detected by a HPLC (EDT-300, EICOM) with fluorescent detection (Soma S-3350; excitation/emission = 340/440 nm) and quantified with a PowerChrom (AD Instruments, Australia) using external amino acids standards (Sigma). Precolumn derivatization was performed with o-phthaldialdehyde/2-mercaptoethanol at 10 C for 3 min. The derivatives were then separated in a liquid chromatography column (MA-5ODS, EICOM) at 30 C with 30% methanol in 0.1 M phosphate buffer (pH 6.0), being degassed by an on-line degasser (DG-100, EICOM).

Results: Electrical stimulation in the NMC, NGC, and dNPGC suppressed neck and genioglossus muscle tone. However, changes in amino acid release in the hypoglossal nucleus depended on the site of stimulation. Electrical stimulation in the NMC induced a significant increases in both GABA ($p < 0.05$, df = 12, t-test) and glycine ($p < 0.05$, df = 16, t-test) release. In contrast, GABA ($p > 0.9$, df = 18, t-test) and glycine ($p > 0.8$, df = 16, t-test) release in the hypoglossal nucleus was not changed when the stimulation was applied to the NGC and dNPGC. Neither NMC nor NGC/dNPGC stimulation induced a change in glutamate release in the hypoglossal nucleus.

Conclusions: Our present found that both glycine and GABA release in the hypoglossal nucleus were increased during NMC stimulation. In contrast, release of inhibitory amino acids in the hypoglossal nucleus did not change when electrical stimulation was applied to the NGC/dNPGC area. Results from present study suggest that the dorsal and ventral medial medullary-induced muscle tone suppression might be mediated through different neuronal circuitry.

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1739.H

Auditory Evoked Potentials During Stage 2 NREM Sleep in the Elderly

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Introduction: The elderly consistently display a decrease in SWS, which is mainly due a decrease in the amplitude of delta activity.[1] Given the hypothesized relationship between the generation of delta EEG and K-complexes,[2] it is of interest to test the hypothesis that K-complex amplitude and production rate are also reduced in the elderly. The best way to determine the true K-complex amplitude is to average K-complex responses and examine the amplitude of the N550 component in the resulting evoked response.[3]

Methods: Six young and six elderly adults who were neurologically healthy and free from medication spent two non-consecutive nights in the sleep laboratory. EEG was recorded from six gold plate electrodes (Fz, Fcz, Cz, Cpz, Pz and O2) referenced to A1+A2. 1000Hz tone clicks, of varying intensity from 70 to 100 decibels above measured awake detection threshold, were presented binaurally during stage 2 sleep. Trials were classified based on whether they produced: a K-complex (KC); a vertex sharp wave (VSW); both responses (KC/VSW); or some other response, and averaged separately for each response type. Data are presented from the first three elderly subjects and the first four young controls, and are collapsed over all stimulus intensity levels.

Figure 1

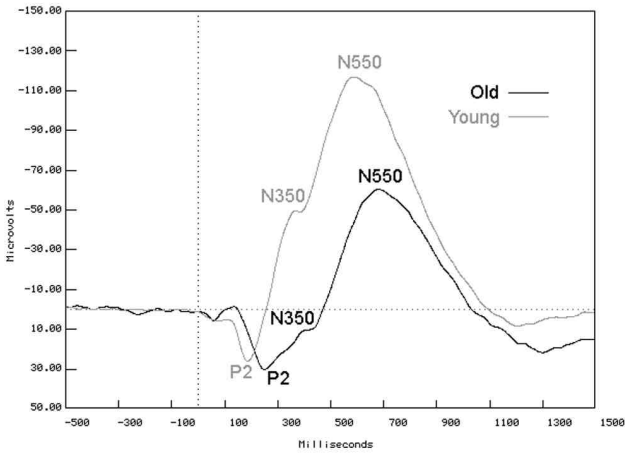

Figure 1. Grand mean waveforms at Fz for old and young subjects. Data plotted are from the averages of K-complex trials.

Results: The waveforms produced by averaging all K-complexes (KC and KC/VSW) in both groups are presented in Figure 1. The elderly show a substantial reduction in N350 and N550 amplitudes compared to the young subjects. They also show an increase in the response latency for N550. The averages of trials with no phasic response are presented in figure 2. The elderly show an augmented but delayed P2 component, followed by a long-lasting positive EEG shift. In young subjects the proportions of responses were KC 26%; KC/VSW 26%; VSW17%; leaving 31% of trials showing no phasic response. In the elderly the proportions of responses were KC 18%; KC/VSW 5%; VSW 12%; leaving 65% with no phasic response.

Figure 2

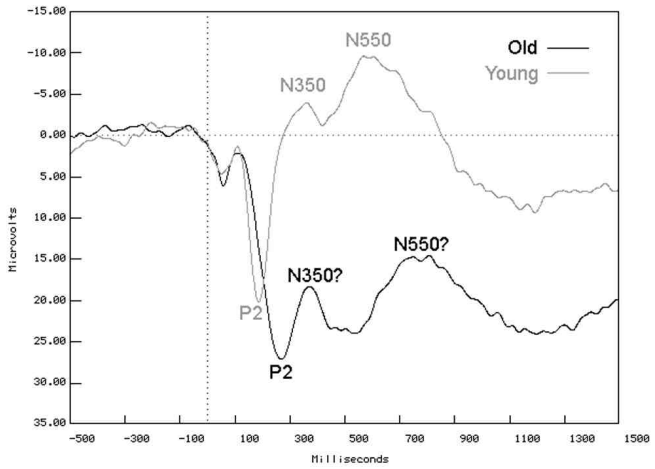

Figure 2. Grand mean waveforms at Cz for old and young subjects.
Data plotted are from the averages of trials not showing a K-complex.

Conclusions: There is a marked reduction in the amplitude and a small increase in the latency of the K-complex averaged N550 component. This is consistent with the previously reported reduced delta amplitudes and with the suggestion that K-complexes and delta activity share the same generator mechanisms. The very small N350 in the K-complex average is due to the reduced proportion of vertex sharp waves occurring prior to K-complex responses in the elderly. The enhanced P2 component and the long-lasting positive deflection in the EEG in the elderly indicate that age differences exist other than reduced EEG amplitude. The usual interpretation of a positive slow wave of this type is that it reflects inhibition of processing. Whether this explanation holds true for the present data is yet to be determined.

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1717.H

Cortisol Response to a Mild Stress Correlates with Impaired Sleep in Healthy Seniors

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Introduction: Increased stress responsivity along with a longer-lasting glucocorticoid increase is a common finding in aging studies. Increased cortisol levels at the circadian nadir also accompany aging. We used 24-hour free urine cortisol to assess these age changes in healthy seniors. We hypothesized that free cortisol levels would explain individual differences in age-related sleep impairments.

Methods: The study compared sleep, cortisol, and sleep-cortisol correlations under baseline and 'stress' conditions in men and women. Subjects were studied in a General Clinical Research Center under baseline conditions and a mildly stressful procedure (24 hours of indwelling iv catheter). Eighty-eight healthy, non-obese subjects (60 women, 28 men) from a large study of successful aging participated in the study. Mean ages were 70.6 (6.2) and 72.3 (5.7) years for women and men respectively. 24-hour urine was collected for cortisol assay (RIA) in baseline and 'stress' conditions. Sleep architecture and sleep EEG were analyzed (after an adaptation and screening night) on baseline and 'stress' nights via human-rated polysomnography and EEG power spectral analysis.

Figure 1. Scatterplot of 24-hr urine cortisol and sleep efficiency

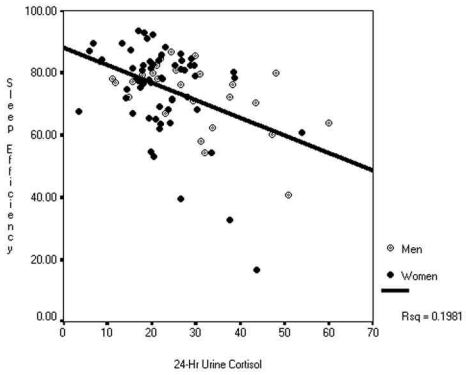
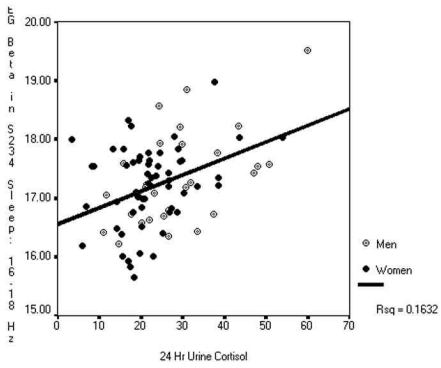


Figure 2. Scatterplot of 24-hr urinary cortisol values and EEG beta



Results: Healthy older women and men with higher levels of free cortisol (24-hour urine level) under a mild stress condition had more impaired sleep (lower sleep efficiency, fewer minutes of stages 2,3,4 sleep, and more EEG beta-activity during NREM sleep). Similar results were obtained when 'stress reactivity' measures were used (cortisol and sleep values adjusted for baseline values) but not when baseline values alone were used.

Conclusions: These results indicate that free cortisol (as indexed by 24-hour urine values) can index individual differences in stress responsivity in healthy senior adults, revealing functional correlations (decreased sleep efficiency, increased EEG beta activity during sleep). These results indicate that cortisol stress response (known to be prolonged with 'normal' aging) may contribute to sleep impairment in some seniors. Another

well established age effect, cortisol increases at the circadian nadir, may also be related to age-enhanced stress responsivity and impaired sleep, a subject for future studies.

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1703.H

Sex Hormones and Sleep in Postmenopausal Women: Estrogen / LH Balance and Sleep Quality

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Introduction: It is likely that age-related changes in many physiological systems, including the hypothalamic-pituitary-gonadal system, interact to cause sleep problems in otherwise healthy older women. Several lines of evidence indicate that the presence of high LH levels well beyond the menopausal years may impact on sleep quality. For example, hot flashes, which occur in synchrony with LH pulses, and result in thermoregulatory instability and disrupted sleep, continue to occur well into the postmenopausal years in 35% of women who experience them during menopause. In addition, the circadian peak in LH pulse amplitude is phase-advanced to the early morning hours in postmenopausal women, which corresponds to the time during which many older women complain of frequent awakenings and an inability to return to sleep. The present study was designed to further investigate whether sex hormones, including gonadotropins, are associated with objective measures of sleep disturbance in older, postmenopausal women.

Methods: Seven postmenopausal women (mean age 68 ± 20 y; range: 57 – 84 years, 17 ± 7 years since complete cessation of menses) spent three consecutive nights in the sleep laboratory. Subjects' bedtimes and waketimes on each night were based on reported habitual times. On the first adaptation night, all were screened for PLMS and apnea. The second night provided further adaptation to the lab environment. On the third night, from 2000h until the later of 0800h or habitual waketime, blood samples were collected every 20 minutes. The samples were subsequently assayed for estrogen (E2) and luteinizing hormone (LH) levels. Each hormone series was examined for significant pulses, operationally defined as an increase of 1 SD above that subject's mean E2 or LH level. All sleep recordings were scored according to standard criteria. Polysomnographic (PSG) variables were compared with E2 and LH levels, and temporal relationships between LH and E2 pulses and awakenings from sleep were examined.

Table 1

Spearman's rank-order correlations between sex hormone levels and sleep efficiency in seven older postmenopausal women. *(* p < .05)*

SUBJ	E2	LH	E2 / LH	SE (TST/SPT)
1	19.2	45.5	0.42	79.0
2	10.9	13.7	0.79	77.5
3	18.6	19.3	0.96	85.8
4	1.0	47.0	0.02	67.4
5	10.9	15.5	0.70	89.0
6	3.9	14.7	0.27	81.4
7	18.0	13.3	1.36	94.1
rho	0.46	-0.54	-0.68 *	

Results: As expected, high intersubject variability in both sleep measures and hormone levels was observed. Neither PSG nor hormone measures were associated with chronological age or years since menopause. While mean LH levels were significantly correlated with wakefulness after sleep onset (WASO; Spearman's rho = 0.75, $p < .05$), neither LH nor E2 levels alone were significantly associated with any other sleep variables. However, the ratio of mean E2 to mean LH levels for a given individual was significantly correlated with several PSG measures, including sleep efficiency (see table), number of awakenings (rho = -.82, $p < .05$) and WASO (rho = -.82, $p < .05$). The number of LH pulses detected during the 12-hr sampling period ranged from 3 to 8 (median = 4; total number of pulses = 31). LH pulse amplitudes ranged from an increase of 8% to 44% over the mean. The majority of LH pulses (25/31) occurred after initial sleep onset; of these 25, 15 occurred within 20 minutes before an awakening (the 20-min blood sampling rate limits further resolution of this temporal relationship). While 23 E2 pulses were detected, these were of generally low amplitude and were evenly distributed between the sampling periods prior to and during sleep. E2 pulses were not temporally related to either LH pulses or to awakenings from sleep.

Conclusions: In older postmenopausal women, EEG sleep measures were strongly associated with the ratio of circulating estrogen to LH levels. Moreover, a majority of LH pulses were temporally associated with awakenings from sleep. One interpretation of these preliminary findings is that estrogen may exert a protective influence against LH-induced sleep disturbance. Conversely, in the presence of low estrogen, even relatively low LH levels might result in disrupted sleep. These results are consistent with the hypothesis that altered levels of both sex steroids and gonadotropins may contribute to sleep disturbance in aging, and support the idea that alternate hormone therapies, which target LH suppression, may be useful for treating age-related sleep disturbance.

Research supported by NIH grants R03 AG14197, R01 AG15370, R01 MH45067, R01 AG12112, R01 MH54617, M01 RR00047, P20 MH45762, K02 MH01099 and a Reader's Digest Research Fellowship.

1678.H

Sleep Maintenance Insomnia - How Effective is Intermittent Bright Light Treatment at Home?

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Introduction: Previous findings[1] demonstrated that, in elderly with sleep maintenance insomnia (SMI), exposure to bright light (BL) for 12 consecutive days significantly delayed their temperature minimum (Tmin) and increased sleep efficiency (SE). However, the daily, 2-hour treatment regimen used in that study was time-consuming and sometimes inconvenient. The following study examined the efficacy of a maintenance schedule whereby treatment was reduced to twice-weekly exposure after a more acceptable phase relationship between core body temperature (CBT) and sleep had been established.

Methods: Fifteen older subjects (7f, 8m; aged 63-84 years, mean 71.5) with chronic (>1yr) complaints of SMI and exhibiting a Tmin earlier than 04:00 hours were studied. Following baseline sleep and circadian rhythm assessment, all participants were treated with timed exposure to BL (2100-2300h: >4000lux) for 9-11 consecutive days in their homes, in order to delay Tmin. Immediately following this acute home treatment, sleep and CBT were again recorded in the lab. Measures of sleep quality (SQ) were compared with baseline values to assess acute treatment efficacy. For the next 3 months, subjects were instructed to use the lights twice weekly while otherwise going about their normal daily activities. The active group received BL from 2100-2300h, the control group from 1500-1700h. At the end of each month, subjects returned to the lab for a

3-day session of sleep and temperature recording. Throughout the entire study, subjects completed a daily questionnaire to assess subjective SQ and treatment compliance.

Results: Results of the acute treatment are based on 15 subjects. Eleven of those subjects (8 active, 3 control) completed the entire 3-month maintenance protocol.

Acute: The average Tmin at baseline was 02:59 hours (±59 min). BL exposure during the acute treatment resulted in a significant phase delay of Tmin ($p<0.001$) of 93.9 min (±81.1). This was accompanied by a significant delay ($p<0.05$) of sleep onset and wake time after the acute treatment by 44 min (23:09→23:53) and 32 min (6:32→7:04), respectively. However, no changes in objective sleep measures were observed. The average SE at baseline was 74.06% (range: 57-87%) and remained at 74.89% after treatment. There were also no changes in sleep latency, number of awakenings, or percentage of sleep stages. At baseline, the average Tmin occurred 18.5 min after the midpoint of sleep, whereas the minimum occurred 77 min following mid-sleep after the acute treatment. Thus, the phase angle between temperature and sleep showed a delay of almost 1 hr ($p<0.02$).

Maintenance: A two-way ANOVA (Condition x Time) across the maintenance phase revealed no significant effect of temperature. That is, both active and control subjects maintained their phase delay to the same extent. End-point analysis of subjective sleep measures assessed during the maintenance phase showed an significant improvement in self-rated SQ in the active group ($p<0.03$), while no change was reported in the control group.

Conclusions: Night time bright light exposure on 9-11 consecutive days resulted in the expected delay of Tmin. This phase delay was not associated with a statistically significant increase in SE, however. A reason for the lack of improvement in objective sleep quality may be that the phase shift, although statistically significant, was not large enough to obtain the necessary optimal phase angle between sleep and temperature. Alternatively, the SMI experienced by these subjects may have other-than-circadian etiology. After 3 months of treatment the active group reported a significant improvement in subjective SQ. Further analyses of maintenance polysomnographic sleep data are underway to clarify whether long-term administration of appropriately timed BL led to an increase in objective SQ, as well. In addition, whether compliance to the maintenance treatment regimen was associated with changes in SQ is being examined.

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Research supported by P20 MH45762, R01 MH45067, R01 MH54617, R03 AG14197, R01 AG15370, K02 MH01099, R41 AG15246 and Swiss National Science Foundation Fellowship to AS

1051.H

Inducing Jet-lag in Older People: Directional Asymmetry

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Introduction: While most studies of jet-lag have been of healthy young adults, the question of how elderly people cope with such phase shifts is also important. First, the study of the response of the aging Circadian Timekeeping System (CTS) to challenges such a phase shift may give useful insights into how the entrainment processes of the CTS might function under normal everyday situations. Second, increasing numbers of seniors are engaged in shift work as older people find that they need to return to work in order to supplement their income. In young adults there is a directional asymmetry in phase shift tolerance, favoring the delay direction. The present study sought to test the hypothesis that, because of changes in the CTS associated with aging (e.g. to favoring earlier bedtimes and wake times), the directional asymmetry for older people might favour the phase advance direction.

Methods: Twenty healthy elderly subjects (12f, 8m, mean age 81y, range 67y - 87y) each experienced a 15 day time isolation protocol in which they lived individually in a special laboratory apartment in which sleep and circadian rhythm measures could be taken. There were two experiments, one (6f, 4m) involved a 6h phase advance of the sleep-wake cycle, the other (6f, 4m) a 6h phase delay. Each started with five baseline days, immediately followed by the phase shift. The subject was then held to the phase shifted routine for the remainder of the study. Rectal temperatures were recorded minute-by-minute throughout the entire experiment and each night of sleep was recorded using polysomnography. Mood and performance were also assessed. Statistical significance was tested by analyses of variance.

Results: A directional asymmetry in phase shift effects was apparent, with significantly more sleep disruption (see below) and circadian rhythm amplitude disruption ($p<0.002$) after the phase advance than after the phase delay. Sleep disruption was reflected in reduced time spent asleep ($p<0.05$), and in changed REM latency ($p<0.025$), which increased in the phase advance direction, but decreased in the phase delay direction. Although the phase advance led to a significant increase in wakefulness in the first half of the night ($p<0.005$), the phase delay did not lead to an equivalent increase in wakefulness during the second half of the night ($p>0.25$). Examination of both raw and "demasked" circadian rectal temperature rhythms confirmed that phase adjustment was slow in both directions, but was relatively faster (and more monotonic) after the phase delay than after the phase advance, particularly in the raw data ($p<0.005$).

Conclusions: The practical implications of this work are that, for older people, phase delays are more likely to be better tolerated than phase advances, and that daily routine, sleep/wake schedule, and work schedule choices that lead to phase delays are to be preferred over ones that lead to phase advances. Thus, old and young are similar in the directional asymmetry they exhibit following a phase shift, despite age-related differences in the timing of the CTS.

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1272.H

Recuperating During the Day: Effects of 25 Hours Sleep Deprivation on Sleep in the Middle Years of Life

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Introduction: Our understanding of the mechanisms by which sleep deteriorates during the aging process has been provided almost exclusively by comparisons between young and elderly subjects. We have recently shown important changes between 20 and 60 years of age on sleep and sleep EEG spectral power.[1] It has been suggested that the sleep of elderly subjects might be particularly vulnerable to a circadian phase misalignment. The aim of the present study was to investigate, in young and middle-aged subjects, differences in the effects of a 25-hour sleep

deprivation on recovery sleep initiated in the morning, a time during which circadian sleep propensity is decreasing.

Methods: Thirteen subjects were studied. They were separated in two groups according to their age: Young: (20-39 years, 3 women, 5 men) and Middle-aged (40-59 years, 2 women, 3 men). All subjects came to the sleep laboratory for consecutive 4 nights and 2 days. Baseline sleep was recorded on the third night. The morning following the baseline night, subjects entered a mini-constant routine during which they were kept awake in bed for the next 25 hours. The sleep recuperative episode started in the morning following the 25 hours of sleep deprivation. Two-way ANOVAs with repeated measures (Group X Sleep episode) were used to compare the effects of the sleep deprivation between the two groups.

Results: Compared to the young subjects, middle-aged subjects showed a steeper increase of the number of minutes of wakefulness during daytime recovery sleep (interaction: p=0.0016; fig. 1). Analyses per third of the sleep episode revealed that this steeper increase of wakefulness in the middle-aged was significant only for the last third of recovery sleep (p=0.004). Slow-wave sleep (SWS) duration was significantly enhanced in both groups during daytime recovery sleep (p<0.001), but no significant interaction was found (Fig.2). During daytime recuperative sleep, both groups of subjects showed, compared to baseline sleep, a reduced sleep latency and a decrease in the number of minutes of stages 1, 2 and REM (no interaction; Sleep episode effect: p<0.02, all cases).

Figure 1

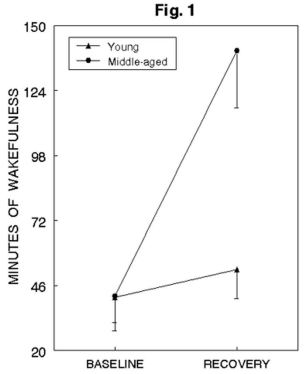
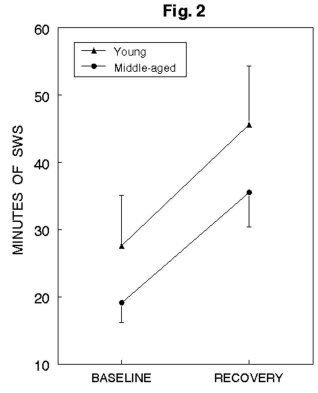


Figure 2



Conclusions: Compared to young subjects, sleep consolidation of middle-aged subjects is dramatically perturbed if sleep is initiated in the morning, despite 25 hours of sleep deprivation. The paralleled increase in SWS duration following the sleep deprivation in both groups corroborates the observation that older subjects can still respond to sleep deprivation with SWS rebound. Interestingly, the steeper increase of wakefulness in the middle-aged subjects during daytime recovery was more prominent at the end of the sleep episode when sleep homeostatic drive was reduced. These results suggest that people in their forties and fifties already show a higher vulnerability to an abnormal phase angle between sleep and the circadian signal, even in a situation of increased sleep homeostatic pressure at sleep onset. These results may help to understand the increase in subjective complaints related to shift-work and jet-lag in the middle years of life.

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1575.H

Effects of Morning or Evening Social and Physical Activity on Sleep and Performance in the Elderly

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Introduction: In the elderly, reduced exposure to social and physical activity may contribute to the age-related changes in circadian rhythmicity and sleep. We previously showed that increased levels of social and physical activity in the morning and evening can improve sleep and daytime neuropsychological performance in healthy older adults.[1] We conducted a study to determine whether timing of the intervention is critical to its effects.

Methods: Twelve elderly subjects (4 male and 8 female), with a mean age of 73.9 (range 67-82) recruited from retirement facilities were studied before, during and after a 14-day period of intervention with structured social and physical activity. Subjects participated in morning (0900-1030) or evening (1900-2030) sessions consisting of stretching, low impact aerobics, and game playing. The study design was a cross-over, with a month interval between treatments. Rest-activity was monitored by sleep logs and activity monitors during the 7-day baseline period and throughout the 14 days of intervention. During the last two days of the baseline period and during the last two days after the completion of the activity intervention, subjective mood, neuropsychological performance, polysomnographic sleep and salivary melatonin/cortisol levels were measured. Treatment effects were assessed by comparing the averages of the two baseline days and of the two post-treatment days for the entire 12 hour testing period as well as at all nine individual time points. To evaluate overall treatment effect for the performance tests, ANOVA with the Bonferroni method was employed.

Results: Exposure to either morning or evening social and physical activity significantly improved several parameters of neuropsychological performance. Morning social/physical activity sessions resulted in significant improvement in the throughput (accuracy/reaction time*100) for 4 of the 8 performance tasks. Improved performance was observed in mathematical processing (p=0.018), digit symbol substitution (p=0.023), visual search task (p=0.004) and M before C test (p=0.042). Evening social/physical activity sessions improved performance for 7 of the 8 performance tasks: Sternberg 4 memory task (p=0.035), mathematical processing (p=0.028), running memory (p=0.006), symbol copy (p=0.014) digit symbol (p=0.001), visual search task (p=0.004) and M

before C (p=0.016). There was no significant effect of evening activity on subjective measures of vigor or mood. Analysis of the hormonal and polysomnographic data is in progress.

Table 1. Effects of Morning and Evening Activity on Neuropsychological Performance Measures

Performance Task	AM Activity	PM Activity
Sternberg 4	0.052	0.035*
Mathematical Processing	0.018*	0.028*
Running Memory	0.053	0.006*
Spatial	0.659	0.481
Symbol Copy	0.294	0.014*
Digit Symbol	0.023*	0.001*
E Search	0.004*	0.004*
M before C	0.042*	0.016*

* p < 0.05, Baseline vs. Post-treatment

Conclusions: These results demonstrate that exposure to either morning or evening social and physical activity improves measures of neuropsychological performance in the elderly. Therefore, the ability of increased social and physical activity to improve daytime performance is not solely dependent on the timing of the intervention. However, improvement in more measures of performance was seen following exposure to the evening intervention. Taken together, these results suggest that increasing the total amount of activity, particularly in the early evening, may be a useful intervention to improve sleep and daytime function in older adults.

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1836.H

Self-Reported Ontogeny of Sleep

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Introduction: There exists a substantial amount of polysomnographic data on normal and disturbed patterns of sleep and a large amount of self-report data on disturbed sleep, but very little data on self-reported normal sleep. Dozens of epidemiological studies assessing sleep usually ask respondents to confirm or deny the presence of insomnia, but collect little additional data on sleep pattern. The present study randomly sampled a metropolitan community and collected 2-weeks of sleep diaries to study normal sleep patterns.

Methods: We used random-digit dialing to solicit participation from at least 50 men and 50 women in each decade from age 20 to 80 and older. Volunteers were paid between $15 and $175 (it was more difficult to recruit older adults and they were paid more) for completing 14 sleep diaries and seven questionnaires evaluating associated daytime functioning, such as fatigue and sleepiness. This paper will focus on the sleep diaries.

Results: We have collected data from 727 people, and we will have nearly 800 subjects by the meeting. At present, we have completed analyzing the data of 522 people, and their results follow. The sample is composed of 243 men and 279 women, ranging from 21 to 98 years of age. The racial breakdown is 70.0% White, 26.8% Black, and 3.2% Asian and Hispanic. We will report analyses on seven sleep measures: SOL, # awakenings, WASO, TST, SE, sleep quality rating, and naps. ANOVA, MANOVA, and multiple regression analyses will contrast age groups by decade, gender, and race. Below is a sampling of the typical results we will report. Significant age group differences were found for all variables except sleep quality rating. For example, there was a significant negatively sloped linear trend for SE peaking in the age 20 decade (88.9%, $_{SD}$ = 6.1) and bottoming in the age 80 decade (80.8%, $_{SD}$ = 11.4), \\unerF\\/under(6,515) = 4.81, $_{p}$ <.001, and there was a significant quadratic trend for TST peaking in the age 20 (437.8 min., $_{SD}$ = 69.6) and age 80 (435.3 min., $_{SD}$ = 97.1) decades and bottoming in the age 50 decade (401.7 min., $_{SD}$ = 57.2), $_{F}$(6,515) = 3.36, $_{p}$ <.01. Within each of the seven decades, we performed a MANOVA comparing men and women on the set of seven sleep variables. All seven MANOVAs were nonsignificant. To gain more power, we collapsed age groups and compared all men and women, and this analysis proved significant, Wilks' A =.97, $_{F}$(7,514) = 2.29, $_{p}$ <.05. Univariate tests showed that women had poorer sleep that was statistically significant, but of small magnitude on SOL (men = 19.9 min., $_{SD}$ = 14.6; women = 25.3 min., $_{SD}$ = 20.3) and SE (men = 87.3%, $_{SD}$ = 8.4; women = 85.3%, $_{SD}$ = 10.1). We performed the same series of analyses comparing Whites and Blacks. However, the current data set had an insufficient number of Blacks in the 50 through 80 decades, limiting the age group analyses to the first three decades. The MANOVAs were significant in all three decades, and all univariate tests showed blacks slept worse than whites. Returning to our entire sample, the overall MANOVA was significant, Wilks'A =.89, $_{F}$(7,498) = 8.87, $_{p}$ < .001. Univariate tests showed no significant difference on sleep quality rating. For awakenings during the night, Blacks ($_{M}$ = 1.38, $_{SD}$ = 1.1) were significantly lower than Whites ($_{M}$ = 1.60, $_{SD}$ = 1.1). Blacks slept significantly worse than Whites on all of the remaining five variables, as shown below.

Table 1

	Black		White	
Variable	M	SD	M	SD
SOL (min.)	28.2	19.0	20.9	17.6
WASO (min.)	30.1	39.1	22.5	22.0
TST (min.)	401.7	77.6	420.0	61.6
SE (%)	82.9	12.3	87.3	7.8
Naps (min.)	25.3	25.9	14.6	22.4

Conclusions: Based upon people's perceptions, these preliminary results find that (1) sleep changes across the life span, but change is not necessarily linear nor consistently declining; (2) the sleep of men and women differ little; and (3) Blacks in the young adult and middle-aged range sleep worse than Whites.

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1552.K5

Spect Imaging of Pre- and Postsynaptic Dopaminergic Functions in Patients with Restless Legs Syndrome

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Introduction: The restless legs syndrome (RLS) is a sleep-related disorder characterized by leg paresthesia and motor restlessness. A large

number of patients with RLS also show periodic leg movements during wakefulness and during sleep (PLMS). Pharmacological evidence suggests that RLS and PLMS may be caused by a central nervous system dopaminergic (DA) dysfunction. The aim of the present study was to evaluate both the pre- and postsynaptic DA striatal status in patients with RLS and PLMS and in control subjects.

Methods: Ten drug-naive patients diagnosed with primary RLS (45.0 ± 8.7 years) and ten age- and sex-matched healthy control subjects (45.9 ± 7.5 years) participated in this study. The diagnosis of RLS was based on the presence of the four mandatory criteria.(Walters et al.,1995) In addition, all the patients showed a PLMS index greater than 10 and none of the controls showed a PLMS index greater than 10. One night of polysomnography was recorded for all the participants. Sleep and PLMS were scored in the standard fashion. Pre- and the postsynaptic dopaminergic striatal functions were assessed with [123I]β-CIT and [123I]IBZM single photon emission computed tomography (SPECT), respectively. SPECT studies were performed on two consecutive weeks after the polysomnographic recording, using a dual-detector system (ADAC Vertex), with 64 projections of 40 seconds each over 360°, on 64X64 matrices. Complete description of SPECT methods are reported elsewere.(Lobezzo et al., 1996)

Results: No between-group differences was seen for any of the polysomnographic variables, except for the PLMS index, which was higher in the patients and sleep efficiency, which was higher in the controls. A significant decrease of the [123I]IBZM binding was seen in the patients compared to the controls (1.74 ± 0.12 vs. 1.87 ± 0.10; $p<0.006$). Moreover, 9 of the 10 patients showed a mean striatal D2-receptor binding below the control group mean. On the other hand, the study of the DA transporter ([123I]β-CIT) binding revealed no difference between patients and controls (4.88 ± 0.56 vs. 4.88 ± 0.42). There was no between-group difference for degree of striatal asymmetry of [123I]IBZM binding and [123I]β-CIT. No relationship was seen between any of the polysomnographic variables and the [123I]IBZM or the [123I]β-CIT binding.

Conclusions: The results of the present study support the hypothesis that a central DA dysfunction is involved in the physiopathology of RLS and PLMS. Several mechanisms may be responsible for the decrease of the D2-receptor binding; however, since [123I]β-CIT binding is normal, a decreased number or affinity of D2-receptors is more likely than an increased level of synaptic DA with attendant down-regulation of D2-receptors

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1192.K5

Iodine-123-IPT SPECT Imaging In Idiopathic Restless Legs Syndrome: Preliminary Findings

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Introduction: Based on PET and 123I-IBZM SPECT studies, a deficiency of the striatal D2-subtype dopamine receptor in patients with restless legs syndrome (RLS) and periodic limb movement disorder (PLMD) is assumed. The suggestion of an involvement of the dopaminergic system in both disorders is supported by the response to dopaminergic treatment and the ability of dopamine receptor blocking agents to aggravate RLS. The purpose of this study was to investigate striatal dopamine transporter function in idiopathic RLS patients using 123I labeled (N-(3-iodopropene-2-yl)-2beta-carbomethoxy-3beta-(4-chlorophenyl) tropane (IPT), a cocain analog with a high affinity for the dopamine transporter, and SPECT.

Methods: 27 patients with idiopathic RLS according to the criteria of the International RLS study group (mean age 62 years, mean duration of RLS 17.8 years) were investigated. 14 patients were drug-naive, 13 patients were pretreated with L-dopa which was stopped 2 days before the scanning. To confirm the diagnosis and to exclude other specific sleep disorders, two nights of polysomnographic (PSG) recording including the evaluation of periodic leg movements during sleep (PLMS) were performed in all RLS patients. To assess specific tracer uptake in the striatum (S), the region of interest (ROI) technique was used. Mean specific activity in basal ganglia regions was calculated by subtracting the mean counts per pixel in the background (BG) from the mean counts per pixel in the striatal region and dividing the result by the mean counts per pixel in the BG (S-BG/BG). The results were compared with 9 age-matched controls (mean age 63 years) and 14 patients (mean age 45 years) with unilateral Parkinson's disease (PD, Hoehn & Yahr stage I).

Results: RLS patients showed mildly, but significantly reduced mean striatal IPT-binding compared with controls (S-BG/BG ratio of RLS patients: right side (rs): 3.9 ± 0.5, left side (ls) 3.9 ± 0.4; controls: rs 4.5±0.5, ls 4.4±0.6; $p< 0.05$). There was no significant difference between binding-ratios in drug-naive versus L-dopa pretreated RLS-patients. RLS and PD patients clearly differed in IPT binding (PD: ipsilateral side 3.2±0.4, contralateral (= affected) side 2.5±0.3 side, $p<0.05$). PSG revealed a PLMS-index greater than 5/hour in all RLS patients. No significant correlation between striatal IPT binding and either the PLMS-index (r=0.23, n.s.) or sleep efficiency (r=0.33, n.s.) was found.

Conclusions: The results of the study suggest a subtle, but significant reduction of dopamine transporter binding in some patients with idiopathic RLS compared to age-matched controls. IPT binding in RLS patients was significantly less affected compared to the affected side in early PD patients. In contrary to the PD patients, there was no side-to-side asymmetry in IPT binding in RLS patients. However, our findings are preliminary because the controls were only partly screened in the sleep laboratory for PLMD or other specific sleep disorders.

1431.K5

Magnetic Resonance Imaging Shows Reduced Brain Iron Concentrations for Patients with the Restless Legs Syndrome

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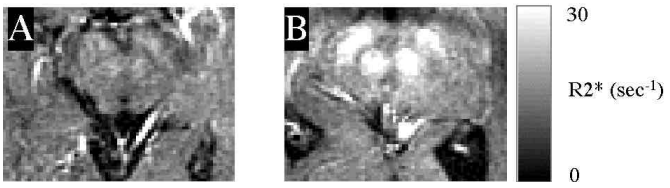
Introduction: In a recent study of a consecutive series of Restless Legs Syndrome (RLS) patients all had reduced CSF ferritin and elevated CSF transferrin. This finding indicates possible reduction in brain iron. Iron treatment has been found to reduce RLS symptoms in some patients. Moreover, iron is essential for the production of dopamine and brain imaging studies of the dopamine system in RLS patients have generally found mild abnormalities involving the nigral-striatum system and particularly the putamen. This has led to the hypothesis that low brain iron causes the dopamine abnormalities seen in RLS patients. A direct assessment of regional brain iron concentrations in these areas with dopamine abnormalities would test the hypothesized iron deficit model of RLS. Fortunately a new method has been developed for magnetic resonance imaging (MRI) that provides a measure, R2', that is fairly specific to relative brain iron concentrations and permits accurate comparisons between subjects.

Methods: The first five consenting primary RLS patients and five age-matched controls were studied with MRI following a protocol approved by the Johns Hopkins Institutional Review Board. The groups were well matched for age (average ± s.d.: RLS = 66.2 ±10.5, Normal Controls = 66.4 ±16.8.). All subjects were rated prior to starting the study on the nominal Johns Hopkins Restless Legs Severity Scale (JHRLSS) which assigns a value of zero to those subjects without RLS. Regional iron concentrations were determined from the MRI scans by two independent professionals who were blind to the patient's diagnosis. Inter-reader correlation exceeded 0.98. Data were analyzed based on directional hypotheses using the Spearman rank-order correlation between R2' and the JHRLSS and the t-test for comparing RLS subjects to controls. The substantia nigra, caudate and putamen were evaluated

Results: Figure 1 gives an example of the MRI image used for identification of areas showing the clear visualization of the red nucleus and substantia nigra despite the marked differences between a 70 year old patient with severe RLS and a 71 year old control. The Spearman correlations between R2' and RLS severity were significant for both the putamen (Rho= -0.64, p=0.028) and the substantia nigra (Rho=—0.69, p=0.02). The lower values of R2' for RLS patients compared to controls was marginally significant for the putamen (p=0.06) and significant for the Substantia Nigra (p=0.03) There were no significant results for the caudate. The putamen showed the expected high iron concentrations with age but the RLS patients showed the opposite.

Figure 1. A 70 yr old RLS patient, B: 71 yr old control



Conclusions: These results demonstrate that MRI can be used to assess regional brain iron concentrations in RLS patients. More subjects and more brain areas need to be evaluated to confirm these findings, but the results match those expected from other imaging studies and are consistent with the hypothesis of brain iron deficiency causing the dopamine abnormalities in RLS patients.

1339.K5

Impairment of Cortical Inhibition in Restless Legs Syndrome - Shortening of Silent Period Induced by Transcranial Magnetic Stimulation

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Introduction: To investigate inhibitory circuits in the motor system of patients with idiopathic restless legs syndrome (RLS) by transcranial magnetic stimulation (TMS). It has been suggested that RLS symptoms are due to enhanced excitability of spinal cord mechanisms, facilitated by the loss of supraspinal inhibition.[1] Silent period (SP) induced by TMS is supposed to result for the most part from intracortical inhibition which is mediated by inhibitory interneurons activated via recurrent collaterals from pyramidal cell axons and/or nerve fibers afferent to the motor cortex.[2]

Methods: Fifteen patients with idiopathic RLS according to the criteria of the International RLS Study Group and 15 age and sex matched controls being free of psychoactive drugs were investigated. Diagnosis was ascertained by polysomnography. Most patients were rated to be markedly or severely ill by Clinical Global Impression Scale and experienced daytime symptoms in 60%. TMS studies were performed in the morning and in the evening, recording parameters both in leg and arm muscles. The duration of the SP in the tibialis anterior muscle (TA) in the evening was considered as primary endpoint.

Results: The duration of the SP in TA was significantly shorter in RLS patients (90 ± 17.7 ms) compared to controls (126 ± 45.1 ms) when measured in the evening (p = 0.013). There was also a tendency of SP in TA to be shortened in the morning (95.2 ± 22.5 ms vs. 131.7 ± 66.0 ms, p = 0.080). SP in the abductor digiti minimi muscle (ADM) was not significantly different between RLS patients and controls in the evening (122.7 ± 32.5 ms vs. 136.5 ± 56.1 ms, p = 0.751) and the morning (118.7 ± 32.4 ms vs. 138.9 ± 52.2 ms, p= 0.383). Active motor thresholds in TA were significantly higher in the evening (p = 0.013) and in the morning (p = 0.015) but not in ADM. Inhibitory thresholds and central motor conduction time did not significantly differ between patients and controls.

Conclusions: Cortical inhibition is impaired in patients with severe RLS specially in the evening. Significant shortening of SP in leg muscles with a much less altered SP in arm muscles may result from an increased excitatory possibly sensory input to the motor cortex.

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1355.K5

Prolongation of Shortened Cortical Silent Period After Transcranial Magnetic Stimulation in Patients with Idiopathic Restless Legs Syndrome by Levodopa

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Introduction: To investigate the influence of levodopa on the shortened

silent period after transcranial magnetic stimulation (TMS) in patients with idiopathic restless legs syndrome (RLS). The cortical silent period - as indicator of the motor system excitability - is shortened in leg muscles of RLS patients.[1] Dopaminergic substances such as levodopa and dopamine agonists are the preferred agents in the treatment of RLS.[2] However, the therapeutic mechanism is unclear.

Methods: TMS studies were performed in fourteen patients with severe idiopathic RLS (mean age 56.6 ± 8.3 years, range 45 - 72) receiving no psychoactive drugs and were repeated after administration of a single evening dose of 200/50 mg levodopa/benserazide. Parameters were recorded at 8 p.m. in the evening and 8 a.m. in the morning, both in leg and arm muscles. The change of the SP duration in the tibialis anterior muscle (TA) in the evening was considered as primary endpoint.

Results: After levodopa administration the duration of the SP in TA was significantly longer (107.57 ± 23.85 ms) compared to baseline (92.71 ± 16.89 ms) when measured in the evening (p = 0.002; exact Wilcoxon signed rank test). There was no significant difference of SP in TA in the morning when levodopa was administered the preceding evening (103.0 ± 21.28ms vs. 97.71 ± 21.07 ms, p = 0.599). SP in the abductor digiti minimi muscle (ADM) was not significantly different between levodopa and baseline in the evening (132.64 ± 42.59 ms vs. 124.0 ± 33,29 ms, p = 0.391) and the morning (124.57 ± 37.7 ms vs. 118.86 ± 33.57 ms, p= 0.418). Levodopa also produced no significant changes in active motor thresholds, inhibitory thresholds and central motor conduction time.

Conclusions: Levodopa prolongs an abnormally short cortical silent period in the tibialis anterior muscle in patients with RLS. Whether this is a specific effect of levodopa on inhibitory and/or excitatory mechanisms at the spinal level, the basal ganglia or directly at the cortical level remains to be investigated.

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1559.K5

Heart Rate Variability During Wakefulness and Sleep in Restless Legs Syndrome

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Introduction: A recent study shows an increased heart rate (and increased low frequency power in the spectral analysis) in all stages of sleep in psychophysiological insomniacs compared to controls.[1] In another study we found in healthy subjects an initial increase of parasympathetic activity (high frequency component in spectral analysis) in the awake period immediately preceding sleep.[2] Aim of the present study was to investigate the autonomic cardiovascular function before and during sleep in patients with restless legs syndrome (RLS) compared to age-matched controls.

Methods: Ten never-treated RLS patients (8 females and 2 males; mean age=54 yrs) and 10 controls (7 females and 3 males; mean age=55 yrs) were included in the study. All patients fulfilled the clinical criteria mandatory for the diagnosis of RLS (Walters AS, Mov Disord 1995). All subjects underwent a full night polysomnography including monitoring of respiration and periodic legs movements (PLM). Heart rate variation were measured by power spectrum analysis (sleep periods with PLM were excluded from the analysis). The time intervals analysed were chosen from: 1) awake state from 30 to 15 min. before sleep onset (W1); 2) awake state from 15 min. before sleep onset to sleep onset (W2); 3) stage 2 NREM; 4) slow wave sleep; 5) REM sleep. We focused on the two regions of interest in the spectrum: low frequency (LF) component (index of sympathetic activity) and high frequency (HF) component (index of parasympathetic activity). We analyzed the normalized spectral powers (ratio between the power of each spectral component and the total spectral power minus the power in the band 0-0.05 Hz). We applied ANOVA (non-parametric Friedman test) to determine the changes within each group in the different conditions. Differences between the two study groups were evaluated by the Mann-Whitney test.

Results: The results are summarized in the tables below. The study revealed a decreased power in LF during sleep compared with wakefulness, with minimal values during stage 3-4 NREM sleep, both in RLS patients and controls. A significantly increased power in HF and a significant decrease in LF/HF ratio during slow wave sleep, but not during stage 2 NREM, in comparison to wakefulness ($p < .01$) and REM sleep ($p < .01$) were found in RLS patients. LF/HF ratio was significantly higher in patients than in controls during wakefulness immediately before the sleep onset ($p < .02$), during stage 2 NREM ($p < .01$) and during slow wave sleep ($p < .01$).

Table 1

	RLS Pts		
	LF	HF	LF/HF
W1	58.2 (7.0)	41.8 (7.0)	2.01 (0.2)
W2	53.3 (9.4)	46.7 (9.4)	1.98 (0.4)
St. 2 NREM	46.7 (7.3)	53.3 (7.3)	1.26 (0.6)
St. 3-4 NREM	33.8 (8.6)	66.2 (8.6)	0.74 (0.3)
REM sleep	56.2 (11.9)	43.8 (11.9)	2.03 (1.1)

	Controls		
	LF	HF	LF/HF
W1	64.3 (10.1)	35.7 (10.1)	1.73 (1.0)
W2	58.9 (9.2)	41.1 (9.2)	1.47 (0.4)
St. 2 NREM	39.8 (7.6)	60.2 (7.6)	0.85 (0.3)
St. 3-4 NREM	28.5 (9.3)	71.5 (9.3)	0.45 (0.2)
REM sleep	54.5 (10.6)	45.5 (10.6)	1.43 (1.2)

Conclusions: Our study shows that a significantly higher sympathetic activity may be observed in RLS patients compared to controls in the awake state immediately before the sleep onset. An increased sympathetic activity has been observed in RLS patients also during NREM sleep stages. A previous study in RLS patients[3] showed cardiac acceleration in relation to PLM, with and without EEG signs of microarousals. Our data on spectral analysis of heart rate show a sympathetic hyperactivity in RLS patients even in the sleep periods without PLM. This implies that chronic RLS patients could be at increased risk for the development of cardiovascular disorders that are related to increased sympathetic activity, as suggested for patients with other forms of chronic insomnia.[1]

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1313.K1

Negative Pharyngeal Pressure Drives Genioglossus but not Tensor Palatini Muscle Activity Awake and Asleep

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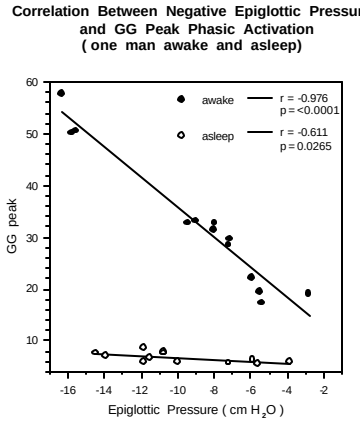
Introduction: Defining the mechanisms controlling pharyngeal dilator muscle activation awake and asleep is important if the pathophysiology of sleep apnea is to be understood. However, the principle stimulus to pharyngeal dilator muscle activation during both wakefulness and NREM sleep remains unclear, but may be mediated via local reflex mechanisms. We hypothesized that negative pharyngeal pressure will drive the activation of these dilator muscles. As some of the upper airway dilator muscles possess tonic activity (e.g. tensor palatini, TP), while others also have respiratory phasic activity (e.g. genioglossus, GG), we also hypothesized that these muscles may have different responses to local stimuli. Thus, we assessed the relationship between 2 dilator muscle electromyograms (EMG) and potential stimuli such as epiglottic negative pressure, airflow, and pharyngeal resistance.

Figure 1



Methods: Fifteen normal subjects were studied, during both wakefulness and stable NREM sleep. The EMG of both GG and TP were assessed using intramuscular electrodes (% of maximum units) during basal breathing as well as during inspiratory resistive loading (4 loads in triplicate, 5,10,15,25cmH2O/l/sec), while quantifying epiglottic and choanal pressures (Millar catheters) plus flow.

Results: There was a strong correlation between nadir epiglottic pressure and peak phasic GGEMG on a breath-by-breath basis during wakefulness in most subjects [10 of 15 had $R > 0.7$ ($p<0.05$), mean R for the group 0.61, $p<0.05$]. These correlations were less robust during NREM sleep [in 9/15 $R > 0.6$ ($p<0.05$), mean R for group 0.4, ns]. The slope of the epiglottic pressure vs genioglossus EMG relationships was greater during wakefulness than sleep (awake vs asleep –0.7 vs –0.4 %max/cmH20, $p<0.05$). One representative example is presented in the Fig. No significant correlation between epiglottic pressure and TP EMG was observed. Peak airflow and pharyngeal resistance also did not correlate with GGEMG or TPEMG.

Conclusions: Epiglottic negative pressure may importantly mediate the activation of the genioglossus muscle during wakefulness. A decrease in the slope of the negative pressure/GG relationship indicates reduced sensitivity of this mechanism during NREM sleep. The TP muscle may be driven by central mechanisms rather than local ones.

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1080.K1

Negative Pressure Reflex Response of the Genioglossus in Awake OSA Patients and Normal Subjects

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Introduction: A previous study found that the response of palatal muscles (levator palatini, palatoglossus) to negative pressure pulses during wakefulness was reduced in obstructive sleep apnea (OSA) patients compared to normal subjects.[1] Other investigators have found higher basal genioglossus (GG) activity in awake OSA patients compared to normal subjects.[2] The higher activity is believed to be compensatory for unfavorable upper airway anatomy. One mechanism of compensation might be via upper airway reflexes. If so, one would expect the GG reflexes to be intact in OSA patients. The response of the genioglossus to negative airway pressure could differ from palatal muscles in OSA patients. To clarify this issue we compared the genioglossus response in aged matched groups of normal subjects and patients with severe OSA.

Methods: Eleven normal male subjects with no history of snoring and a mean ± SD age of 42.4 ± 10.4 years and eleven male patients with OSA of age 47.3 ± 7.7 years and an RDI > 40/hr were studied during wakefulness in the sitting posture. Brief negative pressure pulses (-10 cm and -20 cm H2O) were applied randomly and without warning via a nasal mask in early inspiration. The genioglossus EMG was measured using a mouthpiece electrode custom made for each subjects from a dental impression. The moving time average of genioglossus activity (EMGgg) was obtained using a time constant of 50 msec. The EMGgg was scaled using the maximum voluntary value as 100%. The EMGgg at the time of negative pressure application was used as baseline. The maximum value of EMGgg within 150 msec of pressure onset, the change in EMGgg from baseline, and the % change were determined (means ± SEM). The groups were compared using the paired t test.

Results: The table below shows that the chg and % chg in the EMGgg at both levels of negative suction pressure did not differ between normal subjects and OSA patients.

Table 1

cm H2O	EMGgg	normal	OSA	nl vs OSA
- 10	chg (%max)	11.9 ± 2.4	14.9 ± 3.3	ns
- 10	% chg	65.5 ± 8.4	78.3 ± 16.6	ns
- 20	chg (%max)	20.9 ± 2.7	22.9 ± 4.7	ns
- 20	% chg	126.8 ± 13.4	125.6 ± 25.9	ns

Conclusions: We conclude that the GG response to negative pressure is not impaired during wakefulness in OSA patients compared to normal controls. This suggests that unlike palatal muscles, the genioglossus response to negative upper airway pressure during wakefulness is preserved in patients with OSA.

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1312.K1

Upper Airway Muscle Responsiveness to Rising PCO2 During Slow Wave Sleep

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Introduction: In obstructive sleep apnea, disordered breathing events typically occur during stages I and II NREM sleep and during REM sleep. The relative paucity of events during slow wave sleep (SWS) is poorly understood. One hypothesis has been that hypercapnia, which may develop during SWS (stages 3/4), stimulates pharyngeal dilator muscle activation thereby protecting airway patency. Increased pharyngeal dilator muscle activation has previously been shown to occur with hypercapnea during wakefulness. We therefore tested the ability of 2 upper airway dilator muscles to respond to rising PCO2 during sleep.

Methods: Ventilation and end tidal CO2 (ETCO2) were measured in 16 subjects during wakefulness, stage II and SWS. The genioglossus (GG) EMG and tensor palatini (TP) EMG (intramuscular electrodes) were measured as well. All measurements were performed during both basal breathing (awake, stage 2 sleep and SWS) and during CO2 administration (ETCO2 6mmHg above the eupneic level) during SWS (n=8) or stage 2 sleep (n=6).

Results: ETCO2 increased by 1.1±0.2 torr from stage II to SWS (43.3±0.6 to 44.4±0.6 mmHg, $p<0.05$), with no significant change in GG or TP EMG.Despite significant increases in minute ventilation with induced hypercapnia (8.0±0.3 to 11.8±0.5 lpm, $p<0.001$), there was no change in the GGEMG or the TPEMG when compared with stable stage 2 or SWS.

Table 1

	Ve	ETCO2	GGEMG	TPEMG
Awake	8.3±0.4	39.1±0.7 *	7.0±1.4	7.5±2.1
Stage 2 sleep	8.0±0.3	43.3±0.6 *	7.4±1.4	4.1±0.9
SWS sleep	7.8±0.5	44.4±0.6 *	8.2±1.5	4.0±1.0
CO2 administration	11.6±0.6 §	50.8±0.9 *	8.0±1.35	4.6±1.1

* All groups differ from each other at a level of $p<0.05$, § Different from all other conditions ($p<0.05$).

Conclusions: These data indicate that supra-physiological levels of CO2 (50.8±0.9) are not a major stimulus for pharyngeal dilator muscle activation during stable NREM sleep (either SWS or stage 2). Whether the combination of rising PCO2 and increasing pharyngeal negative pressure during sleep will activate these muscles is unclear, and deserves further investigation.

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1226.K1

Preoptic/Anterior Hypothalamic (POAH) Warming Suppresses Laryngeal Dilator Muscle Activity During Sleep

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Introduction: Reduction in upper airway dilator muscle activity during sleep is thought to be a key pathophysiological element of obstructive sleep apnea (OSA). Some evidence suggests that abnormal regulation of airway dilator muscle activity in OSA is coupled to a sleep regulatory abnormality. For example, sleep deprivation worsens OSA. POAH thermoregulatory processes were found previously to facilitate sleep. We hypothesize that POAH thermoregulatory processes may also modulate respiratory motor functions during sleep. We have previously reported that POAH warming can suppress diaphragmatic activity during sleep in the rat (McGinty et al, 1997) and laryngeal dilator activity in the cat (McGinty et al, 1998). The present report extends those preliminary data.

Methods: Gold-plated prong electrodes mounted on an acrylic base were placed chronically in the laryngeal dilator muscle, the posterior cricoarytenoid (PCA), and in the diaphragm of three cats. EEG, EOG, and neck EMG electrodes, POAH thermocouples, and bilateral water perfused thermodes for local POAH warming were also implanted. The EMG from both muscles was recorded simultaneously during different states of vigilance (Awake, NREM and REM sleep). Trials of POAH warming of 0.4 to 1.2 degrees C. lasting 1-2 minutes were then carried out in each state. Integrated respiratory motor amplitudes were displayed and analyzed with the Spike 2 software (Cambridge Electronic Design) together with the other polygraphic signals. We compared successive diaphragm and PCA integrated signals from matched pre-warming and warming samples.

Results: PCA recordings showed discrete inspiratory bursts, closely coupled to diaphragmatic inspiratory bursts as reported previously (Orem and Lydic, (1978). PCA inspiratory burst onset preceded the diaphragmatic burst onset by about 0.31, 0.45, and 0.21 sec in Awake, NREM and REM, respectively. During REM sleep, PCA integrated amplitude declined markedly. During NREM sleep mild POAH warming induced small but consistent reductions in both diaphragm (range: 4.9%-7.2%) and PCA peak amplitudes (20.4%-36.2%, $p<.05$). POAH warming during NREM sleep also reduced integrated PCA signal amplitude (26%) and the PCA-diaphragm onset time difference (31%). POAH warming did not have consistent effects in REM, although responses were seen in some animals.

Conclusions: Our findings demonstrate that activation of POAH thermosensitive neurons can suppress airway dilator muscle as well as diaphragmatic muscle activity during NREM sleep. POAH warming had greater effects on airway dilator muscle activity than on diaphragm, which could increase airway collapsibility during inspiration. Weight gain and snoring in OSA patients often begins in early adulthood, suggesting a coupling between metabolic control and airway regulation. Elevated activation of POAH thermosensitive neurons could induce reduced metabolic rate, reduced airway dilator muscle activity, and increased sleepiness. Therefore, abnormally elevated activity of these neurons could play a role in the pathogenesis of OSA.

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1326.K1

Intertrigeminal Region and Parabrachial Complex Lesions Dramatically Alter Sleep Disordered Breathing in the Rat

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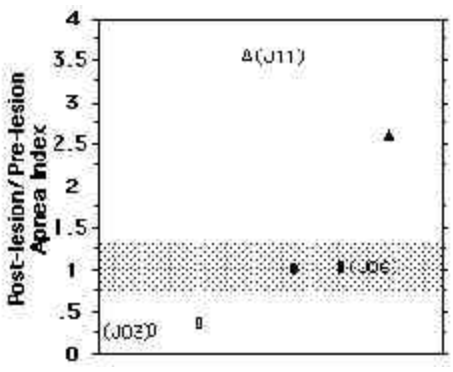
Introduction: Although sleep apnea syndrome affects at least 3% - 5% of the adult population in this country and available data suggest that significant morbidity and increased mortality result from this disorder, the mechanisms underlying all types of sleep-related apnea remain poorly understood. The intertrigeminal region (ITR) of the lateral pons is innervated by sensory subnuclei in the nucleus of the solitary tract (NTS) that receive inputs from vagal, glossopharyngeal and trigeminal (via the spinal trigeminal nucleus) nerves; each of which mediate apneic airway-protective reflexes. Thus, the ITR represents an important airway reflex integrating site which can trigger apnea via direct projections to the respiratory rhythm generating neurons in the ventrolateral medulla. NTS neurons also project to the parabrachial complex (PBC). In contrast to the ITR, stimulation of the lateral PBC stimulates respiration in anesthetized animals. We explored the roles of ITR and PBC neurons in spontaneous sleep-related apneas by producing neurochemical lesions of these areas in rats.

Methods: Six adult male Sprague-Dawley rats were instrumented for chronic sleep state monitoring by EEG and EMG electrodes, and had bilateral stainless steel guide cannulae placed targeting the ITR/PBC region. After a 7 day recovery period sleep and respiration were recorded for 6 hours prior to, and 7 days after ibotenic acid injections (1.0 µg in 0.1 µl). All injection sites were histologically verified. Sleep states were identified by computer algorithm, and apneas were detected as respiratory pauses > 2.5 seconds.

Results: The impact of lesions on expression of REM-sleep related apneas is summarized in figure 1. Rats with lesions in the ITR (e.g. experiment J03) exhibited less than half the rate of apneas with respect to the pre-lesion control. Excitotoxic injections into the parabrachial complex (e.g. experiment J11, in which the tip of the cannula is just dorsal to the ventrolateral tip of the superior cerebellar peduncle) produced more than twice the expected number of apneas. Control injections dorsal or lateral to the parabrachial complex (e.g. experiment J6) had no impact on apnea expression. Values in figure 1 represent post-lesion/pre-lesion apnea indexes. The shaded region represents the average day to day variability determined in previous recordings of over 50 animals.

Figure 1



Conclusions: These findings demonstrate that the ITR and PBC can exert potent modulating influences over the spontaneous expression of sleep related apnea in the rat. Disrupting the functional integrity of the ITR can stabilize respiration during sleep, while disrupting the PBC can exacerbate sleep disordered respiration. Further investigation of the mechanisms underlying theses influences may yield new strategies for the management of sleep-related breathing disorders.

Supported by National Institute on Aging grant AG14564

1733.K1

The Respiratory Related Evoked Potential During NREM Sleep in Mild OSAS: Evidence for the Blunting of Cortical Responsiveness to Increases in Inspiratory Effort.

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Introduction: The application of a brief mid-inspiratory occlusion produces a series of respiratory related evoked potential (RREP) components[1] that are very similar to those seen in response to auditory stimuli.[2] The most likely stimulus for the RREP is the increase in mechanical effort required to breathe against the occlusion. This is also the most likely stimulus for the arousals seen in OSAS.[3] Berry and Gleeson have also reported that the arousal threshold effort level for OSAS patients can be more than double that of control subjects.[3] They propose two major reasons for this. First, OSAS patients may have impaired airway mechanoreceptor function. Second, the threshold may indeed be elevated, either intrinsically or in response to the effects of sleep fragmentation. The RREP provides a unique mechanism for objectively studying the cortical responsiveness to increases in ventilatory effort, without producing arousals that lead to sleep fragmentation.

Methods: Six patients with mild OSAS (mean RDI 9.62 ± 3.65) were compared to six age- and BMI-matched controls. Silent, mid-inspiratory occlusions lasting 1 second in duration were applied during periods of both wakefulness and stable stage 2 NREM sleep. EEG was recorded from six gold cup surface electrodes (Fz, FCz, Cz, CPz, Pz and O2) referenced to linked ears. An EOG, EMG, airflow signal, epiglottal and mask pressure signals were also recorded.

Figure 1

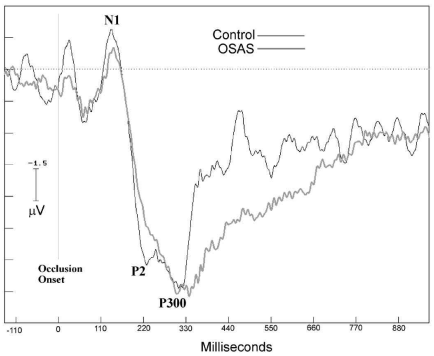

Figure 1. Grand mean RREP waveforms for OSAS and control groups. Data were recorded at Pz while subjects were awake.

Results: Awake: N1, P2 and P300 components were identified in the responses of both groups (see figure 1). N1 was significantly smaller in the OSAS patients. P2 and P300 did not differ significantly between the two groups in either amplitude or latency. Stage 2: the N550 in the

OSAS group was much smaller than in the control group. This was most likely influenced by two factors. Firstly, a significantly larger percentage of K-complexes were observed during stage 2 sleep in the control group (20.09 ± 4.02) compared to OSAS (6.11 ± 2.37) group ($p < .01$). Secondly, the amplitude of the N550 component in the average of K-complex trials was also significantly larger in the control group (-116mV) compared to OSAS (-80mV) ($p < .05$) group.

Figure 2

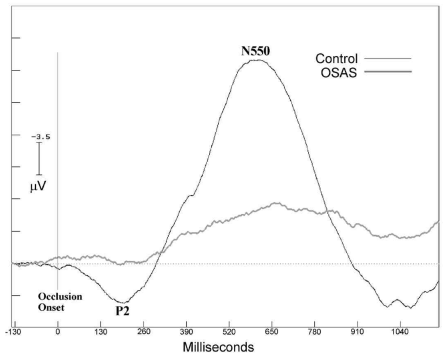

Figure 2. Grand mean RREP waveforms for OSAS and control groups. Data were recorded at Fz while subjects were in stage 2 NREM sleep.

Conclusions: Patients with mild OSAS have a "blunted" response to the respiratory occlusion stimulus. This appears not to be related to an absence of mechanoreceptor function, as the RREP appears normal when awake. The data thus support the hypothesis that OSAS have an elevated response threshold.

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1569.A

Focal Depletion of Dopamine in the Sensorimotor Striatum of the Rat Recapitulates Parkinsonian-like Sleep-Wake Disturbances.

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Introduction: The effect of Parkinson's Disease (PD) upon human sleep-wake architecture includes sleep fragmentation, increased non-slow wave sleep (NSW), reduced slow wave sleep (SWS), sleep onset REM, increased phasic muscle activity, and a loss of REM muscle atonia. The understanding of the pathophysiology underlying these disruptions, and subsequently strategies aimed at restoring sleep-wake architecture, are impeded by the lack of animal models that manifest similar sleep disturbances. We hypothesized that injection of the monoaminergic neurotoxin, 6-hydroxydopamine (6-OHDA), into the striatum of the rat would induce PD-like disturbances to sleep-wake architecture.

Methods: Five male Sprague Dawley rats (Charles River) were used. Three received bilateral striatal injections of 6-OHDA (7 μl; 4.3 μg/μl mul) and were then instrumented with bipolar EEG recording electrodes. Bipolar EMG electrodes were then placed into each rear leg, neck, and eye muscles. Two control animals were also instrumented in an identical manner. Both 6-OHDA and control animals were placed into identical but separate compartments of a light-regulated (12:12 light-dark cycle), sound attenuated, environmental cubicle where food and water was provided ad-libitum. Inside the cubicle each animal was tethered to bioelectric amplifiers via wires and commutators permitting unrestrained movement. Following a 48 hour acclimatization period, continuous digital polysomnographic recordings were obtained during the subsequent 72 hours (acute phase). Animals were then removed from the cubicle and maintained under suitable housing, in a 12:12 LD cycle, for the next 17 days. Following this, animals were reintroduced into the environmental cubicles for another 72 hours of continuous polysomnographic recording (chronic phase). Polysomnographic records were manually scored in 30 second epochs. Animals were then deeply anesthetized, transcardially perfused, and brains sectioned and stained for Nissl substance and tyrosine hydroxylase to assess the extent of the lesion.

Results: During the acute period following 6-OHDA lesioning of the striatum, sleep architecture differed from yoked-control animals in the following respects. First, baseline phasic muscle activity and rear limb movements were markedly increased. Second, bouts of wakefulness and sleep were less consolidated. Third, the overall amount of time spent in NSW increased while the percent of time in SWS decreased. Fourth, abrupt transitions to REM sleep punctated bouts of wakefulness. Finally, lower limb movements occurred sporadically throughout most REM bouts. In contrast, during the second recording period representative of a more chronic state, sleep-wake architecture resumed a more normalized distribution. However, lower limb movements continued to occur sporadically throughout sleep, and particularly, during most REM sleep bouts.

Conclusions: In the rat bilateral injections of 6-OHDA into the striatum is followed by increased phasic muscle activity and limb movements during sleep, while sleep-wake architecture becomes similar to that described in both the human and non-human primate parkinsonian states. This suggests that the 6-OHDA rat may provide a useful model with PD like patterns of sleep-wake architecture. Future research is directed at further deciphering the cellular and subcellular substrates by which striatal dopamine depletion contributes to the disrupted sleep characteristics of PD and potentially other disorders with similar sleep features (e.g. REM Behavior Disorder; narcolepsy).

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1576.A

Acute Changes in Lighting Conditions Alter Immediate Early Gene Expression in Rat Lateral Geniculate Complex

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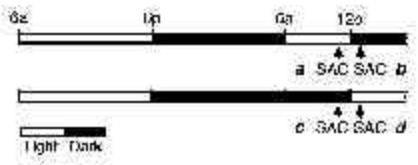
Introduction: Changes in lighting conditions can induce immediate changes in sleep-wakefulness in many animals. The mechanisms for these effects are largely unknown, but may include retinorecipient regions in the subcortical visual shell. We have demonstrated that lesions in the pretectum and superior colliculus significantly attenuate light-induced sleep-wakefulness changes in the albino rat.[1] Similarly, lesions to the hamster pretectum and superior colliculus, or their afferent connections with the lateral geniculate complex, block benzodiazapine-induced phase shifts of the circadian activity rhythm.[2] We hypothesize that regions of the subcortical visual shell, specifically the intergeniculate leaflet (IGL) and the ventral lateral geniculate nucleus (vLGN), respond to acute changes in lighting conditions, and may modulate circadian activity.

Methods: We used immediate early gene (IEG) expression as a functional marker to measure the responses of lateral geniculate complex neurons to abrupt changes in lighting conditions. Adult male F344 albino rats were maintained on a 12:12 light-dark cycle. One group of rats was subjected to a light to dark shift (L—>D) (Fig. A) and another to a dark to light shift (D—>L) (Fig. B) in the middle of the subjective day. Rats were sacrificed 5 minutes before or 60 minutes after the lighting change. This paradigm produced four experimental conditions: constant light (a), acute dark (b), constant dark (c), and acute light (d). Rats were perfused with 4% paraformaldehyde and brains were sectioned at 50 microns. Sections were reacted immunocytochemically for the presence of c-Fos and analyzed quantitatively with Image Pro software.

Results: In the IGL, rats exposed to a D—>L shift showed a significant increase in c-FOS staining. In contrast, rats exposed to a L—>D shift showed noticeably attenuated c-Fos immunoreactivity. In the vLGN, most of the c-Fos staining was localized at the medial border. This population of neurons showed a statistically significant increase in c-Fos immunoreactivity in response to a D—>L shift, but showed no change in cFos immunoreactivity in response to a L—>D shift. No c-Fos immunoreactivity was detected in the dorsal lateral geniculate nucleus (dLGN), regardless of lighting condition.

Figure 1. Lighting Paradigm



Conclusions: Discrete populations of neurons in the lateral geniculate complex respond to acute light-dark shifts, as indicated by changes in IEG expression. In the IGL, acute increases in light, as well as chronic light exposure, is associated with high cFos expression. In the vLGN, a distinct population of neurons near the medial border responds to acute increases in illuminance, but not to chronic exposure to light. These data extend earlier findings that light exposure enhances c-Fos expression in the IGL, by suggesting that the vLGN also detects acute changes in light. Given the extensive interconnections between the lateral geniculate complex and the suprachiasmatic nucleus, it is possible that these retinorecipient regions may also modulate circadian rhythms.

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1873.A

Daily Sleep Quantities in Kittens Receiving Low Doses of MK-801 by Osmotic Minipump Infusion (IP) for one week.

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Introduction: We have recently shown that suppression of rapid eye-movement (REM) sleep in monocularly deprived kittens during their postnatal critical period for visual system development shows an exaggeration of the anatomical effects monocular deprivation has on cell growth in the visual system. This supports our hypothesis that REM sleep may play a role in CNS development but does not suggest any specific mechanisms by which REM sleep affects brain maturation. Other work recently demonstrated that systemic injections of the non-competitive NMDA channel-blocker, (+)-5-methyl-10,11-dihydro-5h-dibenzo[a,d]cyclohepten-5,10-imine hydrogen maleate (MK-801) block the ocular dominance column shift usually observed in monocularly deprived kittens.[1] Ocular dominance columns are a physiological correlate of cell growth in primary visual system. These results suggest that REM sleep suppression could be having its effects on visual system development through NMDA receptors either in visual cortex, visual thalamus, or both.. However, injections of MK-801 (0.5 mg/kg/day) in adults have been reported to increase sleep amounts in the first 72 hours after injections,[2] and it is not known what effects any dose of MK-801 has on sleep in critical-period kittens. In this study we assessed the effects of two MK-801 dosage regimens on vigilance states to determine whether REM sleep amounts are affected.

Methods: Four kittens from a single litter were implanted with EEG and EMG electrodes, following aseptic procedures and our standard developmental schedules.[3] Osmotic minipumps (Alzet, ALZA, Inc.) also were placed in the intraperitoneal space and fitted with a saline-filled catheter of sufficient length that, given the mean pumping rate (0.1λ/hr), drug delivery was calculated to commence only after the sleep-baseline day recorded on post natal day (PN) 41. Two kittens received 0.1 mg/kg/day and two received 0.25 mg/kg/day via minipump infusion during the seven days between PN42 and PN50. Sleep recording was sustained from the PN41 baseline day to PN50.

Results: Percentages of recording time spent in the three main vigilance states are given in Table 2 in terms of dosage and recording day. Baseline amounts of REMS were similar at the two dosage levels and comparable to the baseline REMS percentages in our earlier studies.[3] However, whereas NREMS and WAKE amounts for the LO-dose pair are similar to earlier baseline recordings, NREMS appears to be quite a bit higher in the HI-dose pair on the baseline day. Though the NREMS percentages of the HI-dose pair decreased during the week, they remained above the expected baseline level.

Table 1. Effects of MK-801 dosages on proportions of state (% recording time).

	LO(0.01mg/kg) n = 2			HI(0.25mg/kg) n = 2		
	REMS	**NREMS**	**WAKE**	**REMS**	**NREMS**	**WAKE**
BASELINE						
Mean	29.10	41.95	25.53	24.86	58.96	14.47
SE	4.48	7.65	13.13	4.04	9.29	14.45
DAY 1						
Mean	27.52	47.58	21.69	22.63	55.01	20.55
SE	0.32	1.94	2.36	7.20	14.87	23.05
DAY 3						
Mean	28.30	42.15	25.83	24.59	51.18	20.15
SE	1.90	6.48	3.33	0.40	6.53	7.99
DAY 6						
Mean	32.79	43.62	20.23	18.79	52.99	23.25
SE	0.82	1.23	1.29	0.97	10.50	12.54

Conclusions: The high amount of NREMS on baseline day of the HI-dose pair suggests that drug infusion probably commenced during the baseline day. Previous behavioral observations indicating that at the lower MK-801 dosage, kittens do not appear to sleep more than expected[2] are supported by the sleep amounts recorded in this study. Because REM sleep quantities were little affected in the LO-dose animals, these results suggest that using MK-801 to test the role of REM sleep in visual system synaptic plasticity would not be confounded by direct effects of this dosage on REM sleep quantities.

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1874.A

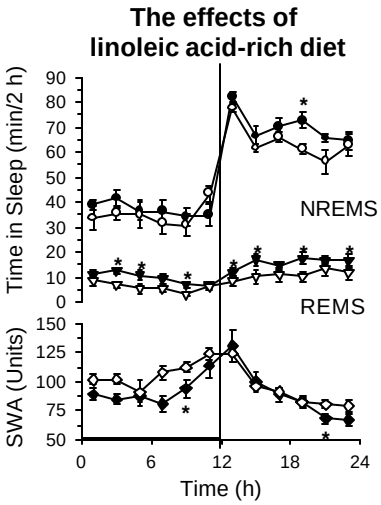
The effects of linoleic acid-rich diet on sleep in rats

Ebe E, Frank C, and Kapas L

Introduction: Various lipids are involved in the modulation of complex neural functions, e.g., sleep. Several endogenous and exogenous lipids, such as oleamide and lipid A, respectively, promote sleep (e.g., Krueger et al., 1986). Other lipids, such as linoleic acid, play a role in the regulation of hibernation (Frank 1992). Linoleic acid is an essential polyunsaturated fatty acid. Arachidonic acid, the common precursor to all prostaglandins, is synthesized from linoleic acid. Prostaglandins are implicated in sleep regulation. The aim of the present experiment was to study the effect of linoleic acid-rich diet on sleep.

Methods: Adult male Sprague-Dawley rats were implanted with EEG and EMG electrodes. The rats were kept on a 12:12 h light-dark cycle. The experimental protocol included 2 baseline days on which the rats (n = 5) were fed (ad libitum) standard Purina 5001 Rodent Chow (normal diet), followed by 29 days on which the rats were fed (ad libitum) a 10% olive oil /90% Purina 5001 Rodent Chow mixture (linoleic acid-rich diet). Sleep was recorded on the two baseline days, the first two days of the linoleic acid-rich diet, and the 28th and 29th days of the linoleic acid-rich diet.

Figure 1. Open symbols: sleep and SWA on normal diet (average of two baseline days); solid symbols: sleep and SWA on linoleic acid-rich diet (average of days 28 and 29 on linoleic acid-rich diet); horizontal solid bar: dark period of the day; asterisks: p < 0.05.



Results: The linoleic acid-rich diet had no significant effect on sleep the first two days that it was given to the rats. Four weeks on the linoleic acid-rich diet, however, did induce significant changes in sleep. On day 28/29, NREM sleep significantly increased across the 12-h light period (386.4 \pm 9.6 min baseline vs. 424.8 \pm 10.9 min on the experimental day, a 38.4 \pm 6.0 min (9.9%) increase ($p < 0.05$)). The diet also caused significant increases in REM sleep over both the 12-h dark (a 21.7 \pm 4.8 min (60%) increase ($p < 0.05$)) and the 12-h light periods (a 29.7 \pm 4.0 min (46%) increase ($p < 0.05$)). Also, there were strong tendencies to decreased slow-wave activity (SWA) of the EEG during NREMS in the dark period on days 28/29 of the diet.

Conclusions: Linoleic acid-rich diet induced long-term changes in both NREMS and REMS. The effects may be due changes in the composition of membrane lipids, increased production of somnogenic gastrointestinal peptides, such as cholecystokinin, or other factors.

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1235.A

Epileptiform vs. Sleep Spindle Activity In Rats Using Clonazepam As A Vehicle

Anch A,[1] Morrissey M,[1] Dyche J,[1] Laposky A,[2] Duntley S[3]
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Introduction: While most studies investigating rodent spindle activity have not distinguished epileptiform spindles (ES) from sleep spindles (SS), Kandel and Buzaki (1997) recorded field potentials and unit activity in different areas of the rat cortex and demonstrated marked differences in frequency and form between ES and SS. However, behavioral observations were not included in their study. The purpose of the present study was to provide further evidence for the distinction between ES and SS during waking and sleep in rats.

Methods: The two rats used in this study had a rare progressive, demyelinating disease of the CNS, characterized by evident seizure activity after 6 - 9 months of age. Infrared videography allowed us to simultaneously observe their behavior while electrophysiologically recording their sleep-activity using electrocortical, electromyographic, and electro-oculagram recording. We used two different measures to differentiate ES from SS recordings. Firstly, we sampled visual observations during ES and SS. Secondly, since benzodiazepines are known to increase SS in rodents (Gandolfo et al., 1994), and since clonazepam has known anti-convulsant effects in rodents (De Sarro et al., 1996), we administered clonazepam (0.9 mg/kg) and the vehicle control by oral gavage to two rats and compared the clonazepam effects on ES and SS in comparison to the vehicle control. The rats in this study had been previously adapted to the recording chamber. A four day interval separated the administration of the clonazepam and the vehicle control procedure. However, prior to the vehicle control (second) run, one of the animals had to be sacrificed, leaving us with 2 animals under the clonazepam condition and one under the vehicle control condition.

Results: The results of the study revealed that SS was not significantly different from clonazepam vs. vehicle control (t=1.401, p=.17). However, ES showed a significant decrease in both animals for the first 12 h of analysis in comparison to the second 12 h (Rat 1 t=3.2, p=.007; Rat 2 t=3.4, p=.005). Total epileptiform activity (ES) was greater under vehicle control than with clonazepam as shown in figure 1. On the other

hand, SS activity was greater under the clonazepam condition than the vehicle control as demonstrated in figure 2. In addition, we also selectively compared ES and SS activity with visual observation. Under no circumstances did epileptiform activity occur during SS. However, in every instance that ES occurred, we observed seizure activity in the rats. There were also qualitative differnces in the waveforms of ES and SS. The frequency of ES activity ranged from 4 - 6 Hz, whereas the frequency of SS activity ranged from 9 -13 Hz.

Figure 1

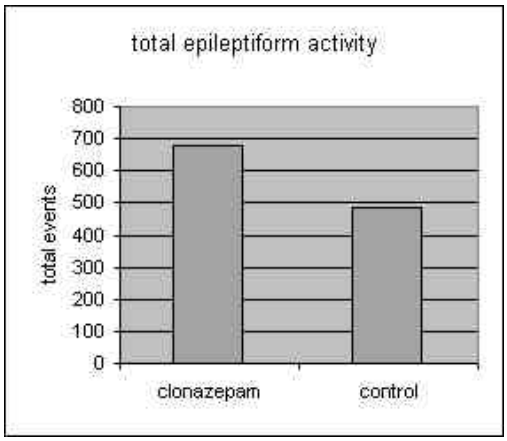
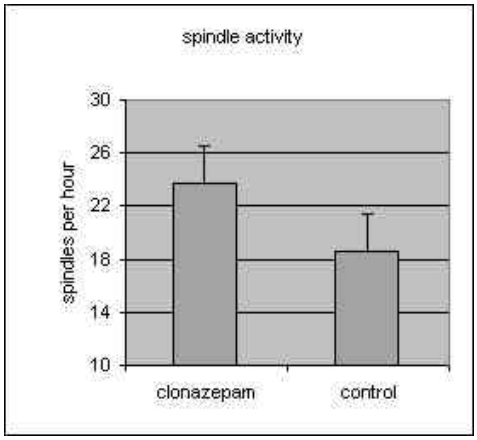


Figure 2



Conclusion: This data supports the notion that there are differences between ES and SS activity in rodent sleep-wake activity. The results of this preliminary analyis may help to clarify some inconsistencies in defining what consitutes a sleep spindle in rat sleep. This may also impact rat sleep stage scoring as well as computer programs designed to score rat sleep

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1883.A

The Development of Hypocretin/Orexin Neurons and Projections in the Rat

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Introduction: The hypocretins (orexins) are formed from a single preproprotein, localized solely in neurons in the lateral hypothalamic area (LHA). Hypocretin/orexin may play an important role in the normal control of REM sleep and arousal. In the present study, we characterize the postnatal development of the hypocretin/orexin system in the normal rat.

Methods: Rat pups at postnatal days 2, 5, 16, 21, and 31 were anesthetized with Nembutol and perfused transcardially with saline, followed by 4% paraformaldehyde. The brains were removed and equilibrated in 30% sucrose. Fifty-micron sections were cut on a freezing microtome. Immunohistochemistry for prepro-hypocretin was performed on free-floating sections, using a polyclonal antibody developed and characterized by Peyron et al..[1] Hypocretin (hcrt) immunoreactivity was visualized with diaminobenzidine as the chromagen. Sections were mounted onto slides and processed for light microscopic analysis.

Results: Hypocretin-immunoreactive (hcrt-ir) neurons are present at the earliest time point studied, postnatal day 2 (P2). At P2, the cell bodies of hcrt-ir neurons are small (10-15 um long), and have very short, thin dendrites. At postnatal day 5, hcrt-ir neurons are larger (15-20 um), and have thicker, more extensive dendrites. At P16, most neurons have reached adult size (20-25 um), and dendritic fields are extensive, but not as dense as in later stages. Hcrt-ir neurons in P21 and P31 are 20-25 um in size and have dense dendritic fields, as in the adult. In the P2 brain, hcrt-ir axons are very sparse, and are found scattered throughout the brain. At P5, an increased density of innervation is seen in a few specific targets, most notably in the infralimbic cortex, and in the locus coeruleus. At P16, it appears that the mature pattern of innervation is in place, although the density of axons is less than in adult. The maturation of hypocretin innervation appears to be completed between P16 and P21, as no further increase in density of hcrt-ir axons is seen from P21 to P31.

Conclusions: Hypocretin-ir neurons and axons undergo a progressive change in density with maturation, which appears to be complete by the end of the third postnatal week, which is similar to that found for serotonergic innervation of basal forebrain[2] and lateral geniculate. This developmental time point may be behaviorally significant as it also coincides with establishment of the diurnal organization in sleep-wake distribution.[3]

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1248.A

The Role of Glutamate in the Production of Arousal by the Posterior Hypothalamus

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Introduction: The posterior hypothalamus has been implicated in the promotion of wakefulness by lesion and chemical microstimulation studies.[1] More recently, transection studies suggest that the specific function of the posterior hypothalamus is generation of the motor components of wakefulness.[2] However, the neurotransmitter(s) involved in this neural regulatory system is/are yet undetermined. In the current study, chemical microstimulation of appropriate sites within the posterior hypothalamus by the microinjection of the excitatory neurotransmitter glutamate and its agonist N-Methyl-D-Aspartic acid (NMDA) was used to examine the role of this neurotransmitter in the production of behavioral arousal.

Methods: Male Sprague-Dawley rats (384-548g, n=13) were anesthetized with Metofane followed by an intraperitoneal injection of 2.0g urethane/kg body weight. Urethane anesthesia produces rats that cycle through States 1-3 EEG corresponding to wake, transition between wake and NREM, and NREM sleep, respectively.[3] Rats were placed in a stereotaxic frame and standard techniques were used to record heart rate, electroencephalographic(EEG), and electromyographic (EMG) activity throughout the experiments (6-8 hours). Microinjection into the posterior hypothalamus was performed using a Hamilton 26-gauge 1 microliter syringe through a 3.0 mm diameter hole drilled in the skull. Injections were sham, vehicle (saline), and either 50 mM glutamate in 0.1 microliter of 0.9% saline or 6.8 mM to 17 mM of NMDA in 0.1 microliter 0.9% saline. Injection order was randomized and was performed unilaterally over 60 seconds during State 3 EEG. Injections were spaced 30 minutes apart. Two or three sites, 1mm apart, were examined in each animal. Positive responses were defined as a change from State 3 to State 1 EEG and a 50% increase in muscle tone exhibited during or within 5 minutes of the injection.

Results: To date 27 sites have been investigated in the posterior hypothalamus at AP 4.2-6.5, ML 0.5-1.5, DV -7.0-(-10.0) with a total of 86 injections. Sham injection was positive for EEG desynchrony during the first insertion of the needle only. Saline responses were positive 9 of 27 times. Positive responses to drug injection exceeded those to saline. NMDA stimulation resulted in 26 positive and 16 negative responses. Glutamate stimulation resulted in 5 positive and 12 negative responses. Most of the positive sites were clustered toward the anterior and medial parts of the posterior hypothalamus at AP 6.2-5.4, ML 1.0-1.5, DV -8.0 to -9.0. Generally, responses increased with increased concentrations of the NMDA.

Conclusions: Preliminary results suggest that glutamate and its agonist NMDA produce behavioral arousal when microinjected into the posterior hypothalamus.

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1249.A

High Frequency Polygraphic Observations During Rapid Eye Movement Sleep

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Introduction: Conventionally, electroencephalogram (EEG) has been measured in the lower frequency range than 30Hz. This limitation of the concerned band width comes from the difficulty in recording the wide-band EEG rather than its physiological insignificance, e.g., contamination of electromyogram (EMG). Actually, gamma-band (40Hz or higher) EEG activities have been attracting physiological interests in the context of cognitive functions. However, signal processing techniques could not completely exclude the contamination due to the overlap of the concerned band width between EEG and EMG. In this paper, in order to investigate the high frequency polygraphic signals beyond the conventionally concerned frequency range, we focus on a rapid eye movement (REM) sleep, where anti-gravity muscles are completely relaxed (muscle atonia). This recording condition is expected to disclose the high frequency phenomena in the polygraphic signals.

Methods: Nocturnal sleep of four young male adults aged 24 was recorded. Informed consent was obtained from the subjects. The EEG,the submental EMG, electrooculogram (EOG(L) and EOG(R); left and right) were recorded against A2 and subject to A/D conversion with 12bits resolution. The recorded bandwidth was from 0.5Hz to 500Hz. The sampling frequency was 1kHz. Detail structure of the high frequency EEG recorded from P3-A2 were investigated for three separate frequency ranges, 1-15Hz(low), 15-45Hz(mid), and 60-90Hz(high). On the other hand, for the analysis of fast phasic potentials in the polygraphic signals, the raw digitized data were used.

Results: The study disclosed that the rhythmic activities with different frequencies appeared one after another in the frequency range up to at least 90Hz. This result implies that the features in EEG activity during REM sleep which Rechtschaffen and Kales reported concerning the low frequency range are still valid for characterizing the EEG activities in the mid and high frequency ranges (Rechtschaffen and Kales, 1968). In addition, the extremely wide bandwidth of 500Hz analyzed here disclosed the phasic potentials of 15msec duration related to the rapid eye movements which had the consistent topographic pattern. The pattern, frontal positive and occipital negative, suggests the dipole located deep in the brain. The size of the phasic potentials in EOGs tended to be larger than those in EEG, which suggests possibility that some neuronal activities in the brain were electrotonically observed through optic canals. This phasic potential may be related to a neurogenic potential generating ponto-geniculo-occipital (PGO) wave observed in cats during REM sleep.

Conclusions: REM sleep is considered to be only a physiological state which allows one to measure the high frequency EEG activities without contamination of EMG due to muscle atonia except for twitches. The result here suggests that the rivalry among small neural assemblies activated synchronously is realized during REM sleep, which might be understood within our hypothesized framework of disinhibition and activation associated with REM sleep. In addition, the phasic potential we found may be an important discovery in human neurophysiology.

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1251.A

Consistency in Slow Dynamics of Single Neuronal Activities in Lateral Geniculate Nucleus Region

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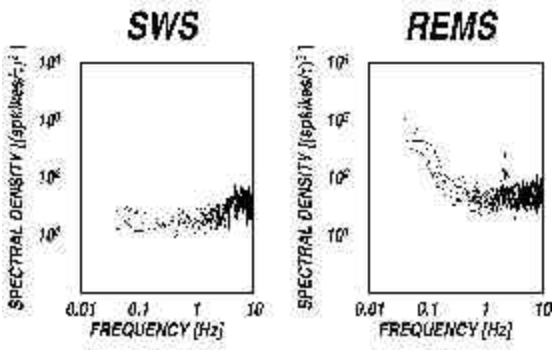
Introduction: We have investigated dynamics of single unit activities recorded from neurons of various areas of the brain during sleep (Yamamoto et al.,1997). Their power spectral densities show white noise-like spectrum in the low frequency range during steady state of slow wave sleep (SWS), and 1/f-like spectrum during rapid eye movement sleep (REMS). This phenomenon, "transition in slow dynamics", is expected to be a general property of neurons in central processor systems such as neocortex, thalamus, and mesencephalic reticular formation (Yamamoto et al., 1997). Here, we attempt to confirm this idea in the lateral geniculate nucleus (LGN) region.

Methods: For recording single neuronal activity from the LGN region (A5.0-7.0, L8.5-9.5), we made a stainless-steel wire electrode insulated by parylene with an electrolytically polished tip. The present report is based on 6 neurons from 4 adult cats (2 male, and 2 female). Non-overlapping 2 minutes segments of unit activity were extracted from the records of REMS and SWS episodes. A power spectral analysis was performed on the successive spike-counts measured with 50msec time window. The spectrum was plotted double logarithmically and its slope was calculated as a parameter for evaluating the shape of the spectrum by a least-mean-square method in the frequency range, 0.04-1.0Hz.

Results: Discharge pattern during SWS was characterized by intermittent bursts each of which contained 2-7 spikes (mean rate: 13.2 spikes/s SD:1.7); more tonic and fluctuating discharge pattern was observed during REMS (mean rate: 33.3 spikes/s SD:7.5). All of the neuronal activities showed the flat (white) spectrum during SWS, and the 1/f-like spectrum during REMS. The spectral slope of the averaged spectrum for each neuron during SWS was around zero (MEAN:-0.06 SD:0.09), and that during REMS was non-zero, negative (MEAN:-0.57 SD:0.14). Figure 1 shows the superimposed power spectra for an identical neuron in REMS and SWS, which shows episodic consistency in slow dynamics of a single neuronal activity in the LGN region.

Figure 1



Conclusions: Here, we found that the slow dynamics of single neuronal activities in the LGN region showed the 1/f-white transition between REMS and SWS similar to the other areas studied previously. In addition, the spectral profile of neuronal activity was shown to be kept across the sleep episodes within an identical neuron. From this consistency, the dynamics of neuronal activities might disclose the intrinsic properties of a neuron such as structure of local circuit and kinetics of ionic channels.

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1894.A

Activation of Prostaglandin E Recepter EP_4 Subtype at the Ventral Surface of the Rostral Basal Forebrain Increases Sleep in Rats

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Introduction: Prostaglandin (PG) E_2 continuously infused into the third ventricle during diurnal hours augmented wakefulness and suppressed both slow-wave sleep (SWS) and paradoxical sleep (PS) in rats.[1] PGE_2 is known, however, to act as a sleep promoter when continuously infused into the subarachnoid space underlying the ventral surface of the rostral basal forebrain,[2] where a PGD_2-sensitive sleep-promoting zone (PGD_2-SZ) was demarcated. The actions of PGE are mediated by specific cell receptors, and the PGE (EP) receptor has been divided into at least 4 subtypes (i.e., EP_1, EP_2, EP_3 and EP_4). In this study, we investigated the effect of novel EP agonists[3] specific to respective PGE receptor subtypes on sleep-wake activities by infusing into the third ventricle during diurnal hours or into the PGD_2-SZ during nocturnal hours.

Methods: Adult male rats were chronically implanted with electrodes for polygraph recordings and a single or paired cannula(e) for infusion of an EP agonist into the brain. In the first series of experiments, each agonist was infused through the single cannula into the third ventricle during the diurnal hours (rest phase of the animal) to determine which subtype of the EP receptors participated in the suppression of sleep or augmentation of wakefulness. In the second series of experiments, we infused each agonist into the PGD_2-SZ through the paired cannulae during the nocturnal hours (active phase) to determine the subtype of the EP receptor involved in the increase in sleep. On the polygraph recordings, wakefulness, SWS and PS were determined visually. The amounts of wakefulness, SWS and PS were calculated and the results were compared between baseline and experimental recordings.

Results: By the 6-hr infusion into the third ventricle, the EP_1 agonist significantly decreased SWS, whereas the EP_4 agonist markedly increased SWS. The EP_2 and EP_4 agonist significantly decreased PS. With the infusion into the PGD_2-SZ, EP_2, EP_3 and EP_4 agonists significantly increased the amount of SWS (infusion rate through each cannula: 100 pmol/min). The EP_4 agonist exhibited an extraordinarily potent effect: the total SWS increment during the 6-hr infusion was 131 ± 9 min (mean ± S.E.M.) (baseline, 126 ± 5min; EP_4 agonist, 257 ± 8min; n=8; p<0.001, by paired t-test). This agonist did not change the brain temperature during the period of infusion into the PGD_2-SZ. The EP_2 agonist was noticed to markedly increase PS. The amount of wakefulness was decreased by EP_2, EP_3 and EP_4 agonists. Infusion of the EP_4 agonist into the PGD_2-SZ at lower doses (1 and 10 pmol/min per each cannula) produced significant increases in SWS and PS: SWS was dose-dependently increased at 10 and 100 pmol/min, whereas significant increases in PS

were observed at 1 and 10 pmol/min.

Conclusions: PGE_2 was shown to possess both sleep- and wakefulness-promoting activities; however, the EP receptor subtypes responsible for respective activities were not known. The results of this study indicate that the awaking effect of PGE_2 is mediated mainly by EP_1 receptors situating around the third ventricle, whereas the sleep-promoting effect of PGE_2 is brought about mainly through activation of EP_4 receptors located at or near the PGD_2-SZ.

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1636.A

Anatomical Identification of the Feline Ventrolateral Preoptic Area (VLPO)

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Introduction: Sherin et al. (1996) describe a group of neurons in the rat VLPO that are selectively active during sleep (as indicated by c-fos protein accumulation). These VLPO neurons project to the tuberomamillary nucleus (TMN), the site of HA neurons that are selectively active in wakefulness (W). Approximately 80% of these VLPO neurons projecting to the TMN contain inhibitory neurotransmitters (GABA or galanin). Furthermore, recent work has demonstrated that the VLPO neurons also project to other brainstem monoamine nuclei concerned with the control of behavioral state including the raphe nuclei and the locus coeruleus. Earlier work had found that the preoptic anterior hypothalamic area (POAH) in rats, cats, and rabbits contains neurons that discharge preferentially during slow wave sleep (SWS), and, furthermore, lesions of this area produce significant reductions in SWS. Thus, data supporting a role for the POAH in promoting sleep has a long history, but the characterization of the VLPO within this region is relatively new. Several histological markers have been used to identify the VLPO in rat, including the presence of Fos immunoreactive neuronal nuclei in animals that have spent the period prior to sacrifice predominantly asleep. Fos-positive nuclei can be seen throughout the rat POAH, but are most densely clustered in the VLPO. The VLPO can also be clearly demarcated as a galanin-immunoreactive (gal +) cell group in colchicine-treated rats. It is important to histologically identify the VLPO sleep-related neurons in a species other than rat. Hence, the present study examined the feline POAH with staining for galanin, and Fos protein.

Methods: Methods included c-fos and galanin immunohistochemistry, and in situ hybridization for galanin mRNA.

Results: Galanin immunohistochemistry. Three male cats were anesthetized with pentobarbital, and colchicine was stereotaxically injected into both lateral ventricles (200µg/20µl per injection; total 400µg/subject). 36 hours later cats were overdosed with pentobarbital and transcardially perfused with 0.9% saline followed by 4% formaldehyde. Gross anatomical landmarks used for initial localization of the VLPO region in both species included the optic chiasm, supraoptic nucleus, and ventral border of the brain. Galanin immunostaining indicates that the ventral POAH of cat contains abundant gal + neuronal soma and fibers, but compared to the single dense cluster of gal + cells seen in rat, the gal + cells in the feline VLPO area were more diffuse and scattered. Fos immunohistochemistry identifies neurons that produced Fos protein during the time period preceding euthanasia, and was the method used to define the locus of neurons corresponding to the rat VLPO. Six cats were kept awake by gentle handling/playing for 6 h, and 6 were kept awake for 6 h and then allowed to sleep for up to 120 min, followed immediately by anesthesia and perfusion (as above). Variability in sleeping behavior (two slept < 60 min) and in the histological procedures (2 cases were not useable) prevent firm conclusions from the Fos data obtained from the first 8 subjects, and analysis of the final 4 subjects is ongoing. Nonetheless, the preliminary Fos data are consistent with the following observations: cats that were awake for 6 h prior to sacrifice had abundant Fos + staining in cell nuclei in areas known to be active during W (e.g., cortex & septum), and relatively little Fos staining in the POAH in and around the VLPO region. Cats that were sleeping prior to sacrifice had diffuse Fos labeling of POAH cells, covering an area larger than, but encompassing the gal + area described above. However, the majority of these sleeping animals also had Fos staining in brain areas labeled in the W animals, which we interpret as Fos protein levels that remained high in these brain areas because the duration of the sleeping period was not long enough. Double labeling. The vast majority of rat VLPO sleep-active neurons are co-labeled with Fos & galanin (Gaus and Saper,1999). In the absence of a dense cluster of sleep-active neurons in the feline POAH, double labeling with Fos (as above) and in situ hybridization for galanin mRNA should provide important evidence to establish the homology between feline VLPO-like neurons and the rodent VLPO.

Conclusions: The preliminary anatomical work indicates that the feline hypothalamus contains a population of gal + neurons that appears homologous to the population identified as "sleep-active" VLPO neurons in the rat. Feline gal + neurons are more diffusely organized compared to rat, an observation also characteristic of feline brainstem serotonergic and noradrenergic nuclei. Data also indicate that Fos labeled nuclei are located throughout the POAH of sleeping cats including the area of gal + cells.

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1662.A

Relationship of Arousals From Sleep to Sympathetic Nervous System Activity in Normal Subjects

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Introduction: Transient increases in heart rate, blood pressure, ventilation and sympathetic activity often accompany arousals from sleep. In the past we have demonstrated that movement arousals independently predict daytime plasma norepinephrine in a population with various degrees of obstructive sleep apnea (e.g., Loredo et al 1999). We hypothesized that movement arousals would correlate with urine norepinephrine levels in a normal population.

Methods: Ten normal subjects underwent full overnight polysomnography followed by a 24-hour urine collection for catecholamine measure-

ment. All were free from antihypertensive medications.

Results: Age ranged from 29 to 49 years. Body mass index was 26.6 ± 3.7, and the diet was similar during the study period. Respiratory disturbance index was 2.2 ± 2.5 and the periodic leg movement during sleep index was 1.3 ± 3.5. Movement arousal index and cortical arousal index were 12.7 ± 5.8 and 2.7 ± 2.5/hour respectively. Mean nocturnal oxyhemoglobin saturation (SaO2) was 95.2 ± 1.5 %. Movement arousal index was correlated with urine norepinephrine ($r = 0.768$; $p < 0.01$). Cortical arousal index, respiratory disturbance index, periodic leg movement index and nocturnal saturation did not correlate with urine norepinephrine.

Table 1

Pearson Correlation Between 24-Hour Urine NE and Factors Affecting Sympathetic System Activity

Variable	r	p Value
Movement Arousal Index	0.768	0.009 *
Cortical Arousal Index	0.081	0.823
Respiratory Disturbance Index	0.355	0.059
Periodic Leg Movement Index	-0.137	0.479
Nocturnal SaO_2	0.139	0.517

*Based on Bonferroni's correction, a significant p value was determined to be ≤0.01.

Conclusions: These preliminary findings replicate earlier observations that movement arousals are associated with sympathtic nervous system activity as measured by urine norepinephrine. The findings also extend these observations to individuals who do not have sleep disorders.

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1361.A

Changes in Extracellular Adenosine in the Human Brain During Conditions of Sleep and Sleep Deprivation, as Revealed by in Vivo Microdialysis

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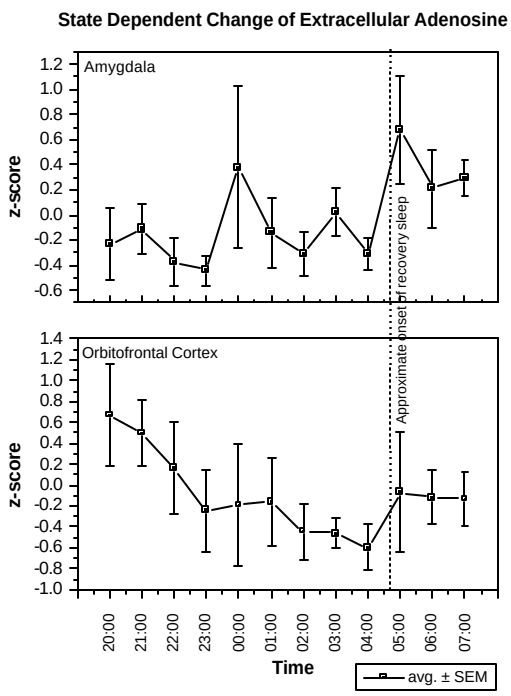
Introduction: A role of adenosine in the regulation of sleep/wake state in mammals has been postulated due to the somnogenic effects of s.c., i.p., i.c.v, and i.v. injection of adenosine and stable adenosine analogs. Furthermore, alteration of the endogenous adenosine signal, through use of adenosine receptor blockers, adenosine reuptake inhibitors, and adenosine deaminase inhibitors, also affects sleep/wake physiology. It has been previously demonstrated in the cat that adenosine concentrations in the basal forebrain increase with mild sleep deprivation and fall during recovery sleep, implying a possible role of adenosine in sleep/wake regulation.[1] As humans regulate sleep and wake in a different manner than do most other mammals, and due to the endemic usage of adenosine receptor blockers such as caffeine and theophylline, it is of great interest to understand the role of adenosine in human state regulation.

Methods: To provide diagnostic guidance for surgical resection of epileptogenic tissue in the temporal lobe of patients with intractable complex-partial seizures, four patients were implanted with depth electrodes targeted to clinically relevant portions of their brains. Within at least one of the depth electrodes in each patient, was a specially designed microdialysis probe (MW < 12.5 kD) used to collect extracellular fluid.[2] Following collection, dialysate was frozen and later assayed for adenosine concentration using reverse phase HPLC with fluorescent detection. Reported are data collected during a period of wake extension from ~19:30 – 05:00 and a brief recovery sleep from ~05:00 – 07:30. In these patients, there occurred no seizures during this twelve hour period.

Results: In each of the four patients, samples were collected from one of the orbitofrontal cortices. In three of the patients, samples were also collected from one or both amygdalae. Data from each structure were separately z-transformed within patients, averaged within patients (if collected bilaterally), then averaged across patients. In the orbitofrontal cortex (n=4), adenosine concentrations displayed a steady decline until sleep onset, at which time there was a brief, but sharp rise in concentration. In the amygdala (n=3), adenosine concentrations remained relatively stable throughout the wake extension period, sharply rising at the time of sleep onset. Calculated extracellular concentrations of adenosine were in the high nanomolar range, and thus likely able to affect either A1 or A2A receptors, but likely not the widespread A2B receptors.

Figure 1



Conclusions: Both the orbitofrontal cortex and the amygdala exhibit state-dependent patterns of adenosine concentration. Though neither structure is known to be directly involved in the regulation of sleep onset or maintenance, changes in adenosine may reflect a state-dependent neuromodulatory role of adenosine in regulating neural activity.

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1708.A

Manipulation of Behavioral States with Hypocretin Type II Receptor Antisense

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Introduction: Hypocretin/Orexins (Hcrt) are newly discovered hypothalamic peptides that early work suggested were involved in wide range of functions, including feeding, energy homeostasis and neuroendocrine systems (Peyron et al 1998). The Hcrt peptide-containing neurons are exclusively located in the lateral hypothalamus, but they send projections throughout the nervous system including the mesopontine cholinergic nuclei (LDT/PPT), the dorsal raphe (DRN) and the locus coeruleus (LC) (Peyron et al 1998). Recently, these peptides have generated interest among sleep researchers because two recent reports have linked cataplexy/narcolepsy to the dysfunction of the Hcrt peptide-receptor system. Lin et al 1999 reported an abnormality in the hypocretin receptor gene in narcoleptic dogs. Chemelli et al 1999 created constitutive knockout mice which lacked the Hcrt gene. These Hcrt knockout mice (-,-) had increased REM sleep along with cataplexy-like episodes that were entered directly from states of active movement. However these important studies left unanswered the question of where Hcrt acts to affect REM sleep and produce cataplexy. We have used a novel antisense technique to investigate this question. We created a 40 bp antisense against the Hcrt type II receptor RNA. We hypothesized that perfusion of the antisense, and consequent blocking of the Hcrt receptor gene expression, in specific brainstem sites would enable us to identify sites of action for Hcrt in control of REM and cataplexy regulation.

Methods: Adult male Sprague-Dawley rats were anesthetized for implantation of standard sleep recording electrodes and two bilateral guide cannulas for microdialysis. The guide cannulas were targeted towards various candidate brainstem sites, among them the LDT/PPT, LC , locus subcoeruleus, DRN, and pontine reticular formation (Paxinos and Watson rat brain atlas). After post-operative recovery, microdialysis probes (CMA-11; 2 mm length) were lowered through both the guide cannulas. After 12 hrs of probe-insertion recovery, the experiment was begun. Throughout the experimental procedures, the rats were freely behaving and were maintained with light (0700h to 1900 h) and dark (1900 to 0700 h) cycle. Food and water was provided ad libitum. In the most recent experiments, we have continuously monitored the animals via the Sony Night Shot video camera. The experimental protocol consisted of four days of treatment, each with electrographic recordings of behavioral state for 14 hrs (1000 h to 2400 h). The electrographic records were simultaneously digitized and recorded in a computer with Data Wave software. The protocol for each day of the experiment was: Control Day: Artificial CSF (ACSF) was continuously and bilaterally perfused for 5 hours (1000 h to 1500 h). Antisense Day 1 and 2: The protocol was the same as the ACSF day except that 20 µM of antisense to the Hcrt receptor II was perfused continuously for 5 hours (1000 h to 1500 h) instead of ACSF. Antisense Day 3: On the third day the antisense was perfused continuously for 3 hours (1000 h to 1300 h) instead of 5 hrs. Similar experiments were done with non-sense (an oligonucleotides with same 40 bp, but arranged randomly) Once the experiment was completed the animals were sacrificed, and the brains processed for histology. The electrographic data were classified into three different behavioral states: Wakefulness, non-REM sleep and REM sleep and scored separately for the light period and the dark period.

Results: Preliminary analysis of the electrographic data was carried out for two periods of 30 min during the light cycle and two 30 min periods during the dark cycle. For 3 animals maximal results were obtained on Antisense Day 2, when REM sleep in the dark (active) period increased about 3-fold while wakefulness decreased. The results indicate that the REM-enhancing effects of antisense were site-specific. Control studies of receptor non-sense perfusion showed no such effects. While final histological localization of the perfusion sites is still pending, there was sufficient variation in effect strength among the various sites to allow us to infer a site-specific effect. We also observed what appeared to be frequent cataplexy-like episodes in the Night Shot video. However, we need to analyze simultaneous electrographic and Night Shot recordings to be certain.

Conclusions: Brainstem perfusion of antisense to Hypocretin II receptor increases REM sleep. While more data are needed, these experiments point the way to determining sites of action of Hcrt on REM phenomena.

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1384.A

Oleamide and Andandamide Modulating Sleep Via Receptor

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Introduction: Devane et al reported the existence of a lipidic molecule, anandamide (ANA), that binds to the cannabinoid receptor. There are evidence in the literature that suggest that systemic and central administration of ANA causes hipomotility, hypothermia, impairs learning and memory processes. In our lab, we described that icv administrations of ANA increases Slow Wave Sleep 2 (SWS2) and Rapid Eye Movement Sleep (REMS) time while Wakefulness (W) and SWS1 remains decreased. In other hand, Cravatt et al described that a lipidic molecule was isolated from cerebrospinal fluid of sleep-deprived cats induces sleep in rats. This molecule was named oleamide (OLE), and in our lab we found that OLE caused a dose-dependent effect increasing SWS1 and SWS2 while W and REMS are abolished. Due that ANA and OLE share common effects after systemic and central administration and both lipids bind to the CB1 cannabinoid receptor, suggest that these lipids could be members of the endocannabinoid family. Many of the alterations caused by ANA and OLE are blockade using the antagonist cannabinoid receptor SR141716A.

Methods: In order to determinate if the alterations in sleep-wake cycle caused by administrations of ANA and OLE could be blocked using the SR1417156A, we carry out the following experiment. Forty Wistar male rats (280-320 g) were implanted with a standard set of electrodes for EEG/EMG recording and a cannula aimed to the lateral ventricle. Seven days after surgery, animals were habituated fot sleep recording sessions. Animals were assigned to 6 different groups: Control (n=10) received 5ul of ethanol (5%) in saline, ANA group (n=10) received 1.25ug/5ul of

vehicle, OLE group received 50ug/5ul of vehicle, SR141716A group (n=5) received 0.3 mg/kg ip of this antagonist. Two additional groups were formed, one group, SR141716A + ANA (n=5) received 0.3 mg/kg of SR141716A and 15 min later 1.25ug/5ul of ANA, the second group (n=5) followed the same methodological manipulation but after SR141716A administration, received 50ug/5ul of OLE.

Results: After administrations all animals were registered and we found that ANA induces an increase in SWS2 as well REMS while W was diminished. OLE caused a decrease in W as well REMS but increase time spent in SWS1 and SWS2. SR141716A induced a decrease in W and an increase in SWS1. Administration of SR141716A before of ANA administration blocked the increase in SWS2 and REMS caused by ANA. In other hand, SR141716A prevent the diminution of REMS as well as W and the increases in SWS1 and SWS2 caused by OLE.

Conclusions: We conclude that alterations in sleep-wake cycle caused by ANA and OLE could be mediated by cannabinoid receptors. This work was supported by Grant from DGAPA-UNAM IN209797 and CONACyT 25488N y 25128N given to OPG y LN.

1719.A

The Effect of a Nitric Oxide Synthase Inhibitor on Sleep: Importance of Time of Administration

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Introduction: Nitric oxide (NO) has been implicated in regulating sleep-wake activity. The effects of NO synthase (NOS) inhibitors depend on the dose and the circadian phase of the treatment. For example, high doses of NO-Nitro-L-Arginine methyl ester (L-NAME) decrease NREMS when injected during the light period, whereas NREMS and REMS are enhanced when L-NAME is administered at night (Ribeiro and Kapás, unpublished). The aim of the present study was to investigate if a low dose of a NOS inhibitor differentially affects sleep when given at light dark onset, and to test whether the effects are mediated by the vagus nerve.

Methods: Male Sprague-Dawley rats were implanted with EEG and EMG electrodes. The rats were kept on a 12:12 h light-dark cycle, light onset at 0600 h. Dark onset: On the control day, all rats received saline intraperitoneally (ip, 2 ml/kg), and sleep was recorded from the animals for 23 h starting at 1800 h (n = 8). On the experimental day, the animals received 5 mg/kg L-NAME at 1800 h. After the recording, bilateral subdiaphragmal vagotomy was performed on these animals. Four weeks later the vehicle and L-NAME treatment were repeated (n = 7). Light onset: Intact, non-vagotomized animals were injected ip at light onset with saline on the baseline day and 5 mg/kg L-NAME on the test day (0600 h, n = 14).

Results: Systemic injection of 5 mg/kg L-NAME at dark onset increased REMS amounts by 23.7 ± 3.5 min, approximately 70% above baseline across the dark period. NREMS was also elevated by 22.1 ± 3.6 minutes. Vagotomy did not block the REMS- or NREMS-promoting effects of L-NAME, in fact, REMS and NREMS amounts were still elevated by 31 ± 4.1 and 19.9 ± 7.8 min respectively. Slow-wave activity (SWA), a measure of NREMS intensity, was suppressed in both control and vagotomized rats. Light onset administration of the same dose of L-NAME did not affect NREMS or REMS amounts, or NREMS intensity (data not shown). Figure Legend: The effect of L-NAME at dark onset on the sleep of control and vagotomized rats. Open symbols: Baseline day. Solid symbols: L-NAME day. Solid bars: Dark periods. Asterisks: $p < 0.05$.

Figure 1

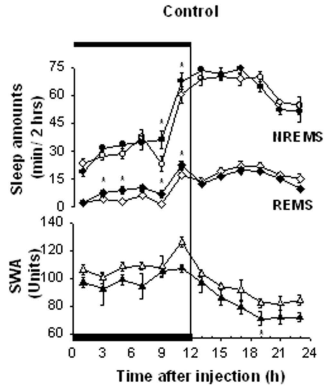
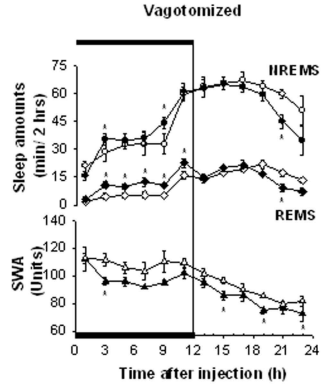


Figure 2



Conclusions: The effects of a low dose of L-NAME on sleep depend on time of administration. Systemic injection of 5 mg/kg L-NAME does not suppress brain NOS activity (Ayers et al.). Sleep increases in response to this low dose of L-NAME are likely peripherally mediated. The vagus nerve mediates the somnogenic effects of several experimental manipulations, e.g., LPS treatment (Kapás et al.). It is unlikely that the vagus plays a role in mediating the somnogenic actions of a low dose of L-NAME.

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1720.A

Conditioned Suppression of REM Sleep in Sprague-Dawley (S-D) and Wistar-Kyoto (WKY) Rats

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Introduction: Anxiety is implicated in disturbed sleep, but the exact

neural mechanisms involved, and the role they play, are poorly understood. Fear conditioning is thought to produce anticipatory anxiety (Davis, 1992) and thus could provide an animal model to begin studying how anxiety affects sleep. Differential responsivity to fear conditioning among strains could provide clues to the genetic bases of anxiety and its influence on sleep. To begin to test these hypotheses, we examined the effects of fear conditioning on sleep in a reactive rat strain (WKY) and in a less reactive strain (S-D).

Methods: Eight rats (4 S-D and 4 WKY) were implanted with EEG and EMG electrodes for determining behavioral state. After recovery from surgery, sleep was recorded under the following conditions: baseline, 4 successive days of fear conditioning in which the rats were presented with 15 light (CS) - shock (UCS) pairings (60 sec ISI), 3 days of exposure to the CS and training context alone (CS-TC; light and shock chamber, but no shock), and a final sleep recording-only day with no behavioral manipulation (SR). CS-TC and SR were separated by 7 days. Sleep was recorded for 6 hours on each day. Comparisons were based on three-hour (hours 1-3; hours 4-6) recording periods. Parameter examined were: sum (total minutes per hour); count (number of episodes per hour) and duration (average episode duration per hour) for wakefulness, NREM, transition and REM.

Results: Significant differences between strains were found during the conditioning phase (CS-UCS) of the experiment but not during the testing phase (CS-TC and SR). Immediately after fear conditioning (shock presented), REM (sum, count, duration) was significantly suppressed during hours 1-3 of recording in S-D but not WKY rats. In both strains, REM sum during hours 1-3 was suppressed on CS-TC days 2 and 3, and on the SR day. Minimal effects were seen in wakefulness, NREM and transition during hours 1-3 and no significant differences were found in any parameters for hours 4-6 of the recording period.

Conclusions: The results demonstrate that REM can be suppressed by the presentation of a CS associated with shock, suggesting that the anticipation of an aversive event can produce strong effects on sleep. Thus, fear conditioning may provide a valid model for examining the neurophysiological processes underlying the influence of anticipatory anxiety on sleep. Strain differences (decreased REM in S-Ds, but not WKYs) in response to shock suggest mechanisms that might explain seemingly conflicting results in the literature. Suppressed REM on the SR day could reflect second-order conditioning to handling or a prolonged alteration (Pynoos et al. 1996) in sleep and wakefulness. Further work will be aimed at refining fear conditioning procedures for application to sleep research.

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1735.A

Infusion of Thalidomide into the Third Ventricle but not in the Basal Forebrain Increased SWS and REM Sleep in the Rat

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Introduction: Thalidomide was first introduced as a hypnotic in the 1950s but was rapidly withdrawn from the market, after it was reported to have caused fetal malformations.[1] In 1998, thalidomide was approved as a drug for the treatment of leprosy and AIDS in USA.[2] This compound was found to modify the production of tumor necrosis factor (TNF) alpha in these patients.[2] Up to the present, there have been only a few reports evaluating the hypnotic effect of thalidomide in animals and human.[1,2] These reports indicated that thalidomide increased both REM sleep and SWS.[1,2] We also found that thalidomide increase the frequency of cataplexy, an abnormal REM sleep phenomenon, in narcoleptic dogs.[1] Although the sleep inducing effect of thalidomide was demonstrated,[1,2] its mode of action is totally unknown. Since this compound was reported not to bind to any of the receptors in the brain known to modulate sleep,[1] it is hypothesized that thalidomide affects sleep by modifying the somnogenic cytokines, such as TNF alpha.[1,2] TNF alpha was recently reported to increase SWS, when it was infused in the rostral basal forebrain, where prostaglandin D2-sensitive sleep-promoting zone had been defined.[3] To determine the site of action of the sleep-promoting effect of thalidomide, we infused this compound into two different locations in the brain of freely moving rats; i.e., the subarachnoid space of the rostral basal forebrain (BF) and the third ventricle (3V).

Methods: The rats were prepared for chronic recording of EEG, EOG and EMG. The interior of the experimental chambers was maintained on a 12-hr light / 12-hr dark cycle (lights on at 8 am). Thalidomide was diluted just before use in sterile physiological saline containing 2% DMSO. Thalidomide or vehicle was continuously administered at a rate of 0.2 nmol/min through chronically implanted cannulae for 6-hr during their active phase (from 23 pm to 5 am). The tip of the cannula was located in the subarachnoid space of the BF or the 3V. [3]

Results: During the infusion of thalidomide into the 3V, the total amount of SWS during the 6 h period was significantly increased by 20% from the vehicle condition ($p<.05$, n=8), and that of REM sleep was also significantly increased by 75% from the vehicle condition ($P<.05$, n=8). There was no effect when it was infused into the subarachnoid space of the BF (n=8).

Conclusions: We have previously reported that systemic administration of thalidomide significantly increased REM sleep and SWS in human and canine.[1,2] In this study, thalidomide increased sleep parameters when it was infused into 3V but not in the BF. However the effects were weak because the concentration was not increased due to poor solubility of this compound. The mode of action of this drug has not yet been clarified. Further investigation on the site of its action would give us more informations on the mechanism of sleep regulation.

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1404.A

The Absence of Penile Erections During Paradoxical Sleep-Like State Induced by Bicuculline Administration in the Pontine Tegmentum

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Introduction: Paradoxical sleep (PS) is characterized by a general muscle atonia, rapid eye movements, cortical activation, and penile erections. Our previous data suggest an essential role of the forebrain in PS erectile control since such erections are severely disrupted by rostral brainstem transections or lateral preoptic cytotoxic lesions (Schmidt et al., in press). Whereas the executive mechanisms of PS are located within the mesopontine tegmentum and rostral medulla, the brainstem control of forebrain PS erectile mechanisms remains to be explored. Iontophoretic bicuculline (GABA antagonist) administration into the dorsal caudal pontine subcoeruleus nucleus (SubCD) of head-restrained rats recently has been shown to induce a continuous PS-like state involving a muscle atonia and an increase in cortical theta activation (Boissard et al., 1999). These data suggest that the SubCD plays a role in the generation of these PS-related phenomena. The primary objective of these experiments was to determine if the SubCD also plays a role in PS erectile generation.

Methods: Three male rats were implanted for polygraphic recordings of cortical EEG, neck EMG, EOG, and corpus spongiosum of the penis (CSP) pressure for penile erection monitoring as previously described (Schmidt et al., 1999). Bicuculline was iontophoretically administered (25 mmol, 100 nA) into the pontine tegmentum through glass micropipettes in head-restrained rats. Immediately following multiple 15 minute trials of bicuculline administration, the anterograde tracer Phaseolus leucoagglutinin (PHAL) was iontophoretically ejected from a separate barrel of the micropipette assembly at the end of the experiment to localize the ejection site and to determine its efferent projections using classical immunohistochemical techniques.

Results: A continuous PS-like state was consistently induced throughout the bicuculline ejection period, characterized by a neck muscle atonia and an increase in cortical theta activity. Penile erections and rapid eye movements, however, were rarely observed during this PS-like state even though they were commonly seen during naturally occurring PS. Indeed, we found a mean of 14.7±1.8 erections per hour of spontaneous PS, but only 1.8±1.2 erections per hour during the PS-like state ($p<0.03$). An anatomical analysis revealed the ejection site to be the SubCD and demonstrated a strong projection to glycinergic neurons in the ventral gigantocellular reticular nucleus (GiV), a possible relay site in the control of muscle atonia. Similar projections were not observed, however, to structures implicated in erectile control such as the lateral preoptic region, hypothalamic paraventricular nucleus or the medullary nucleus paragigantocelularis (nPGi).

Conclusions: These data suggest that the SubCD plays an important role in PS-related muscle atonia and cortical theta activation, but not in the generation of PS-related erections or rapid eye movements. The neuroanatomic data further support our conclusion that the SubCD does not play a direct role in PS erectile generation since projections to structures implicated in erectile mechanisms were not found. In contrast, the strong projection observed from the SubCD to medullary glycinergic neurons in the GiV is consistent with the hypothesis that the SubCD plays a major role in PS-related muscle atonia. Further research is required to elucidate the brainstem control of PS-related erections and its functional link with forebrain PS erectile mechanisms.

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1406.A

Sleep and Circadian Control of Sleep Period Cardiac Activity

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Introduction: We have previously shown that central cardiac Sympathetic Nervous System (SNS) activity falls progressively over the sleep period, while Parasympathetic Nervous System (PNS) activity rises before normal sleep onset, peaks soon after sleep onset and then falls during the second half of sleep. We have suggested that this pattern occurs as a consequence of a sleep influence over the SNS and circadian system control over the PNS. The present study was designed to test this hypothesis. Cardiac activity was measured before and during normal sleep in two conditions. In one condition subjects went to sleep at their normal time, while in the second, sleep onset was delayed by 3 hours. It was hypothesised that sleep related changes in SNS activity would be delayed in accordance with the delay of sleep onset, while the sleep period variation in PNS activity, because it was controlled by the circadian system, would remain at the same clock position.

Methods: Six subjects were run in each condition on two occasions. For each recording session data collection began 2 hours before normal sleep onset and continued until morning awakening. Subjects maintained a supine position during this period. All 2 minute artefact free epochs were then identified throughout the entire recording session. Values were obtained for each epoch for each measure and the data binned into 30 minute intervals. The cardiac variables measured were: Heart Rate (HR); Blood Pressure (BP); Pre-Ejection Period (PEP) and the 0.1 hz peak, as measures of the SNS; and Respiratory Sinus Arhythmia (RSA), as a measure of the PNS.

Results: Contrary to our previous study (1) RSA, the measure of PNS activity, was not independent of sleep, such that in the delayed sleep onset condition the increase in RSA was significantly delayed ($p<.05$) until sleep onset occurred. Similarly, the measures of SNS activity (PEP and the 0.1 hz peak) were also primarily influenced by sleep (significant delay for 0.1 hz peak, $p<.05$), although PEP did indicate a significant reduction in SNS activity during the delayed sleep onset period ($p<.05$). HR and BP showed both sleep and circadian influences in a manner consistent with previous data.

Conclusions: In the present study the previously reported circadian

influence over the PNS was not confirmed. We tentatively conclude that if such an effect exists it is relatively weak, requiring constant routine methodology for it to be observed.

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1745.A

Dynamics of Sleep and Waking in a Large-scale Model of the Cat Thalamocortical System

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Introduction: A number of experimental studies have investigated spatial and temporal properties of neural activity patterns in the thalamocortical system during the sleep-waking cycle. In-vitro studies have revealed how intrinsic properties of thalamocortical and cortical neurons can produce burst- and tonic firing. These intrinsic properties combined with network interactions between thalamic and reticular neurons produce the firing patterns that characterize different arousal states. Large-scale computer models of the thalamocortical system can usefully complement in-vivo experiments in investigating anatomical and physiological factors that contribute to network dynamics by providing detailed access to the interactions among thousands of neurons in parallel. We have developed such a large-scale model to explore the dynamics of simulated activity patterns during conditions resembling spontaneous waking and sleep.

Methods: An anatomically realistic large-scale model of the cat thalamocortical system (~60,000 neurons and 5 million connections), previously used to investigate neural responses to visual stimuli (Lumer et al. 1997a, 1997b), was modified to incorporate experimentally observed intrinsic currents. The cellular properties of the model neurons were augmented by three additional ionic currents: a depolarizing cation current, commonly called Ih, a depolarizing Ca2+ current, called It, and a hyperpolarizing K+ current, called Ik+.

Results: The interplay of Ih and It caused thalamocortical cells to shift from a state of tonic firing (corresponding to waking) to a state of burst-pause firing (corresponding to the spindles and slow waves of sleep). As in physiological observations, this occurred when Ik+ was increased, mimicking the reduced depolarizing influence of modulatory diffuse ascending systems during sleep. These modifications at the single cell level resulted in global dynamics that resembled those observed with electroencephalography during different behavioral states. The spatial and temporal coherence of firing was analyzed by computing crosscorrelations between many individual neurons as well as population-averaged activities of groups of neurons. During slow-wave and spindle sleep spatiotemporal coherence was high, with the crosscorrelations showing essentially zero phase lag as well as infinite correlation length in their maxima. Random permutation tests, used to compare the network with intact and lesioned network pathways, show that the cortex and reticular thalamic nucleus are both important in maintaining synchronous oscillations. Corticothalamic projections onto thalamic interneurons also contribute significantly to the maintenance of synchronous activity. Finally, presentation of simulated visual stimuli in different arousal states demonstrate that, although excitation from the periphery can still influence cortical firing, the specificity of neural responses is considerably reduced during sleep.

Conclusions: A large-scale computer model of the cat thalamocortical system was used to investigate anatomical and physiological factors influencing the dynamics of neural activity in different arousal states.

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1096.B

Cardiac Autonomic Nervous System Activity Is Not Related To Slow Wave Activity During Normal Sleep In Humans.

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Introduction: The two branches of the cardiac autonomic nervous system may be differentially influenced by the circadian system and sleep.[1] Cardiac sympathetic activity, measured with pre-ejection period (PEP), is mainly influenced by sleep – changing after sleep onset. In contrast, cardiac parasympathetic activity, measured with respiratory sinus arrhythmia (RSA), shows a 24 hour variation during constant wakefulness. While earlier work found no systematic relationship between heart rate and slow wave activity (SWA) during normal sleep,[2] the two autonomic systems may show different relationships with the cyclical alterations in SWA. This study aimed to investigate the relationship between SWA and noninvasive measures of the two branches of the cardiac autonomic systems during normal sleep.

Methods: Four male and four female subjects (23.0 ± 2.1 (SD) yrs), of average BMI (23.6 ± 3.3 kg/m2) participated. Each subject maintained a constant sleep-wake schedule for a week (verified by actigraph recordings), before at least one adaptation night. Following this, each subject participated in the experimental night, during which each subject was in bed with lights out at their normal sleep onset time and slept until their normal wake time. Standard polysomnography (C3-A2) and temperature recordings were made, producing the following variables for each 30 second epoch: SWA (0.33-3.0 Hz/mV), core and peripheral temperature. Impedance cardiography was also employed to produce heart rate, PEP, and the root mean squared successive differences (RMSSD) between the R waves in the ECG. (RMSSD was used as RSA cannot be calculated reliably for periods shorter than 2 minutes).

Results: As found previously,[2] heart rate did not systematically alter with the oscillations in SWA during sleep (average Pearson r = 0.26). RMSSD and PEP also did not show any systematic linear variation with SWA (average Pearson r = -0.19, and r = -0.22 respectively). The direction of all of these correlations is due to the progressive changes in these variables across the sleep period; SWA ($F(5,35)=12.66$, $p=0.001$) and HR ($F(5,35)=3.17$, $p=0.018$) decreased and PEP increased ($F(5,35)=5.57$, $p=0.001$). The pattern in HR and PEP was similar to changes reported previously in stage 2 NREM sleep.[3] RMSSD did not show a linear increase or decrease ($F(5,35)=1.59$, $p=0.19$).

Conclusions: Changes in cardiac parasympathetic and sympathetic

activity do not appear to be driven by the same processes producing the cyclical variation in SWA. Instead, the general downregulation of cardiac activity across the sleep period is likely to be due to a circadian influence and / or consolidated sleep. We are currently analysing the temperature data, NREM-REM transitions and collecting more data.

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1752.A

Cocaine Sensitization Versus Tolerance

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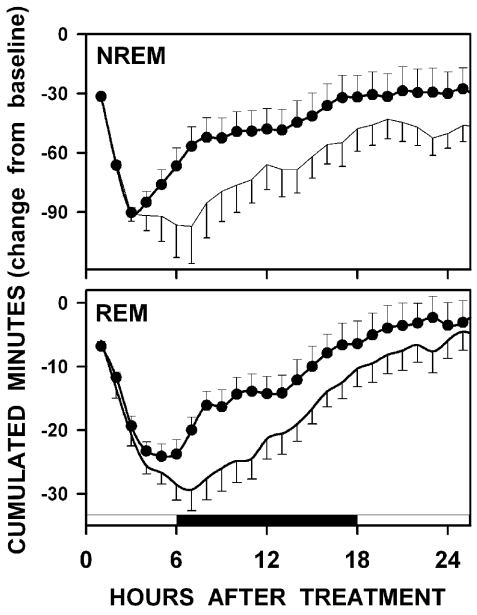
Introduction: Cocaine and other dopamine reuptake blockers are followed by less recovery of NREM sleep than similarly potent doses of other classes of stimulants (Seidel & Edgar, 1998). Our studies of these compounds, however, typically involve repeated administration of varying doses to the same animals, in all cases separated by at least 1 week. We are thus concerned that tolerance may develop, despite the "washout" interval; or sensitization, because a single cocaine exposure has been reported to sensitize animals to the behavioral effect of subsequent cocaine administration for up to one week (Zahniser et al. 1988).

Methods: Adult male Wistar rats (N=13) were surgically prepared with a cranial implant that permitted chronic EEG and EMG recording, and with a miniature transmitter in the abdomen for monitoring body temperature and locomotor activity. Sleep-wake states were discriminated using SCORE,TM an on-line sleep-scoring system validated for rodents, which also collected the concurrent telemetry data. Animals entrained to LD 12:12 lived continuously in separate chambers and were injected i.p. (1 ml/kg) 5 h after lights-on with 10 mg/kg cocaine (Sigma) dissolved in sterile 0.25% methylcellulose (Upjohn) once per week for two consecutive weeks. Hourly group means for all variables were computed for 30 hours before and after treatment. In addition, for each hour post-treatment, the change-from-baseline value for NREM sleep was computed, the baseline value being the minutes of NREM during the same circadian time 24 hours earlier. This change-from-baseline value was cumulated for each hour post-treatment. The "maximum NREM deficit" was defined as the most-negative point on the cumulation curve. REM sleep was similarly analyzed.

Results: The NREM deficit after week 1 treatment was -90 ± 2 minutes 3 hours after treatment, but the maximum deficit was reached 7 hours post-treatment and was -97 ± 18 minutes. After the week 2 treatment, the maximum NREM deficit was -90 ± 2 minutes 3 hours after treatment. Variance was greater following treatment during week 1 compared to week 2. Similar trends (that is, longer duration of effect after week 1 than after week 2) were observed for REM sleep, for average duration of uninterrupted bouts of both wake and sleep. Recovery of the "lost NREM sleep" by the end of 24 hours post-treatment did not significantly differ from week 1 to week 2 (-46 ± 8 versus -27 ± 11 minutes, respectively, N=13, P > 0.1). Locomotor activity, body temperature, drinking) showed no significant differences when comparing treatments after week 1 and week 2.

Figure 1. Cumulative deficits in NREM and REM sleep: cocaine 20 mg/kg after the first (light line) and second acute dose (heavy line) separated by 1 week.



Conclusions: A single dose of 20 mg/kg cocaine i.p. in rats does not significantly alter their response to a single dose of 20 mg/kg one week later. The trends in the data were more suggestive of tolerance than sensitization, but the differences in any event did not approach statistical significance.Figure 1. [revised caption]Cumulative deficits in NREM and REM sleep: cocaine 20 mg/kg after the first (light line) and second acute dose (heavy line) separated by 1 week.

References:
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1099.A

Temporal Relationships Between Sleep Spindles and K-complexes

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Introduction: There are suggestions of both excitatory and inhibitory functions for K-complexes and sleep spindles (Pivik et al 1999). The temporal relationships expressed in the spontaneous occurrence of these events is relevant to these considerations and were the focus of this investigation.

Methods: Normal male subjects including 6 children (5-7 years old), 18 preadolescents (8-12 years old), 10 adolescents (13-16 years old), and 10 adults (20-25 years old) were used in this study. Stage 2 recordings (C3/M2) from the second of two consecutive adaptation nights were scored for spindles (14-16 Hz, ≥ 0.5 second waveforms with ≥ 3 oscil-

lations ≥ 20 mμ for 5-12 year-olds and ≥ 25 mμ for 13-25 year-olds [de Maertelaer et al 1987; Goetz et al 1983]) and K-complexes (≥ 75 mμ, ≥ 0.5 second waveforms with an initial negative spike followed by a slower positive component). Three-minute, artifact-free periods distributed equally across the night (32%, 1st third; 33.2%, 2nd third; 34.8% 3rd third) were analyzed in three-second bins with waveform onset determining bin allocation. Scoring categories, using spindle onset as the point of reference, were *Isolated*: no K-complex in the previous, same or subsequent bin, *Onset-pre, no overlap*: spindle onset precedes and does not overlap with K-complex onset, *Onset-pre, overlap*: as in the previous category but with overlap, *Onset during*: spindle onset during K-complex and *Onset-post*: spindle onset after K-complex ends. Two-rater reliability was 89% for spindles and 94% for K-complexes.

Table 1. Descriptive data (% and frequencies) by subject group and scoring category

Group	Three Minute Periods	Onset Pre, no overlap	Onset Pre, overlap	Onset During	Onset Post	Isolated
5-7	50	24.7% (82)	14.8% (49)	7.5% (25)	19.6% (65)	33.4% (111)
10-12	121	20.5% (243)	9.8% (116)	10.5% (125)	16.2% (192)	43.1% (511)
13-16	70	18.8% (177)	11.6% (109)	11.7% (110)	15.4% (145)	42.6% (402)
20-25	56	15.8% (47)	7.7% (23)	9.4% (28)	11.4% (34)	55.7% (166)

Results: There were significant decreasing linear trends with increasing age for *no overlap* ($p < .01$) and *onset post* ($p < .01$) categories (Table 1). *Onset pre, overlap* showed a decreasing curvilinear trend ($p < .05$) and *isolated* events increased in a significant curvilinear fashion ($p < .01$) with age. For all groups spindles and K-complexes were most likely to occur independently ($p < .02$).

Conclusions: Spindles and K-complexes did not generally occur in close temporal contiguity during the childhood-young adulthood developmental period. These results are consistent with opposing rather than complimentary functions for these events.

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1102.A

Sleep Spindle in Human Prefrontal Cortex

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Introduction: The generation mechanism of sleep spindle has been well established in animals. The reticular thalamic nucleus (RT) is the generator of sleep spindles, and the activities are conducted to thalamocortical neurons and subsequently to the cortex. In humans, two variations of sleep spindle were well known, one is about 14 Hz appearing centro-parietal region and the other is about 12 Hz appearing frontal region. In surface EEG studies, the 12 Hz frontal spindles increase the frequency in early childhood. However, they showed the largest power in the infants (about 5 years old), and rapidly decrease their power in the first decade of life.[1] The changes of frontal spindle characteristics are important to observe maturation of central nervous system, namely thalamocortical systems. To investigate human sleep spindle distributions and their characteristics in the cortex, we examined natural sleep ECoG of epileptic patients with subdural electrodes in the prefrontal cortex.

Methods: Subjects were eight epileptic patients (seven male and one female, 20-35 (average 30.4) y/o) with cortical electrodes attached on the orbitofrontal cortex for a clinical purpose to evaluate indication of neurosurgical treatment of epilepsy. One case was also attached on the frontal eye field (area 8) and the anterior cingulate cortex. In addition to ECoG, a Cz-A1 scalp electroencephalogram (EEG), an oblique electro-oculogram (EOG) and a chin electromyogram (EMG) were recorded to monitor consciousness state and to score sleep stages. For ECoG and EEG, a 0.5 Hz low cut filter and a 3000 Hz high cut filter were used, but a 50 Hz hum filter was not used. For sixty 2048 point (2.73 sec) epochs of the third or fourth NREM periods (mainly stage 2 sleep), Fast Fourier transformation (FFT) was performed on singals from OFC and surface Cz. Power spectra of all cases were examined in sigma band (12-16 Hz). This protocol was approved by the local ethics committee. A written informed consent was obtained from each patient.

Results: Average peak frequency in Cz EEG power spectra of all the cases was 13.6 Hz in sigma band. Seven of eight cases indicated the peak in sigma frequency band in orbitofrontal cortex ECoG. Average peak frequency in orbitofrontal ECoG power spectra of the seven cases was 11.8 Hz (ranged from 11.0 to 12.1 Hz). The same sigma peak as in the orbitofrontal cortex was also observed on the frontal eye field and the anterior cingulate cortex.

Conclusions: In this study, the peaks showed in the ECoG spectrum of human prefrontal cortex were approximately 12Hz. It was reported that thalamic projections to the prefrontal cortex were mainly from mediodorsal nucleus (MD).[2] The facts that prefrontal cortical area receiving fibers from MD manifested 12 Hz spindling and their changes across age are of further interest.

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1767.A

Localization of the Dopamine Transporter (DAT) in the Thalamus and Hypothalamus of the Human and Non-Human Primate.

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Introduction: Dopamine has an under-recognized and poorly defined role in modulating the wake/sleep cycle. With the increasing realization that: 1) dopamine deficient states are characterized by deficient arousal; and 2) that the alerting properties of several drugs correlate best with their ability to bind to the dopamine transporter (DAT) (Nishino, Mao, Sampathkumaran, Shelton, and Mignot, 1998), there is compelling need to precisely delineate those neural substrates underlying the connection between dopamine and sleep/wake architecture. The thalamus and hypothalamus represent brain regions where dopamine may modulate normal and pathological sleep/wake patterns.

Methods: Immunohistochemical staining for DAT was studied in five human brains and three rhesus monkey (maccaca mulatta) brains. Adjacent series of sections were processed for: a) tyrosine hydroxylase (TH) immunoreactivity; b) acetylcholinesterase (AChE) histochemsitry; and c) orexin A and B immunoreactivities (antibodies Santa Cruz Biotechnology, Inc.). Particular attention was payed to mapping the specificity of DAT within thalamic and hypothalamic subnuclei with reference to maps of thalamic AChE staining (Hirai and Jones 1989) and delineation of hypothalamic nuclei as presented by Saper (1990).

Results: The thalamic reticular nucleus and the so-called nonspecific midline nuclei demonstrated the most dense DAT terminal staining. Moderate densities of immunoreactive terminals were seen in the pallidal recipient zones of the ventroanterior/lateral nuclei, and limbic related nuclei such as the mediodorsal, periventricular, and anterioventral nuclei. Staining in the principal sensory nuclei was sparse to undetectable. The hypothalamus also showed regional specificity of dopamine innervation with the densest innervation being in the paraventricular nucleus and a very dense specific concentration corresponding to areas of orexin positive cells. Moderate staining was seen in the lateral tuberal nucleus. The tuberomammillary nucleus showed light staining. The dorsomedial nucleus and mammillary bodies were devoid of DAT immunoreactivity.

Conclusions: The specific subnuclei that receive dopamine innervation in the thalamus and hypothalamus are important in the modulation of wake/sleep cycles. Dopamine modulation of state can occur in one of two ways. First, "direct" pathways in which dopaminergic terminals innervate nuclei known to directly affect cortical activity; for example, innervation from A8 and A10 to the nucleus basalis of meynert (NBM) which diffusely innervates the cerebral cortex. The other, best described as "indirect", include dopaminergic pathways that innervate nuclei that in turn project to state related nuclei; for example, the innervation of the orexin cells which, in turn, modulate multiple components of the "ascending reticular activating system" (viz., dorsal raphe, pedunculopontine tegmental nucleus, and locus coeruleus). These results need to be considered in light of the distribution of different dopamine subtype receptors (e.g., the pharmacologically defined D1-like or D2-like, and D1-D5 molecularly defined subtypes), since each display different affinities for dopamine, unique second messenger responses, and most importantly, differential expression in different neural subpopulations.

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1123.A

Long-term EEG/EMG Monitoring in Mice: A Minimally Restrictive Approach

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Introduction: Our recent demonstration of sleep-onset REM (SOREM) periods in orexin (-/-) mice necessitated the development of a minimally restrictive technique to record EEG/EMG. Although video monitoring had shown that these mice demonstrated attacks while untethered, no SOREMs were revealed during initial EEG/EMG recording, probably because the cable resistance was sufficient to awaken the mouse immediately at REM sleep onset. Here we describe details of this recording technique.

Methods: The EEG/EMG implant was based on a six-pin double in-line PC board-mount breakaway connector. The connector was modified to form four EEG electrodes, each 1.3 mm × 0.3 mm (h × w) positioned 4.6 mm × 2.9 mm (l × w). Two EMG electrodes were soldered to the center pins and all contacts were gold plated after assembly. Male mice (14–15 weeks old, 30–35 g at the time of surgery) were anesthetized with sodium pentobarbital (Nembutal, 50-60 mg/kg ip) and held in a stereotaxic frame. The cranium was exposed and four burr holes were drilled, anterior and posterior to bregma, bilaterally (AP 1.1, ML ±1.45 and AP -3.5, ML ±1.45). The implant was then stereotactically inserted into these holes, held in place and cemented to the skull with a quick-drying glass ionomer dental cement (ESPE, Norristown, PA; Ketac-Cem Aplicap). The EMG electrodes were secured to the nuchal musculature. This design for the EEG/EMG implant allowed precise insertion of electrodes, targeting the frontal and occipital cortices at a consistent depth, just touching the dura, while minimizing surgical trauma. Immediately after recovery from anesthesia, the mouse was housed individually and the head-mounted connector was coupled, via a 15 cm light weight cable, to a telephone handset swivel which served as a slip ring commutator. The cable was made from Teflon-insulated multi-strand wire (Cooner Wire, Chatsworth, CA: #A5633) threaded through PE120 tubing. The commutator assembly was suspended from a counter-balanced arm (Instech Laboratories, Plymouth Meeting, PA; #MCLA) mounted to the side of a standard cage to allow complete freedom of movement. Food and water were available ad libitum throughout the experiment. All mice were habituated to these conditions for a minimum of 14 days before recording. Mice then remained cabled and 24 h EEG/EMG signals were recorded intermittently to check the long-term integrity and viability of the recording system over several months.

Results: When compared with data from the first recording periods, wild-type mice showed long-term reductions in the duration of nonREM and wakefulness episodes, particularly during the dark period, as sleep became more fragmented. This was associated with increased time spent in both REM and nonREM sleep during the dark period. In contrast, orexin (-/-) mice showed only a trend towards increased sleep fragmentation during the dark period without consistent long-term changes in sleep state times.

Conclusions: This technique has proved effective at revealing the presence of SOREM periods in orexin (-/-) mice. Prolonged cabling and recording of mice over periods as long as several months has also demonstrated the integrity of the system and its adaptability to studies in which prolonged mouse EEG/EMG monitoring is required.

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1126.A

EEG Theta Oscillations Observed From Subdural Electrodes in the Anterior Cingulate Cortex

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Introduction: In previous studies we found gamma and beta-1 oscillations in recordings from the medial temporal lobe (MTL) using subdural electrodes.[1,2] Simultaneous recordings from scalp electrodes did not show these oscillations. Thus, we have continued to record cortical activities directly during wakefulness and sleep. A recent case with electrodes attached to the anterior cingulate cortex demonstrated regular theta oscillations.

Methods: The subject was a thirty-five year old male suffering from partial epilepsy. His first epileptic event included abnormal behavior and generalized seizure accompanying a high fever (40 degrees C) when he was 14 year old. The seizure was poorly controlled by medication, and he has since been admitted to hospitals in status epilepticus on several occasions. He was recently referred to the department of neurosurgery for possible surgical treatment of his epilepsy. Subdural electrodes were surgically attached to the MTL, but failed to detect an epileptic focus. An all-night sleep recording was made from standard scalp placements while MTL activity was monitored. Two months later, subdural electrodes were placed on orbitofrontal and anterior cingulate cortex sites and all night sleep recording was made. Both all-night recordings were made approximately one week after electrode placement surgery, when the patient demonstrated he could perform daily hospital activities. In addition to the subdural electrocorticogram (ECoG), a simultaneous surface electroencephalogram (EEG) from the vertex (Cz), an oblique electrooculogram (EOG), and a chin electromyogram (EMG) were recorded. All signals were recorded on a digital tape recorder and later downloaded to a computer for further analysis. Sleep stages were scored using the Cz EEG, EOG and EMG, following standard criteria.This protocol was approved by the Tokyo Institute of Psychiatry's ethics committee.

Results: In the first recording, gamma and beta-1 oscillations were observed in the MTL as we have previously reported for other patients.[1,2] In the ECoG signal from anterior cingulate cortex, a very regular and continuous theta (about 6 Hz) oscillation was observed during wakefulness and REM sleep, but not during NREM sleep. However, during wakefulness the simultaneously recorded Cz EEG showed a regular alpha rhythm. Therefore, we conclude that the theta rhythm in the anterior cingulate was independent from the EEG alpha rhythm. Although not simultaneously recorded, the same subject also showed beta-1 oscillations in the MTL. Therefore, the theta oscillation is also very likely to be independent from beta-1 oscillations in the MTL.

Conclusions: Although there have been no extensive reports of hippocampal theta oscillations in humans or other primates, theta band power is known to change during task performance and across consciousness states in humans. These changes are believed to be related to hippocampal theta (or rhythmic slow activity, RSA) observed in some other mammals. The present results indicate these changes may reflect changes observable in the anterior cingulate cortex.

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1453.A

Temporal Relationship Between Nocturnal Erections and REM Sleep in Healthy Men

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Introduction: Nocturnal erections are a well-known phenomenon in healthy men. The registration of nocturnal erections is an important tool in the diagnosis of erectile dysfunction. However, applications up to now predominantly have assessed erectile events without consideration of the corresponding sleep profile. Therefore, in the present paper, the temporal relationship between erectile events and REM episodes was investigated.

Methods: 24 healthy male volunteers, 26-56 years old, participated in the study. Subjects suffering from sleep disturbances or sexual dysfunctions were excluded. Each subject spent 3 successive nights in the sleep laboratory. After an adaptation night two polysomnographies with registration of EEG, EOG and submental EMG were performed over 8 hours for each subject. In addition, nocturnal penile tumescence and rigidity were measured applying the Rigiscan device (Dacomed Corp., USA). Due to technical manipulation, the data digitally stored in the Rigiscan were converted on-line to analog signals; thus, exact synchronization with the sleep EEG was guaranteed. As an inclusion criterion, all subjects revealed normal nocturnal erections regarding peak tumescence and peak rigidity values. Sleep EEG were scored visually according to the criteria of Rechtschaffen and Kales.

Results: On average, 4.5 ± 1.1 erections occurred per night, where 88.7% were associated with REM episodes. The mean duration of the erections (29.4 ± 14.7 min) was longer compared to the REM episodes (23.6 ± 12.3 min). Regarding the temporal relationship, a large variability was observed: Erections started before as well as after the beginning of the REM episodes. The relative temporal overlap between erections and REM episodes was 0.58 ± 0.27. On average, erections started with a latency of 3.8 ± 6.8 min after the beginning of the REM episodes. A regression analysis considering all erectile events and REM episodes registered in the study group revealed a significant decrease of the latency in the course of the night.

Conclusions: In accordance with previous reports, a close association of erectile events with REM sleep was found. On average, erections started a few minutes after the beginning of REM episodes. The latency between REM episodes and erections revealed dynamic properties with a significant decrease during the night. This indicates different mechanisms regarding central control of REM sleep and nocturnal erections. This is consistent with former findings of a dissociation of nocturnal erections and REM sleep regarding penile tumescence under the influence of antidepressive drugs (e.g. Steiger et al 1987) as well as in depressive patients (Thase et al 1992). Assessment of the temporal coupling between nocturnal erections and REM sleep reveals a further biological parameter for the investigation of psychiatric disorders and the influence of psychotropic drugs.

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1131.A

Non-Linear EEG Measures During Cyclic Alternating Pattern (CAP) and NonCAP Sleep

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Introduction: A number of papers has shown a decrease in correlation dimension (D2) as sleep moves towards slow-wave stages with values for REM sleep lying between those for sleep stages 1 and 2. The nonlinear structure of the sleep EEG has mostly been investigated by means of the widely known algorithm by Grassberger and Procaccia (1983). It is also well known that this kind of approach assumes stationarity of data and needs relatively large time series in order to provide reliable results (Theiler 1986). It appears rather difficult to satisfy these criteria for at least a large proportion of the sleep EEG which contains a great amount of nonstationarities, such as sleep spindles, K-complexes, vertex waves, short-lasting arousals, etc. It is also well known that there exists a peculiar organization of phasic events during sleep, connected with fluctuations in arousal level, which has been called "cyclic alternating pattern" or CAP (Terzano et al. 1988). For all these reasons, we decided to study the nonlinear aspects of sleep EEG taking into account the peculiar organization of these phasic events.

Methods: Height healthy subjects aged 18-20 years participated to this study. Polysomnography was performed in all of them, signals were sampled at 128 Hz and stored on hard disk; the C3 or C4 derivation was used for all the subsequent computational steps, which were performed on EEG epochs (4096 data points) selected from sleep stage 2 (S2) and slow-wave sleep (SWS), in both CAP and nonCAP conditions. The dynamical properties of the EEG were assessed by means of the NLCP test recently introduced by Stam et al. (1998). This test uses 3 different "model" time series in order to predict nonlinearly the original data set. The first is the original data set itself, the second is an amplitude inverted copy of the original time series, and the third is a time reversed copy. With this test it is possible to reject the null hypothesis that the original time series is linearly filtered white noise, when predictability using the amplitude inverted copy (AMA) is worse than that using the original data set (PRED). Moreover, when predictability using the time reversed model (TIR) is worse than that of the original model itself, also the hypothesis that the time series represents a static, nonlinear transform of an underlying linearly filtered white noise can be rejected.

Table 1

	S2-nonCAP mean±S.D.	S2-CAP mean±S.D.	Wilcoxon p=	SWS-nonCAP mean±S.D.	SWS-CAP mean±S.D.	Wilcoxon p=
PRED	52.77±11.07	87.80±19.85	0.018	88.29±26.42	97.94±13.45	NS
AMA	-0.13±4.24	11.94±6.34	0.012	-0.75±7.39	6.58±5.83	0.018
TIR	0.25±4.79	8.02±11.27	N S	3.01±5.45	6.75±5.88	NS

Conclusions: Based on the results of this study, sleep might be considered as a physiological dynamically evolving sequence of different high/low dimensional states of the EEG, which we could track by detecting nonlinearity mostly in correspondence with CAP sequences. Our results clearly show that the occurrence of phasic events, in form of signal nonstationarities, often induces the appearance of detectable nonlinearity in the EEG; thus, CAP might be considered as a state with short periods of low-dimensional nonlinearity which interrupt a baseline EEG not distinguishable from high-dimensional noise (NCAP). CAP rate has already been shown to be a reliable index of microstructural sleep disruption in a series of sleep and neurological disorders; for this reason we think that, in the future, the nonlinear analysis of the EEG might be used as a quantitative computer-aided tool for the study of sleep disruption in different clinical conditions.

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1786.A

The Effect of 192-Saporin Lesion on A1 Adenosine Receptor mRNA Levels in the Basal Forebrain

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Introduction: An accumulating body of evidence supports a role for adenosine as a mediator of sleep-wakefulness. In particular, previous studies have shown that cholinergic neurons of the pons are under the tonic inhibitory control of adenosine (Rainnie et al, 1994). In addition, adenosine levels in the basal forebrain increase after spontaneous waking and prolonged wakefulness (Porkka-Heiskanen et al., 1997). While adenosine mediates its effects via binding to several adenosine receptor subtypes, the A-1A receptor subtype predominates in the basal forebrain region (Dixon et al., 1996). The adenosine inhibition of acetylcholine release may take place via adenosine A1A receptors located on cholinergic cells in the basal forebrain. To test this hypothesis, we selectively lesioned basal forebrain cholinergic cells using 192-saporin.

Methods: 192-saporin (4 ug/ul, TV=1 ul) was administered ICV into adult male Sprague Dawley rats (~300 g). Two weeks after the 192-saporin injection, the rats were deeply anesthetized with Nembutal, then perfused with DEPC-saline followed by formaldehyde. Brain sections were cut (~30 um) and either mounted for in situ hybridization or processed for histochemistry/immunohistochemistry. Control animals were either injected with saline or were untreated.

Results: ChAT immunoreactive cells in the basal forebrain were virtually eliminated by treatment with 192-saporin compared to saline injected controls. In contrast, A-1 mRNA was present in 192-saporin as well as saline-treated and untreated controls.

Conclusions: The findings raise the possibility that the inhibitory effect of adenosine on acetylcholine release may not be a direct effect on cholinergic cells, but may occur indirectly via an effect on A-1 receptors located on non-cholinergic cells.

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1470.A

State-dependent Uncoupling of Hypothalamic Thermoregulatory Responses by Selective Brain Cooling

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Introduction: Selective cooling of the brain is achieved in the cat by thermally conditioning the carotid blood prior to its entering the circle of Willis (Hayward and Baker 1969). Therefore, a temperature difference exists between the vertebral blood (systemic cooling only) and the carotid blood (both systemic and selective cooling), which is determined by the heat loss from the carotid rete. In its turn, the latter heat loss depends on the temperature of the venous blood returning from the systemic heat exchangers of the head. The difference between pontine temperature and hypothalamic temperature is a quantitative indicator of selective brain cooling (Parmeggiani et al 1998). The present study was carried out to clarify the functional significance of selective brain cooling during quiet wakefulness (QW) and NREM sleep, the behavioral states characterized by homeothermic regulation (Parmeggiani 1980).

Methods: The animals (2 cats) were implanted under anesthesia (clonazepam 0.5 mg/kg i.m.; sodium pentobarbital 40 mg/kg i.p.) with EEG and EMG electrodes and transducers (Yellow Springs thermistors) that measured hypothalamic (anterior hypothalamic area), pontine (tegmental field of the upper pons) and ear pinna (indicator of systemic heat loss) temperatures. A Grass polygraph was used to record the variables under study. The experiments lasted 6±1 h at 24±1\degC ambient temperature in a sound attenuated box. The range of spontaneous changes in ear pinna vasomotion throughout wakefulness and sleep was expanded by exposing the abdominal wall to neutral (27±1\degC) and warm (37±1\degC) temperature by means of a water-perfused radiator. The animals were sacrificed by means of sodium pentobarbital and histological sections of the brain (fixed in formalin, embedded in celloidin, stained with the Nissl method) were prepared for control of thermistor locations. Values of the recorded variables, measured just before the end of each behavioral state' of the ultradian wake-sleep cycle, were analyzed.

Results: The difference between pontine temperature and hypothalamic temperature, the quantitative indicator of selective brain cooling, is decreased during QW (<0.1\degC) and increased during NREM sleep (>O.1\degC). Such changes result primarily from parallel changes in systemic heat loss that secondarily affect selective brain cooling. Hypothalamic and pontine temperatures show a negative and a positive correlation, respectively, with systemic heat loss. The positive correlation of pontine temperature, an indicator of extra-hypothalamic core temperature, with systemic heat loss shows that an extra-hypothalamic thermal error signal for vasomotion affecting extra-hypothalamic thermoreceptors maintains the state-dependent influence of selective brain cooling on hypothalamic thermoreception.

Conclusions: Within the ambient thermal zone for vasomotor regulation of core temperature behavioral state-dependent changes in selective brain cooling differentiate the relative functional weights of hypothalamic and extra-hypothalamic thermoreceptor influences on the thermoregulatory system. On this basis, selective brain cooling may underlie a thermal feedback uncoupling vasomotion from metabolic heat production (shivering and brown fat thermogenesis) during QW and from evaporative heat loss (thermal tachypnea and panting) during NREM sleep.

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1801.A

The Effects of Excitotoxic Lesions of the Pontine REM-Induction Area (PRiA) and Ventral Tegmental Nucleus of Gudden (VTg) on Behavioral State in Rats.

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Introduction: The pons is essential in modulating behavioral state, especially rapid eye movement sleep (REMS). The PRiA, the area most sensitive to REMS induction by cholinergic agonists, lies just ventrolateral to the VTg. Acetylcholine, GABA, and glutamate can modulate REMS in this area. The VTg is a GABAergic projection nucleus receiving glutamatergic and cholinergic inputs. Its topography and chemoarchitecture relative to the physiologically defined PRiA suggest it may modulate REMS. Previous work showed that VTg lesions can induce hyperactivity, but the electrolytic lesions destroyed both cell bodies and fibers of passage.[1] In this study we elucidated the effects of fiber-sparing lesions of the VTg and PRiA on behavioral state control, with emphasis on REMS modulation.

Methods: Five male Sprague-Dawley rats (275-350g) were implanted with electrodes to record behavioral state, and a cannula inserted at the VTg or adjacent control region. After recovery animals were placed in individual recording chambers, where 3-4 days of continuous baseline polysomnographic recordings were made. Animals were then injected via cannula with carbachol (CARB, 40 ng/200 nl) during early afternoon and recorded for 2h. Then a kainate lesion was made in the target region, and the rats recorded continuously 3-4 days postlesion. Animals were then sacrificed and the brains fixed, cut, and stained to delineate cannula placement and extent of lesion as assessed by gliosis and cell loss. Behavioral state was scored in 20s epochs using the SCORE software and t-tests performed comparing pre- and post-lesion percentages of REMS, wakefulness (W), slow-wave sleep (SWS), and quiet wakefulness (Q).

Results: The results are summarized in Tables 1 and 2. Significant differences (*) are at p<.05 for a 2-tailed Student's t-test between pre- and post-lesion. Abbreviations: DR = Dorsal Raphe; PRF = Pontine Reticular Formation; CG = Central Gray

Table 1. Lesion Sites

CASE	Extent of Lesion
Som5	VTg, some DR, dorsal PRF
Som9	dorsomedial PRF
Som11	ventromedial and medial PRF
Som12	medial pontine CG, rostral medullary CG
Som13	half of DR, medial pontine CG

Table 2. Behavioral State Changes as Percent of Total Recording Time

CASE	% REM Pre/Post	% WAKE Pre/Post	% SWS Pre/Post	% Q Pre/Post
Som5	12.9/19.3	31.2/30.6	51.4/43.7	4.6/6.4
Som9	**12.7/4.9***	31.1/37.6	47.6/53.1	**8.6/4.4***
Som11	**10.8/4.7***	45.2/63.8	41.4/29.4	2.6/2.1
Som12	14.9/16.9	58/56.8	23.1/21	4.2/5.3
Som13	**4.5/19.4***	46.8/51.9	**42.6/23.9***	6.1/4.9

Conclusions: The case in which the VTg itself was lesioned coincident with minor DR involvement showed a trend towards increased REMS at the expense of SWS. Lesions of the DR increased REMS at the expense of SWS, as seen in Som13. This effect could not be attributed to CG damage, as Som12 had extensive CG damage with no effect on behavioral state. The two PRF-lesioned animals both demonstrated significant reductions in REMS, consistent with previous work.[2] CARB injections in all animals induced active W, and in the PRF injections induced a coincident loss of limb tone. The VTg does not appear to modulate gross measures of sleep architecture, although it can modulate hippocampal theta rhythms in anesthetized rats.[3] These subtle effects on behavioral state correlates will be examined through spectral analysis (power and frequency).

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1517.A

Do Endogenous VIP and PACAP Act Synaptically at the Pontine Reticular Formation in REM Sleep?

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Introduction: Cholinergic neurons in the mesopontine tegmentum are thought to play an important role in inducing REM sleep by releasing acetylcholine (ACh) in the pontine reticular formation (PRF). Recent evidence, however, suggests that neuropeptides such as vasoactive intestinal polypeptide (VIP) might also act at the PRF and play a role in REM sleep. Intraventricular injections of VIP increase REM sleep,[6] while intraventricular administration of a VIP receptor antagonist reduces REM sleep in the light phase in rat.[5] VIP receptor density increases after REM sleep deprivation in rat.[2] Recently, Bourgin et al.[1] showed that microinjections of VIP in the PRF enhance REM sleep by 100% during the first four hours, and by 30% during the next four hours. To corroborate these behavioural results, VIP has been shown to directly excite PRF neurons in vitro.[3] Collectively, these findings suggest the intriguing possibility that the neuropeptide VIP, as well as ACh, is released in the PRF during natural REM sleep. The goal of the present study, therefore, was to identify the potential source(s) of VIP input to the PRF using anatomical tract tracing techniques and immunohistochemistry.

Methods: The fluorescent retrograde tracer Fluorogold (FG, 0.5-1.0% in saline, 0.005-0.01 µl) was injected into the PRF, at the site where microinjections of VIP have been reported to be effective in enhancing REM sleep in rats.[1] After 2-4 days of recovery, animals received intraventricular injection of colchicine, and were perfused 24 hours later. A 1:5 series of sections throughout the brain were reacted for Cy3-tagged immunofluorescence for VIP. In addition, sections from the mesopontine tegmentum and PRF of FG-injected/colchicine-treated, and untreated rats were examined for immunofluorescence for choline acetyltransferase (ChAT), VIP, pituitary adenylate cyclase activating polypeptide (PACAP), and peptide histidine isoleucine (PHI).

Results: Only sparse VIP-immunoreactive (ir) fibers and terminals were present in the PRF in either untreated or colchicine-treated rats. Following FG injections into the PRF, FG-labeled neurons were seen in a number of forebrain and brainstem regions as previously described,[7] and some of these areas, including the frontal cortex, hypothalamus, amygdala and midbrain central grey, contained VIP-ir neurons. However, no double labeled neurons were identified. In the mesopontine tegmentum, VIP-ir cell bodies were occasionally seen near large ChAT-ir neurons, but these two labels were not colocalized; none of these VIP-ir neurons were retrogradely labeled with FG. VIP belongs to a family of related peptides including PHI, PACAP and PHI, and at least two receptors (VPAC1 and VPAC2) are shared by VIP and PACAP. PHI is also a potential ligand for these receptors. The PRF contains high densities of PACAP binding sites.[4] We therefore examined the density of PACAP and PHI immunolabeling in the PRF. The results were similar to those for VIP; there was only sparse fiber/terminal labeling, and no cell body labeling, for either PACAP or PHI.

Conclusions: The present results indicate that the PRF regions at which VIP microinjections have been shown to enhance REM sleep[1] contains rather low densities of axon terminals immunoreactive for VIP. Although we have examined the entire brain, we failed to anatomically identify possible sources of these VIP-ir fibers, most likely due to their sparsity. The PRF also contained very limited densities of fibers and terminals immunoreactive for PACAP and PHI, two endogenous peptides related to VIP. The sources of sparse fibers and terminals containing VIP, PACAP, and PHI, as well as other potential endogenous ligands that might act at VIP/PACAP receptors in the PRF to enhance REM sleep, remain to be identified.

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1822.A

Sleep in Mice Genetically Selected for High (MGH) and Low (MGL) Blood Magnesium: Relation Between Brain Mg and Paradoxical Sleep

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Introduction: Magnesium (Mg) is the fourth most abundant mineral in the brain. It plays a major role in the metabolism of monoamines and modulates conductivity of many ion channels, such as NMDA receptors. Furthermore Mg is necessary for binding of most neurotransmitters to their receptors. In vivo observations in animals and humans indicate that

dysregulation of Mg homeostasis is implicated in behavioral pathologies and results from some studies suggest a relationship between low blood magnesium and sleep fragmentation. We have previously reported that brain Mg, as well as blood Mg, were correlated with sleep parameters, especially with sleep fragmentation after total sleep deprivation[1] in inbred mice. Here we report on sleep analysis in two lines of mice genetically selected for their blood Mg levels (MGL for Mg Low and MGH for Mg High). These mice have been shown to differ in their cerebral catecholamine levels with increased adrenaline and noradrenaline, and in behavior with increased agressivity and acute stress reactivity in MGL.[2]

Methods: EEG and EMG of six mice in each line were recorded for 48h, with a 6h sleep deprivation (SD) at the beginning of the second day. After the end of recordings animals were sacrificed and blood and brains were collected to measure Mg by atomic absorption spectrophotometry.

Results: As expected peripheral Mg showed highly significant differences between the two lines (Red Blood Cell: 2.99±0.08 vs. 2.13±0.05; $p<0.0001$; Plasma: 1.16±0.02 vs. 0.99±0.04; $p<0.004$, for MGH and MGL, respectively) while brain Mg did not vary between MGH and MGL, even when dissected into 9 subregions. However, as in inbred mice,[1] the distribution of Mg over the brain structures was highly significant. Analysis of sleep recordings revealed a significant increase in the amount of PS during the light period of baseline in MGL line (6.1±0.4 vs. 7.5±0.5 in MGH and MGL, respectively; $p < 0.05$). The SD-induced changes in vigilance states were similar for both lines (significant increase in SWS and decrease in wakefulness). Total amounts of PS over 24 h and during the light period of baseline were negatively correlated with the amount of Mg in the motor cortex of MGH mice ($r = -0.96$; $p < 0.001$ and $r = -0.86$; $p < 0.02$ for 24 h and light period PS, respectively) while in MGL mice the amounts of SWS were negatively correlated with the Mg content of the amygdala ($r = -0.82$; $p < 0.03$ and $r = -0.87$; $p < 0.02$ for 24 h and light period SWS, respectively). In both lines, total brain Mg was negatively correlated with the amount of PS after SD ($r = -0.85$; $p < 0.04$ and $r = -0.86$; $p < 0.03$ in MGH and MGL, respectively).

Conclusions: As previously reported in inbred mice, even highly significant differences in peripheral Mg as found in MGL-MGH lines, do not affect brain Mg content, confirming that brain Mg should have a specific regulation. However, brain Mg has a highly structure specific distribution, where small changes may have substantial effects on brain functions. The difference in the amount of PS and significant correlations between PS and brain Mg in these lines might be relevant to their behavioral differences.

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1183.A

Arousal Occurrence During Sleep in Healthy Subjects: Evidence From a Continuum in the Arousal Response

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Introduction: The most common criteria used in the arousal scoring is based on the ASDA criteria[1] defining microarousal (MA) as a change in the EEG activity lasting 3 sec or more. However, arousals shorter than 3 sec[2] or phases of transitory activation (PAT) occurred in normal individuals and in sleep-disorders patient, affecting much more daytime sleepiness. More recently, phasic events in slow wave activity, such as K-complex and delta bursts, have been described as a level of higher activation during sleep and as a sign of arousal response.[3] So far, most of the studies on sleep microstructure have been carried out considering only one type of arousal and no data are available for the continuum of responsiveness present during sleep. This study has attempted to examine the occurrence of arousals, from delta waves to full awakenings, in a group of young adults.

Methods: The polygraphic recordings of 21 right-handed young adults (mean age:24.1± 2.9 yr) were examined. Arousals were graded into four levels, including standard definition of microarousal (MA), phases of transitory activation (PAT), delta bursts (D-bursts) and K-complexes bursts (K-burst).To evaluate if a pattern of autonomic response occurred during each type of arousal, heart rate (HR) was analyzed for ten beats before and ten beats during the arousal. As an index of sympathetic activation, we measured the ratio of the highest HR during the arousal over the lowest one recorded before (HR ratio). The HR pattern response (HR pattern) during arousal was evaluated comparing the changes in HR recorded during the event over the mean value obtained for the 10 beats before the arousal onset. Spectral EEG analysis was done for all type of arousal during 20-sec before the onset.

Results: 5820 events were scored during the night, that is an index of arousal of 33.3±5.3 (range 22.1-42.5). 32% of the events were scored as MA, in 40% preceded by an isolate K-complex. PAT represented 23% of the total arousals whereas D- and K-bursts represented the 17% and 29% of the total events. While D- and K-bursts tended to occur mostly during the first two sleep cycles, MA and PAT occurred during all sleep cycles with a greater density in light and REM sleep. A significant rise in HR was found during all types of arousal greater when EEG activation was more marked. The HR ratio rose from an average value of 1.17±0.07 and 1.2±0.09 in D- and K-bursts to a value of 1.33±0.09 in MA ($p=0.003$). The greater increase was present during PAT (1.45±0.08). The HR pattern during all type of arousal but PAT consisted in a tachycardia during the first four-five beats followed by a bradycardia in the last ones. During MA and PAT the increase in HR appeared during the first two beats before the onset. Spectral EEG analysis showed before the onset of MA and PAT an increase in delta and fast activities starting two seconds before the onset of the visual activation.

Conclusions: Our results suggest that: 1) a continuum in the arousal response is present during sleep, beginning with an EEG synchronization until a final MA or awakening is reached; 2) the common cardiac activation present in all type of arousal suggests a common pattern in the arousal response during sleep; 3) the type of arousal response may depend on the momentary state of sleep and on individual arousability.

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1199.A

Generation, Propagation and Modulation of Slow Delta Rhythms (0.5-3 Hz) in a Isolated Whole Hippocampi Preparation In Vitro

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Introduction: Oscillatory activities in the mammalian brain have spe-

cific spatio-temporal profiles which arise under various behavioral states such as sleep, arousal, exploration and sensory encoding. Current paradigms to study rhythmogenesis involve two designs, the in-vivo animal model and the in-vitro slice model. In-vivo approaches allows the observation of oscillatory systems in their native state, however such a system is limited in its ability to directly assess the cellular activity of the participating neurons, moreover pharmacological manipulation is difficult. The in-vitro model allows the sampling of individual cells and easy pharmacological manipulation, however the slicing process limits the functional connectivity to a local setting, moreover most oscillations must be induced by chemical stimulation. Khalilov et al (1997) has recently forwarded an intact in vitro hippocampal preparation that provides a bridge between these two models. Our original goal was to examine whether slow GABAergic oscillations could be induced by cesium application in the whole hippocampal preparation, mimicking our recent observations made from hippocampal slices (Zhang et al., 1998). However, in the process of using a modified version of Khalilov's preparation we serendipitously discovered naturally occurring slow delta rhythms (<4 Hz) in the whole hippocampus. Our goal was thus to characterize this spontaneous rhythm.

Methods: Hippocampi were acutely isolated from rats or mice C57BL) and maintained in standard in-vitro conditions for electrophysiological assessments. Simultaneous multiple extracellular and patch clamp recordings were used to monitor rhythmic field potentials and single cell activities from individual pyramidal neurons and GABAergic interneurons. Agonists and antagonists of ionotropic glutamate receptors, GABA-a receptors and muscarinic receptors were applied through bath perfusion. Data was continuously collected and digitized. Frequency spectrum and correlation analysis was conducted offline using Origin software.

Results: Spontaneous field rhythms in the delta frequency (0.5-3 Hz) range were observed in the whole isolated hippocampus at room temperature or at 32C. In the CA1 region these rhythms propagated from the ventral towards the dorsal pole, mediated by GABA-a IPSPs originating from a population of pyramidal neurons. Multiple types of interneurons discharged coherently with the field rhythm suggesting that GABAergic network activity is the source of these oscillations. Muscarinic stimulation desynchronized the slow rhythms and induced theta oscillations (6-14 Hz), bearing a close resemblance to cholinergic activation in the behaving animal.

Conclusions: Our data suggest that these slow delta rhythms represent a basal activity state of the hippocampal assembly. We thus provide the first system to study intrinsic slow delta rhythms in-vitro.

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1558.A

Comparative Analysis of the Distribution of Neurons Important for SWS and REM Sleep in Mice, Rats and Cats

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Introduction: Because of the many similarities in sleep across mammals and birds, the present study compared the anatomical networking responsible for sleep in three species that have been generally used in sleep research, i.e, mice, rats and cats. We focused on the neurons important for slow wave sleep in the VLPO and the orexin containing neurons in the lateral hypothalamus.

Methods: Tissue from male mice (3mo, C57BL/6j), rats (Sprague-Dawley, weight 300-400 gms) or cats were processed for visualization of neurons containing c-Fos (rabbit anti-cFos, Oncogene Science, NY) or orexin (rabbit anti-orexin, Chemicon). The tissue was obtained from animals killed following wakefulness (3-24h) or wakefulness followed by two hours of sleep.

Results: The location of the VLPO in mice (c-Fos and galanin cells) is more medial compared to the rat. Moreover, in both species there is a clear demarcation of the boundaries in the collection of galanin or c-Fos labeled cells. In the cat, the c-Fos labeled cells are more diffuse and a cluster of cells analogous to the VLPO in rodents is not easily evident. We have not been able to determine the distribution of galanin-positive cells in the cat, but based on our observations that the c-Fos labeled cells are diffusely represented, we anticipate the distribution of galanin-labeled cells will likewise not be as tightly clustered as in rodents. On the other hand, the location of the orexin containing cells appears to be similarly clustered in the lateral hypothalamus in all three species. In all three species the locus coeruleus was found to contain a rich terminal field of orexin-containing fibers.

Conclusions: The principle finding of this study was that in rodents, the VLPO segregates as a discrete collection of neurons, but in the cat the VLPO is more diffuse. The grouping of these sleep-active cells in rodents makes it feasible to extract these cells for tissue culture and molecular analysis. The distribution of the orexin-immunoreactive cells appear to be similar in the three species. In all three species, the LC is richly innervated by the orexin-ir fibers, further placing the importance of this system in REM sleep control. Conserved elements of a few genes have been found to control entrainment to light and circadian timekeeping [Dunlap, 1998]. A neuronal network and proteins that are similar across several species also regulate feeding [Friedman and Halass, 1998]. The evidence is growing that sleep, another fundamental behavior, is also represented by a cellular mechanism that is conserved across species that sleep [Shiromani, 1998].

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1861.A

Synchronizing Effects of CAP Components in the First Three Sleep Cycles

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Introduction: The alternation of NREM and REM sleep constitutes the sleep cycle (SC) and its recurrence during the night determines the classical sleep profile. The NREM portion of the SC presents a U-shape outline that delineates an uninterrupted pattern of build-up (descending

branch), maintenance (trough) and demolition (ascending branch) of EEG synchrony. The dynamic production and attenuation of slow wave activities suggests the presence of subtle regulatory mechanisms, which remain unexpressed within the conventional stepwise configuration of sleep. It is known that a vast number of stage shifts are entangled with the spontaneous 20-40 s arousal rhythm of NREM sleep known as the cyclic alternating pattern or CAP (Terzano et al., Electroenceph clin Neurophysiol 69: 437-447; 1988). The present study is a tentative to explore the characteristics and distribution of CAP parameters within the first three SCs that mostly characterize the over-night evolution of EEG synchrony.

Methods: The data were collected from the nocturnal polysomnographic recordings of 25 subjects (12 males and 13 females) with an age range between 10 and 42 years (median: 26 years). The wide age range allowed to ascertain whether the investigated issues were a general phenomenon of sleep. All subjects were healthy individuals with regular life habits, good sleep quality and no daytime complaints. Only the first three SCs were taken into consideration for the study. Inclusion criteria required SCs uninterrupted by intervening wakefulness and containing all stages linked in a regular succession of a descending branch, a trough and an ascending branch. Each selected SC started with the first epoch of NREM sleep and ended with the appearance of the first epoch of stage 2 after a REM period had been completed. All SCs interrupted by sustained wakefulness (> I minute) or including regressive shifts (abrupt variation from deep sleep to light sleep) during the descending branch or within the trough, and all SCs with lack of internal modulation (composed only of stage 2 and REM sleep) were excluded from investigation. Conventional sleep variables and CAP parameters were measured in each SC. Analysis of CAP included quantification of the different arousal components (phase A subtypes).

Results: Among the first three SCs, a total amount of 45 (SCI : 16 ; SC2 : 13 ; SC3 : 16) met the inclusion requirements. The first three SCs showed a similar duration and contained quite stable amounts of NREM sleep. The descending branches always lasted longer than the ascending ones. A progressive decrease of stage 4 ($p < 0.0001$) was found across the three successive SCs. The number of phase Al subtypes remained unmodified across the three SCs (SCI : 48 SC2 : 48 ; SC3 : 48), whereas both subtypes A2 (SCI : 9; SC2: 14; SC3: 14) and A3 (SCI : 2 ; SC2 : 8 ; SC3 10) increased significantly ($p < 0.028$ and $p < 0.0001$, respectively). The phase A subtypes were not randomly distributed within the different portions of the SC. In particular, the (A 1) subtypes composed more than 90% of all the A phases collected in the descending branches and in the troughs, while the A2 and A3 subtypes were the major representatives (64.3%) of the A phases occurring in the ascending branches.

Conclusions: The composition of sleep structure is influenced partly by the previous wakefulness and partly by the circadian system. However, sleep structure is also controlled by internal rules that regulate the alternation between NREM and REM sleep. This two-fold nature of sleep is coupled within the SC framework, which represents the basic and repetitive module of sleep organization. According to the reciprocal-interaction model (McCarley and Hobson, Science 189: 58-60 ; 1975), the SC is generated by a finely-regulated out-of-phase discharge by two cell groups: the REM-on neurons that operate immediately before and during REM sleep, and the REM-off neurons, which are closely related to the generation of NREM sleep. In the transition from light to deep NREM sleep, the phase Al subtypes could be an EEG expression of the cerebral mechanisms related to the REM-off drive. On the contrary, the repetitive subtypes A2 and A3 associated with the rapid demolition of EEG synchrony in the ascending branch, could reflect the neurophysiological processes leading to REM sleep. The non-random distribution of CAP sequences, with their succession of slow (subtypes A1) and rapid (subtypes A2 and A3) EEG rhythms, seem to be responsible for sculpturing EEG synchrony under the driving and alternating forces of NREM and REM sleep.

1901.A

Possible Differentiated Existence Of $GABA_A$ Receptors In Effects Of Influence Of Bicuculline On The Hypnogenic Effects Of GABA-ergic Substances On The Typed Animals

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Introduction: It is known, that the most sensibility to the influence of various types of pharmacological substances on the sleep-wakefulness cycle is the paradoxical phase of sleep (PS). By character of influence on the PS, the pharmacological substances can be conditionally classified into those depressing PS (barbiturates, tranquilizers), and those capable to increase the duration of PS. At the same time according to contemporary view, the molecular mechanism of influence of barbiturates, tranquilizers and GABA-ergic substances is defined by their interaction with membrane supra molecular GABA-benzodiazepine-ionophor-receptor complex. It is also known, that pharmacologically, there exist two types of GABA receptors ($GABA_A$ and $GABA_B$)(Beart 1982). We should also note, that there is much scientific data about the existence as minimum two types of $GABA_A$ receptors ($GABA_{A1}$ and $GABA_{A2}$), from which exactly $GABA_{A2}$ receptors form the complex with benzodiazepine receptors (Korneev et al 1985). However, the investigation of the role of GABA-ergic system exactly in the process of sleep does not have systematic characters. In view of the above, it was interesting to study the role of GABA-ergic system and its receptors precisely in the processes of sleep regulation with help of different pharmacological substances (valproic acid "Convulex" (VA), fllunitrazepam "Rohypnol" (FL), cinazepam "BD-798", bicuculline (BL)), which influence on different links of GABA-ergic system.

Methods: Since the organism's individual sensibility in reactions to stress factors and pharmacological agents is of great importance, the experiments were conducted on animals with different types of individual reactivity. The animals (rats) were beforehand divided in two groups: high activity (HA) and low activity (LA) by means of the motor activity registration under the conditions of unavoidable swimming (Nomura et al 1982). After this nichromic electrodes were implanted into the rats dorsal hippocamp, sensomotoric area of brain and dorsal neck muscles for an electroencephalograph (EEG) registration of the sleep-wakefulness cycle.

Results: Specific antagonist of $GABA_A$ receptors BL (3 mg/kg) fully suppresses hypnogenic effect of VA (400 mg/kg) in HA- and LA-rats by indices of duration of PS and numbers of its episodes. Whereas, the duration of slow-wave-sleep (SWS), which was increased as a result of hypnogenic influence of VA, decreased by BL, just till control level. BL has influenced differently on the hypnogenic effect of FL (3 mg/kg) in HA- and LA-rats by indices of SWS, PS and numbers of its episodes. Effect of BL on the hypnogenic effect of CN (1 mg/kg) was the same as influence of BL on the hypnogenic effect of VA by indices of PS and numbers of its episodes. Whereas, in connection of SWS BL has influenced differently depending on the type of animals.

Conclusions: From the received data we can make hypothesis, that hypnogenic effect of VA in connection of PS is apparently connected with involving of $GABA_A$ receptors. At the same time hypnogenic effects of FL and CN in connection of PS probably generally work through the $GABA_{A2}$ receptors, which are obviously more represent in LA-rats, than in HA-rats. In HA-rats the same effects probably work through the $GABA_{A1}$ receptors. Suppressing the hypnogenic effects of the substances under investigation by BL, in connection of PS, is one

more confirmation of important and direct participation of GABA-ergic system, along with other brain mediator systems, in the genesis and the support of PS, but not SWS. Possible differentiated existence of $GABA_{A1}$ and $GABA_{A2}$ receptors in the different types of animals speaks about the necessity of an individual approach in therapy of various sleep diseases.

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1866.C

Cigarette Smoking and Sleep Duration

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Introduction: Three self-report questionnaire studies (Palmer, Harrison, & Hiorns; Bale & White; McGregor & Balding, as cited in Lexcen & Hicks, 1993) have indicated that smokers sleep significantly less than nonsmokers. However, Lexcen and Hicks suggested that alcohol and caffeine - whose covariation with smoking was not considered in the questionnaire studies - are potential confounding variables that should be taken into account when interpreting sleep differences between smokers and nonsmokers. These substances are more likely to be used by persons who also use tobacco (Istvan & Matarazzo, 1984) and are know to reduce the quantity and quality of sleep. This research was carried out to assess the relationship between cigarette smoking and sleep duration, in a design that took into account caffeine and alcohol consumption.

Methods: A sample of 250 university undergraduates (150 females and 100 males) responded to a comprehensive sleep and health survey that included questions about sleep duration ("During the past month, how many hours of actual sleep did you get per night?"), smoking ("Do you smoke cigarettes now?"), and caffeine and alcohol consumption ("How many cups of regular coffee/tea do you drink per day?", "How many caffeinated sodas do you drink per day?", "How many alcoholic drinks do you consume per week?"). There were 45 smokers and 205 nonsmokers. These two groups were then compared relative to their reported caffeine and alcohol intake, and sleep duration.

Table 1

	Smokers		Nonsmokers			
Variable	*M*	*SD*	*M*	*SD*	*t*	*p*
Sleep/night (hrs.)	6.13	1.37	6.57	1.11	-2.31	< .05
Caffeine/day (mg.)	210.00	226.30	111.80	106.92	2.84	< .01
Alcohol/day (oz.)	.38	.53	.07	.24	3.78	< .001

Results: The means and standard deviations for caffeine and alcohol consumption and for sleep duration are summarized in the accompanying table. Also reported are the t-statistics computed to analyze the differences between smokers and nonsmokers on each variable. Smokers reported sleeping significantly less than nonsmokers and consuming more caffeine and alcohol, thus confirming the results of an earlier study (Lexcen & Hicks, 1993). Next, an analysis of covariance on sleep duration was performed, with smoking status as the independent variable and caffeine as a covariate (alcohol was not included since its correlation with sleep duration was not significant). This analysis yielded that caffeine intake was significantly related to sleep duration ($F(1, 247) = 12.95$, $p < .001$) but smoking was not ($F(1, 247) = 1.71$, its.).

Conclusions: After adjusting for caffeine consumption, the difference in reported hours of sleep per night between smokers and nonsmokers was not statistically significant. It remains to be determined if the regular and heavy use of tobacco is associated with decreased sleep duration, in a design that controls for caffeine and alcohol consumption. It may be the case that, if the number of cigarettes smoked per day is high, a significant negative relationship will be observed. This study underscores the need to consider the other two drugs when assessing the individual contributions of tobacco, caffeine, and alcohol to sleep disturbances.

References:
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(2) Lexcen FJ, Hicks RA. Does cigarette smoking increase sleep problems? Perceptual and Motor Skills 1993, 77:16-18.

1587.C

Ethanol and Sleep Loss: A "Dose" Comparison of Their Impairing Effects

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Introduction: The memory and performance-disruptive effects of ethanol and sleep loss have each been documented. But, studies comparing "doses" of ethanol and sleep loss have not been done. A study has compared ethanol and sleep loss at a high "dose" of each.[1] Thus, this study evaluated the "dose" effects of sleep loss and ethanol over a range of "doses" from "placebo" to a high "dose" of each [i.e., breath ethanol concentrations (BrEC) of .08-.10% and one night (8hrs) of total sleep loss].

Methods: Thirty two healthy subjects, 21-35 yrs old, with normal physical, psychiatric and laboratory test results volunteered. No history of alcoholism and drug abuse and no current drug or alcohol use was allowed. All had a sleep efficiency >85% on a 8-hr NPSG and a MSLT >7 min. They were randomly assigned to an ethanol (n=20) or sleep loss (n=12) group and each received four "doses" of ethanol or sleep loss. For both groups the "doses" were presented in a Latin Square design with 3-7 days between "doses". Each "dose" test day was preceded by a baseline day with an 8-hr TIB. For ethanol, on test days following an 8-hr TIB, ethanol 0.0, 0.3, 0.6, and 0.9 g/kg was consumed at 830-900 hrs. BrEC was measured at 930, 1130, 1330, and 1530 hrs. For sleep loss, subjects had 8, 6, 4 , and 0 hrs TIB with lights out adjusted to achieve the given TIB and time of arising held constant at 700 hrs. This produced 0, 2, 4, and 8 hrs sleep loss. Each day subjects received a standard performance battery at 1000, 1200, 1400, and 1600 hr which included tests of memory (MEM), vigilance (PVT), and divided attention (DAT). After each battery, performance was self-rated (7 point scale: good-poor). All measures were converted to change scores from the prior baseline day for each "dose". Data for the different TIBs was compared to that of each ethanol dose using mixed design MANOVAs with group (ethanol vs sleep loss) as the between factor and "dose" as the repeated factor. "Dose" was compared within the ethanol and sleep loss groups alone by one factor MANOVAs followed by trend analyses. Conservative p levels were used for the "dose" factor.

Results: BrEC differed among the 3 ethanol doses and was .09%, .04% and .02% 0.5 hr post consumption ($F=9.44$, $p<.004$), declining to.07%, .03% and .00% ($F=31.74$, $p<.001$) at 2.5 hr, and reaching .02%, .00% and .00% at 4.5 hr. Given BrEC was at or near zero by 1330 hr, the mean change for the 1000 and 1200 hr tests are presented on the table. The

results for both psychomotor tasks (PVT: F=5.92, p<.001 and DAT: F=4.14, p<.01) showed: 1) increasing "dose" produced greater impairment, 2) "dose" effects for both ethanol and sleep loss were linear, and 3) "doses of ethanol and sleep loss produced comparable impairment. For MEM (F=4.49, p<.01), the "dose" effects were linear, but "doses" of ethanol produced greater effects than sleep loss. For performance self-ratings (F=6.51, p<.001), while sleep loss produced a linear increase in ratings of poor performance, only at the highest "dose" of ethanol did subjects rate their performance as impaired (i.e., a quadratic trend only). Also, a trend (p<.10) for greater impairment ratings were seen with sleep loss.

Table 1

		MEM (# cor)	PVT (Fast RTs)	Self-Rated Perform
Pb	Ethanol	0.00 (0.16)	0.99 (3.40)	-0.02 (0.19)
	Sleep Loss	0.80 (0.21)	7.74 (4.58)	0.08 (0.25)
Lo	Ethanol	0.35 (0.18)	1.86 (3.27)	0.05 (0.20)
	Sleep Loss	0.08 (0.24)	-5.95 (4.41)	-0.29 (0.26)
Md	Ethanol	0.54 (0.14)	-6.13 (5.67)	0.12 (0.17)
	Sleep Loss	0.19 (0.18)	-6.39 (7.65)	-0.58 (0.22)
Hi	Ethanol	0.80 (0.17)	-17.9 (5.76)	-0.80 (0.29)
	Sleep Loss	0.44 (0.22)	-18.0 (7.76)	-1.15 (0.38)

Conclusions: At the studied "doses" ethanol and sleep loss produced comparable effects on psychomotor performance. Ethanol produced greater memory deficits and subjects were less aware of their overall performance impairment.

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(1) Dawson D Reid K. Equating the performance impairment associated with sustained wakefulness and alcohol intoxication. Nature 1997;388:235.

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1592.C

Effect of Caffeine on a Behavioral Measure of Sleep Onset

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Introduction: Behavioral measures offer several advantages in the measurement of sleep disturbance, including cost- effectiveness and portability (Bonato & Ogilvie, 1989). The Magellan MonitorTM (Braebon Medical) is a wrist-worn device that contains programmable circuitry for controlling the delivery of vibratory stimulation, the recording of responses and the storing of results for later downloading to a computer. A piezo-electric response sensor attached to the thumb enables simple responses to be made to the stimuli by moving the thumb. This study examined the effect of caffeine on sleep onset latency (SOL) determined using the Magellan MonitorTM and a self-report measure.

Methods: Sixteen, young (mean age = 20), healthy, female volunteers who gave their informed consent spent three nights in the sleep laboratory. Following an adaptation night, participants received either 4mg/kg of caffeine citrate or placebo prior to their bedtime in a counterbalanced design with a minimum of two nights intervening between conditions. The Magellan MonitorTM was programmed to emit a series of up to five vibratory stimuli of increasing intensity. Stimuli were separated by five seconds. Participants were instructed to respond when they felt a stimulus. A response to any stimulus terminated a series. Each series was separated by a random interval of three to four minutes. EEG and self-report measures were also collected but only behavioral and self-report measures will be reported here.

Results: Data were analyzed using a 2 X 2 analysis of variance with condition (caffeine vs. placebo) and definition (behavioral vs. self-report) as repeated measures. Behavioral SOL was defined as two missed responses. There was a significant effect of caffeine on SOL (F(1, 15) = 5.02, p =.04). Longest SOLs occurred on the caffeine night.

Table 1

	MEAN (minutes)	**S.D.**	**N**
Magellan SOL Caffeine night	**70.23**	**56.66**	**16**
Self-report SOL Caffeine night	**73.88**	**66.08**	**16**
Magellan SOL No Caffeine night	**48.88**	**45.31**	**16**
Self-report SOL No Caffeine night	**31.41**	**32.51**	**16**

Conclusions: The Magellan MonitorTM yields SOL estimates that are consistent with those previously obtained in studies of the effects of caffeine on sleep (Bonnet & Arand, 1992). Clearly sleep onset can be estimated effectively and economically using behavioral measures.

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1657.C

Subjective and Actigraphic Responses of Multiple Sclerosis Patients with Fatigue to Modafinil, a Wake-promoting Agent

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Introduction: Fatigue is a common and disabling problem in multiple sclerosis (MS). Motor activity is decreased in MS (Ng and Kent-Braun 1997) but this has not been related to the presence of fatigue. Modafinil is a wake-promoting agent that is effective in the treatment of sleepiness in narcolepsy. We evaluated its efficacy and safety for the treatment of MS fatigue.

Methods: Seventy two patients aged 18-65 years with stable MS (Kurtzke Extended Disability Status Scale <=6) and fatigue (Fatigue Severity Scale ≥4) were enrolled in a 9-week, multicenter, forced-titration, single-blind, placebo-controlled study. Exclusion criteria included narcolepsy, sleep apnea, other major disorders & use of any medication that could affect fatigue. Patients received pla-cebo during weeks 1-2,

modafinil 200 mg during weeks 3-4, modafinil 400 mg during weeks 5-6 and placebo during weeks 7-9. The Epworth Sleepiness Scale (ESS) was given at screening and after each study phase at which modafinil was given, and measures of fatigue were obtained after each study phase (FSS, visual analog global fatigue scale and Modified Fatigue Impact Scale). Wrist motor activity was monitored (Actitrac, IM systems, Inc) once a minute throughout the 9-week study in the 36 subjects studied at Ohio State and is currently being monitored in non-fatigue controls. Rest/activity cycles were modeled by fitted cosine functions with period set equal to 24.0 hrs and were also summarized by smoothed mean 24-hour waveforms. Dependent variables were mean activity level, amplitude, and times of maximal and minimal activity.

Results: Interim analysis of 43 MS patients (mean age 44 yrs, male/female ratio 1:3.8) indicated sleepiness at screening (ESS = 9.5) which decreased on modafinil (ESS = 6.8 after modafinil 200 mg/day, p = .0001; 7.2 after modafinil 400 mg/day, p = .0013). Significant improvements were found for 6 of the 8 constituent ESS items. Modafinil 200 mg/day (but not 400 mg/day) also significantly improved fatigue (vs. placebo at baseline) for each of the 3 fatigue assessment scales. The most frequent adverse effects (AEs) for modafinil 200 g/day were nervousness (14% vs. 5% for placebo), headache (19% vs. 21%) and asthenia (12% vs. 14%). A total of 39 patients (91%) com-pleted the study; 4 discontinued because of an AE. The mean motor activity level and rest/activity-cycle amplitude of 19 subjects increased with increasing doses of modafinil and decreased during pla-cebo washout, but these effects were small and nonsignificant. Motor activity remained close to zero at night. Modafinil did not shift the phase of the rest/activity cycle.

Conclusions: Modafinil 200 mg/day significantly reduced daytime sleepiness and fatigue in patients with MS, did not appear to disturb nighttime sleep and was generally well tolerated. Despite improvements in daytime sleepiness and fatigue, modafinil did not increase daytime motor activity, perhaps because modafinil facilitates but does not increase behaviors that have been reduced to those that are essential or because motor activity is not in fact reduced in MS fatigue.

References:

(1) Ng AV and Kent-Braun JA. Quantitation of lower physical activity in persons with multiple sclerosis. Med. Sci. Sports Exerc. 29:517-523, 1997.

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1676.C

Effects of Melatonin on Sleep in Macaca Nemestrina and Macaca Mulatta: Dose Dependency

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Introduction: In order to investigate the mechanisms underlying melatonin's physiologic effects and a possible role of the pineal gland in the process of age-related decline in sleep efficiency, it is necessary to conduct studies using appropriate animal models. Our previous observations in non-human primates established that these species, similar to humans, are sensitive to sleep-promoting effects of melatonin (Zhdanova et al., 1998). We now report the results of studies conducted in two non-human primate species, Macaca nemestrina and Macaca mulatta, in order to assess a dose-dependency of melatonin effects on sleep in non-human primates. ep in non-human primates.

Methods: Subjects were two young male Macaca nemestrina (6 and 9 years old), two young male Macaca mulatta (5 and 6 years old) and two old male Macaca mulatta (16 and 17 years old). Monkeys were maintained in individual primate cages under 12:12 LD cycle. Water was available ad libitum and a diet of monkey chow, fruits, vegetables, and nuts was provided three times a day. In the first experiment, in order to establish a minimum effective dose of melatonin for non-human primates, gradually increasing oral doses of the hormone (0.25-10 mg/kg) were administered to two Macaca nemestrina. Each animal received each dose for one week, 2 hours before lights off time, with a week of washout/placebo between the doses. After the minimum effective dose was established, animals received this dose for one month (5 days/week, 2 hours before lights-out time). In the second experiment, after a 4-week baseline recording and a 2-week placebo treatment, all six animals ingested increasing oral doses of melatonin (5, 10, 20, 40, 80, 160 and 320 mg/kg) two hours before lights off time (CT 10), each dose for 3 consecutive days, with no washout period between the doses. At the end of this treatment period animals received placebo for 6 days and then were reintroduced to a 5 mg/kg dose for three more days. Melatonin or placebo solutions were administered orally, mixed with fruit pure. Animals' motor activity was recorded continuously using a specially designed collar containing an actigraphic monitor (Actiwatch, MiniMitter, OR). The actigraphic data were evaluated using the Sleepwatch Software Program (Mini-Mitter Co., OR). Blood samples were withdrawn under general anesthesia (ketamine, 10 mg/kg, im) at 11 AM, an hour after subjects ingested a 5 mg/kg dose of melatonin or placebo. Melatonin concentrations were measured in 0.5 ml aliquots of serum using a radioimmunoassay kit (ALPCO, Windham, NH).

Results: Experiment 1: The minimum effective dose of melatonin, which significantly promoted sleep onset compared to placebo, was 5 mg/kg for both Macaca nemestrina tested. This dose induced 54±6.1 pg/ml plasma circulating melatonin levels, which is within the range of normal endogenous peak levels of the hormone for this species. The effect of a 10 mg/kg dose was significantly different from placebo but not from a 5 mg/kg dose of melatonin. Administration of a 5 mg/kg dose of melatonin for one month neither significantly inhibited nor facilitated a sleep-promoting effect of the treatment. Interruption of daily melatonin treatment immediately restored the timing of sleep onset observed at baseline. Experiment 2: Sleep onset in all four young animals and in one old animal occurred significantly earlier after the administration of a 5 mg/kg dose of melatonin. The minimum effective dose for the second old monkey was 20 mg/kg. No significant difference between the effects of increasing doses of melatonin on sleep onset was observed, with all the doses being significantly different from placebo. All the animals had a similar response to a 5 mg/kg dose at the beginning of the long-term treatment with increasing doses of the hormone and after it ended. No significant interspecies differences in the effects of melatonin on sleep were detected. Serum melatonin levels in Macaca mulatta after ingestion of a 5mg/kg dose were 65.3 + 13.9 pg/ml. While in both Experiments the nocturnal sleep episode was initiated significantly earlier after melatonin treatment ($p<0.05$), no significant shift in the onset of morning activity or in sleep offset was observed. Thus, similar to our earlier report (Zhdanova et al., 1998), we did not document a shift in the circadian phase of motor activity or sleep after melatonin treatment in non-human primates. This observation, however, could be in part attributed to environmental conditions, i.e., regular light/dark cycle and fixed hours of food intake, to which animals were entrained.

Conclusions: This study provides further evidence that sleep in non-human primates is affected by low "physiological" doses of melatonin. No dose-dependency of the effects of melatonin treatment used in pharmacological doses and administered at CT 10 on sleep onset was observed in two species tested. The data also suggest that a repeated prolonged treatment using a minimum effective dose or gradually increasing doses of the hormone does not induce sensitization or tolerance to

melatonin's effects on sleep onset. Melatonin treatment used did not produce an apparent circadian phase shift in motor activity while animals were maintained in 12:12LD cycle, since no change in the sleep offset time was observed. Further studies on the effects of melatonin on sleep and circadian rhythms in monkeys maintained under constant conditions are required in order to clarify the phase-shifting effects of melatonin in diurnal non-human primates.

References:
(1) Zhdanova IV, Cantor ML, Leclair OU, Kartashov A and Wurtman RJ Behavioral effects of melatonin treatment in non-human primates. Sleep Research Online 1(3): 114-118, 1998 http://www.sro.org/1998/Zhdanova/114/

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1087.C

Synergistic Interaction of the Hypnotic Effects of Oleamide and Triazolam

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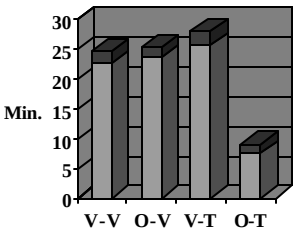
POSTER PRESENTATIONS

Introduction: The unsaturated fatty acid amide oleamide (OA), which accumulates in the CSF of sleep-deprived rats and cats, has previously been shown to induce electroencephalographic sleep following intraventricular (IVT) administration.[1,2] The mechanism by which it produces its hypnotic effects is not yet known. Among the possibilities is that its effects may stem from its reported potentiation of GABA-A or 5HT2C gated ion function. It is also possible that the ammonia generated as a result of OA catabolism could enhance the interaction of agonists with GABA-A receptors. It has also been reported that OA inhibits the cellular uptake or catabolism of the related sleep-inducing fatty acid amide arachidonoylethanolamide (AEA), thus indirectly enhancing sleep via the actions of AEA at the cannabinoid-1 receptor. In this study we have examined the possibility that the actions of OA on sleep involve the GABA-A—benzodiazepine receptor complex, by observing the interaction of OA with the benzodiazepine hypnotic triazolam.

Methods: Seven male 250 gm. Sprague Dawley rats were anesthetized with ketamine/xylazine, and then underwent surgical implantation of EEG and nuchal EMG electrodes, as well as bilateral placement of stainless steel cannulae into the lateralventricles. They were housed in an environment with a 12:12 light:dark cycle such that lights came on at 8:00 AM. After a one week recovery period they were given doses of OA (0.0175 ug) and triazolam (0.125 ug) which preliminary studies had indicated have no effect on sleep when given by themselves, alone and in combination. Injections, in a total volume of 0.5 uL, were given at 10:00 AM, in recordings separated by at least 3 days each. Two hour sleep recordings were performed on a Grass Model 78 polygraph, and sleep stages were determined in 30 second epochs by a rater blind to treatment conditions. Statistical analysis was performed by a one way ANOVA for repeated measures, with post-hoc testing by the Least Significant Difference test.

Results: As can be seen in the Figure, these very low doses of OA and triazolam had no effect on sleep latency when given by themselves. When administered in combination, however, sleep latency was significantly ($p \< 0.0001$) reduced, such that the combination treatment of active OA and triazolam differed from injection of vehicle for both compounds($p \< 0.00001$). These doses of OA and triazolam had no effect, alone or in combination, on total sleep time, NREM or REM sleep, REM latency, or wake time after initial sleep onset.

Figure 1. Abbreviations: V-V: vehicle for both compounds; O-V: OA 0.0175 ug plus vehicle for triazolam, V-T: vehicle for OA plus triazolam 0.125 ug, O-T: OA 0.0175 ug plus triazolam 0.125 ug



Abbreviations:
V-V: vehicle for both compounds
O-V: OA 0.0175 plus vehicle for triazolam
V-T: vehicle for OA plus triazolam 0.125 ug
O-T: OA 0.0175 ug plus triazolam 0.125 ug

Conclusions: In summary, we have found that very low doses of OA and triazolam, which have no effect on sleep when given bythemselves, potently reduce sleep latency when given in combination. As described above, OA has been found in vitro to affect several receptor systems, and we have previously reported that a blocker of the cannabinoid-1 receptor prevents sleep induction by OA.[3] The present study raises the possibility that another mechanism of action by which OA alters sleep may also involve an interaction with the GABA-A—benzodiazepine receptor complex, or with a mechanism affected by this receptor system.

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1744.I

The Relationship of Sedative and Paralytic Administration to Deliberate Self-Extubation

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Introduction: Deliberate, purposeful self extubation occurs commonly in the Intensive Care Unit despite the administration of sedative and paralytic drugs. Such behavior may be the result of agitation, possibly induced by sedatives administered to reduce anxiety. We performed a retrospective study to evaluate the relationship between sedative therapy and self-extubation in the ICUs of a 1000 bed teaching hospital.

Methods: The study was performed using a retrospective, case-control design. The charts of all adult patients at a 1000 bed teaching hospital who self-extubated during 1993 (n=50) were retrospectively reviewed. Self-extubation was defined as both non-medically recommended and purposeful patient removal of the endotracheal tube. Two control patients who did not self-extubate were matched to each self-extubation case on age, gender, dates in hospital and diagnosis. Data collection included demographics, indications for intubation and ventilation, diagnoses, selected laboratory indices, vital signs, use of physical restraints and mental status 24 hours prior to self extubation, and complications following self extubation. Specific doses and medications given to each patient were obtained from retrospective review of medication records. Cumulative drug doses were calculated over the 48 hours immediately preceeding self-extubation in SE patients. Sedative agents were defined by drug class as narcotic, benzodiazepine, or hypnotic type medications. Paralytic agents were defined as non-depolarizing muscle relaxants only. The Charlson Index, a tool designed to quantify comorbidity, was used to evaluate severity of illness and risk of mortality.

Results: More patients in the self extubation group were classified as agitated by nursing staff than in the control group (54% vs 22%). Agitated patients were twice as likely as control patients to be receiving benzodiazepines (62% vs 35%). When compared to controls, patients in the self extubation group were more likely to be receiving benzodiazepines (59% vs 35%), but equally likely to be receiving narcotics. Among non-agitated patients, increased use of both benzodiazepines (57% vs 29%) and narcotics (76% vs 45%) were noted in those who self-extubated vs. controls.

Conclusions: Self-extubation correlated both with increased agitation and with increased use of benzodiazepine sedatives. Use of benzodiazepines correlated independently with agitation, and may not prevent self-extubation even in nonagitated patients. These findings may result from agitation induced by chronic, heavy sedative use. Patients who are receiving benzodiazepines in general and midazolam in particular, should paradoxically be considered at increased, not decreased risk for self-extubation.

1089.C

The Hypnotic Effects of LOH-1-151, an Inhibitor of Oleamide Catabolism

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Introduction: Among the unsaturated fatty acid amides are two substances, oleamide (OA) and arachidonoylethanolamide (AEA), which have been reported to induce sleep. OA is of particular interest in view of previous reports that it accumulates in the CSF of sleep-deprived rats[1] and cats.[2] We have found that intraventricular (IVT) administration of OA 2.8 and 5.6 ug significantly shortens electroencephalographic sleep latency in rats.[1] In order to explore its hypnotic effects further, we are now reporting on sleep following IVT administration of LOH-1-151 (1,1,1-trifluoro-10(z)-nonadecen-2-one) which inhibits the major degradative enzyme of OA, fatty acyl amide hydrolase, Type 1.

Methods: Eleven male 250 gm Sprague Dawley rats were anesthetized with ketamine/xylazine and were surgically implanted with EEG and nuchal EMG electrodes as well as bilateral stainless steel cannulae placed in the lateral ventricles. After a one week recovery period they were given drug injections IVT at 10:00 AM, in a 12:12 light:dark environment in which lightswere turned on at 8:00 AM. In random sequence they were given vehicle (10% ethanol), LOH 0.9 ug, and LOH 1.8 ug in a total volume of 0.5 uL in recordings separated by at least 3 days. Two hour sleep recordings were then made on a Grass Model 78 polygraph, and sleep staging was performed using 30 second epochs by an investigator unaware of treatment conditions. Statistical analysis was performed by a one way ANOVA for repeated measures, with post-hoctesting by the Least Significant Difference test.

Figure 1. Abbreviations: V=vehicle; 0.9=0.9 ug; 1.8= 1.8 ug

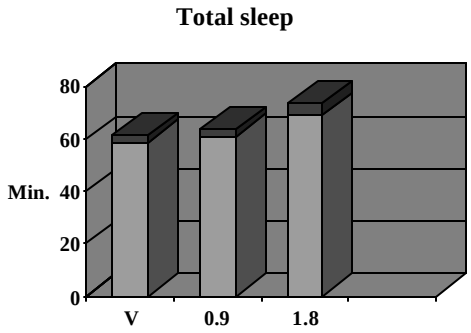
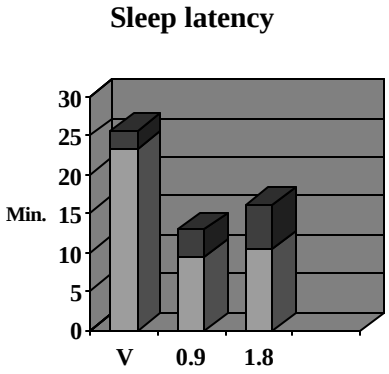


Figure 2. V=vehicle; 0.9=0.9 ug; 1.8=1.8 ug



Results: As can be seen in the Figures, LOH-1-151 significantly (p \< 0.001) shortened sleep latency; post-hoc testing revealed that values following administration of both doses were less than vehicle (p \<0.001). LOH-1-151 also significantly affected total sleep (p \prec 0.04) such that total sleep following administration of the higher dose was significantly greater than vehicle (p< 0.02). NREM sleep tended (p \< 0.06) to increase. There was no significant alteration of total REM sleep time, or waking after initial sleep onset.

Conclusions: In preliminary studies we have found that LOH-1-151 given as 5 mg/kg IP produces motoric sedation. The present work indicates that central administration of LOH, which inhibits catabolism of oleamide, both shortens sleep latency and increases total sleep. These data provide further confirmation of the hypnotic properties of this endogenous unsaturated fatty acid amide, and leave open the possibility that oleamide may play a role in the physiology of sleep and waking.

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1411.C

The Association of Salivary Melatonin with Cognitive Functioning in the Morning

Serizawa S, Spielman AJ, Birnbaum J, Ambrosio P, Conroy D, Bates J, Ross L, Nunes J

Introduction: Endogenous melatonin (MT) is associated with endogenous circadian phase, reduced core body temperature and increased sleepiness. Similarly, exogenous MT administration produces phase shifts of circadian rhythms, reduces core body temperature and induces sleepiness. Some previous studies[1] have shown that exogenous MT appears to modulate or regulate cognitive functioning, while others have not.[2] The present study investigated the effect of MT administration in the morning on sleepiness and cognitive functioning in normal subjects.

Methods: Eleven healthy subjects (4 males and 7 females), 21 to 35 years of age, participated in a pre-experimental week followed by one experimental day. Potential participants were interviewed and given medical and sleep history questionnaires to ensure that they were in good health. During the pre-experimental week, subjects slept at home and followed a habitual prescribed sleep-wake schedule. On the experimental day, subjects had a nocturnal PSG performed in the lab to screen for sleep disorders. On the next day, subjects were awakened at their habitual wake time. Open administration of a pill containing 5.0 mg of MT was ingested 45 minutes after awakening. Illumination level was held below 50 lux. Subjects were asked to allot at least 2 ml. of saliva into a disposable tube every hour. Performance tests and naps (modified MSLT) were obtained every hour and mood scales every 30 minutes until 5.75 hours following wake time.

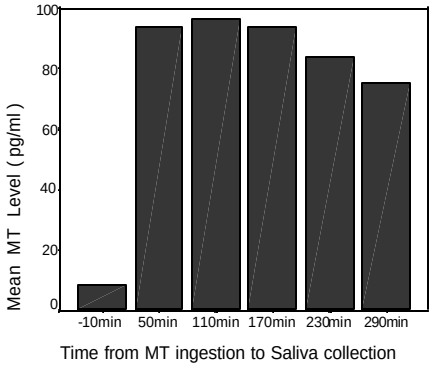
Table 1

Pearson Correlations

		add/subtract % correct	Subjective Sleepiness	Subjective Fatigue
MT Level	*r*	-.27*	.29*	.26
	Sig.	.045	.034	.060
	N	55	54	54

* Correlation is significant at the 0.05 level (2-tailed).

Figure 1



Results: At the first saliva collection 10 minutes prior to MT administration, salivary MT levels (RIA) were low (Figure 1). On the next sample taken 50 minutes after MT administration and all subsequent samples, salivary MT levels were high and dropped off very little over time. Sleep latency on the first nap (mean = 13.0 min), 30 minutes following MT administration, was higher than the mean sleep latency of the second to fifth (mean = 8.9 min, P< 0.05). Cognitive tasks and subjective moods did not differ before and after MT administration. The salivary MT levels were correlated with a small number of performance and subjective variables (Table 1, first MT level was excluded from analysis), as follows: the accuracy of Serial Add/Subtract test, subjective Sleepiness Scale and a trend with subjective Fatigue Scale. No correlation was found between the salivary MT levels and other cognitive tasks, subjective moods and sleep latency.

Conclusions: Conclusions: Administration of 5.0 mg of MT after a full nights sleep increased objective sleepiness. The levels of salivary MT were associated with the degree of subjective sleepiness. There were limited effects on cognitive functions. For a more powerful design see companion abstract (Birnbaum et al) for a comparison of placebo, 0.3 mg and 5.0 mg of MT, delivered double blind, in a within subjects design, on identical parameters.

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1094.C

Effect of Dextroamphetamine or Methylphenidate on the Steady-State Disposition Profile of PROVIGIL® (Modafinil) in Healthy Volunteers

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Introduction: Traditional CNS stimulants, such as dextroamphetamine (DEX) and methylphenidate (MP), or newer drugs, such as PROVIGIL® (modafinil) [US Modafinil in Narcolepsy Multicenter Study Group, 1998], may be prescribed to patients with excessive daytime sleepiness (EDS) associated with narcolepsy to help obtain optimal wakefulness throughout the course of a day. Previously, two single-dose studies investigated the potential pharmacokinetic (PK) interaction between modafinil and DEX (Wong, 1998) and modafinil and MP (Wong, 1998) when taken simultaneously (ie, to achieve faster wakefulness). Both DEX and MP increased the tmax without altering the AUC of modafinil when taken concomitantly. Both of these combination treatments were generally well tolerated. We conducted two multiple-dose studies to investigate the potential alterations in the PK of modafinil by DEX or MP under steady-state conditions when the CNS stimulants were taken 7-8 hours after a morning dose of modafinil (ie, to model a late afternoon dose of a short-acting CNS stimulant to maintain wakefulness).

Methods: 32 healthy male and female volunteers were enrolled in each of two open-label, single-period studies. During phase 1 of each study, subjects received modafinil alone (200 mg, Days 1-7; 400 mg, Days 8-21). During phase 2, volunteers received either modafinil (400mg) alone (Days 22-28) or modafinil plus DEX (20 mg, Days 22-28) or MP (20 mg, Days 22-28). Subjects received the daily dose of DEX and MP 7 and 8 hours, respectively, after the daily dose of modafinil. Blood samples were collected immediately prior to dosing on Days 1, 19-22, and 26-28, and at selected times up to 24 hours after dosing on Days 21 and 28. Plasma concentrations of modafinil and its two main circulating metabolites (modafinil acid and modafinil sulfone) were determined using a validated HPLC method. Possible drug interactions were assessed by comparing changes in PK parameters on Day 28 with data obtained on Day 21 using the Wilcoxon Rank Sum Test. Safety was evaluated throughout the study by recording adverse events (AEs).

Results: Neither DEX nor MP significantly altered the steady-state absorption or disposition PK of modafinil (Tables 1 and 2) under this dosing regimen. Although DEX and MP did not alter the PK of the metabolite modafinil sulfone, they did cause a significant ($p < 0.05$) reduction in the Cmax of the metabolite modafinil acid at Day 28. During phase 2 of the modafinil/DEX study, the most common AEs reported by the volunteers receiving modafinil alone or modafinil plus DEX were headache (2/15, 1/13, respectively), insomnia (2/15, 1/13), and abdominal pain (0/15, 2/13). During phase 2 of the modafinil/MP study, the most common AEs reported by the volunteers receiving modafinil alone or modafinil plus MP were headache (5/16, 3/16, respectively), insomnia (1/16, 4/16), and anxiety (0/16, 2/16). The AEs reported in both studies were mild to moderate in nature.

Table 1

	Modafinil (N=14)		Modafinil + MP (N=16)	
PK Parameter	Day 21	Day 28	Day 21	Day 28
C_{max}, µg/mL	13.5	14.3	13.5	13.3
$AUC_{(0-24)}$, µg•hr/mL	151.8	147.7	143.8	139.4
t_{max}, hr	2.1	2.3	1.9	2.1
$t_{1/2}$, hr	14.2	12.6	11.5	11.0

Table 2

	Modafinil (N=13)		Modafinil + DEX (N=10)	
PK Parameter	Day 21	Day 28	Day 21	Day 28
C_{max}, µg/mL	12.8	13.0	13.8	13.1
$AUC_{(0-24)}$, µg•hr/mL	147.1	142.0	151.7	145.5
t_{max}, hr	2.4	1.9	1.6	2.0
$t_{1/2}$, hr	14.3	12.1	13.5	12.0

Conclusions: Administration of DEX or MP 7-8 hours after administration of modafinil (ie, to model a late afternoon dose of a short-acting CNS stimulant to maintain wakefulness) did not alter the steady-state disposition profile of modafinil in healthy volunteers in comparison to treatment with modafinil alone. Modafinil plus DEX or modafinil plus MP was generally well tolerated. Addition of a low dose of a short-acting CNS stimulant late in the afternoon may be useful for maintaining wakefulness in some patients who take modafinil in the morning.

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1105.C

Polysomnography Pre- and Post-Gabapentin for Insomnia in Alcoholic Outpatients: Preliminary Findings

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Introduction: Several studies conclude that insomnia during early recovery from alcoholism is associated with subsequent relapse to drinking (e.g., Foster & Peters, 1999). Preliminary data suggest that gabapentin improved subjective sleep in alcoholic patients with persistent insomnia (Karam-Hage & Brower, 2000). However, sleep improvement was not objectively verified in that study of 15 patients. We now report three cases of objectively measured sleep in alcoholic patients treated with gabapentin for comorbid insomnia.

Methods: Over 7 wk, 9 patients receiving usual psychosocial treatment for alcoholism at an outpatient facility were referred for psychiatric evaluation of insomnia. The patients met DSM-IV criteria for insomnia and alcohol dependence, and had no other mental disorders except tobacco dependence. Three patients were excluded because their sleep improved markedly during the week before gabapentin was to be started, and 1 patient had sleep apnea detected by baseline polysomnography (PSG). Of the 5 eligible patients, one never returned for the initial medication visit, and one did not show for further appointments or PSG after starting gabapentin. The remaining 3 patients completed 6 wk of gabapentin treatment and, after an adaptation night in the sleep lab, underwent nocturnal PSG before starting (t1) and after the first 2 wk (t2) of gabapentin treatment.

Results: Two of 3 patients abstained from alcohol completely during the 6 weeks of treatment (Table). Dosage ranged from 600 to 900 mg qhs, and no side effects were reported. All 3 patients had improved sleep at t2 as measured by the 3 sleep items from the Hamilton Rating Scale for Depression (Ham-D). Total Sleep Time also increased for all 3 patients. Sleep efficiency increased in 2 of 3 patients from an overall mean of 80.9% at t1 to 91.1% at t2. Sleep latency decreased by 20 min in one patient. No mean changes (> 3%) from t1 to t2 were found in stages 1, 2, delta, and REM sleep percentages; and mean REM sleep latency increased from 91 to 110 min.

Table 1

Age / Gender	30 / F	47 / M	22 / M
Marital Status	M	D	S
Education (yr) / Employed?	12 / Y	18 / Y	16 / Y
Age at 1st alcohol problem	17	42	21
Drinks/drinking d in past 90 d	8	8	10
Drinks in 2 wk before t1 (#)	1	0	5
Days drank in 6 wk post t1	2	0	0
Gabapentin dosage, t2 (mg/d)	900	900	600
Ham-D sleep items sum, t1	5	3	2
Ham-D sleep items sum, t2	1	1	1
PSG total sleep time, t1 (min)	343	275	429
PSG total sleep time, t2 (min)	408	405	431
PSG sleep efficiency, t1 (%)	86	67	90
PSG sleep efficiency, t2 (%)	92	93	89
PSG sleep latency, t1 (min)	4	23	5
PSG sleep latency, t2 (min)	9	3	5

Conclusions: Because we studied only 3 patients, results are necessarily descriptive. Also, one patient slept relatively well at both t1 and t2 despite meeting insomnia criteria. Medication was given in an open-label manner without a placebo group; and psychosocial treatment was not controlled. Nevertheless, gabapentin was tolerated well at these low doses and was associated with improved sleep on PSG in 2 of 3 alcoholic patients.

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1109.C

Effect of Chronic Administration of PROVIGIL® (Modafinil) on the Single-Dose Disposition Profile of Warfarin in Healthy Volunteers

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Introduction: PROVIGIL® (modafinil) is a novel agent for the treatment of excessive daytime sleepiness (EDS) in patients with narcolepsy (US Modafinil in Narcolepsy Multicenter Study Group, 1998). During an in vitro enzymatic induction study in human hepatocytes, modafinil was found to suppress, in a concentration-related fashion, the expression of cytochrome P450 2C9 (data on file, Cephalon, Inc.). This enzyme is important in the metabolism of warfarin (COUMADIN®), a medication used to treat patients with thrombosis, stroke, or myocardial infarction. If suppression of this metabolic enzyme were to occur in patients taking both modafinil and warfarin, the elimination of (S)-warfarin (the more pharmacologically active enantiomer of warfarin) would be reduced with potential clinical consequences. This study evaluated the effect of chronic administration of modafinil on the single-dose pharmacokinetics (PK) of warfarin in healthy volunteers.

Methods: 28 healthy male and female volunteers were enrolled in this placebo-controlled, single-blind, single-period study. Subjects were randomized into two groups, which both received warfarin (5 mg) on Day 1 followed by a 7-day washout period. One group then received once-daily doses of modafinil (200 mg, Days 8-14; 400 mg, Days 15-41) and the other group received once-daily doses of placebo (Days 8-41). On Day 35, both treatment groups received warfarin (5 mg) concomitantly with the scheduled dose of modafinil or placebo. Blood samples were collected immediately prior to dosing on Days 1, 33, 34, and 35 and at selected times up to 168 hours after dosing on Days 1 and 35. Plasma concentrations of (R)- and (S)-warfarin, modafinil and its two main circulating metabolites (modafinil acid and modafinil sulfone) were determined using validated HPLC methods and prothrombin times were assessed by a validated automated method. Safety was evaluated by recording adverse events (AEs).

Table 1

PK Parameter	MOD + W (N = 13)		PBO + W (N = 12)	
	Day 1	Day 35	Day 1	Day 35
(R)-Warfarin				
C_{max}, ng/mL	371.3	380.2	375.2	379.2
[a] t_{max}, hr	0.5	0.5	1.0	0.8
[b] $t_{1/2}$, hr	49.1	53.3	49.5	54.1
$AUC_{0-\infty}$, ng·hr/mL	17149.8	18347.5	17264.9	17622.3
(S)-Warfarin				
C_{max}, ng/mL	381.9	378.6	379.4	395.0
[a] t_{max}, hr	0.5	0.5	0.8	0.5
[b] $t_{1/2}$, hr	35.2	40.3	36.5	38.9
$AUC_{0-\infty}$, ng·hr/mL	8416.5	9858.6	10463.0	11879.3

MOD, modafinil; W, warfarin; PBO, placebo
[a]Median
[b]Harmonic Mean

Results: 26 of the 28 (93%) subjects enrolled successfully completed the study. The single-dose absorption and disposition PK of (R)- and (S)-warfarin were not significantly altered by modafinil treatment (Table 1). The mean steady-state PK parameters of modafinil, modafinil acid, and modafinil sulfone were consistent with those from previous PK studies of modafinil in healthy volunteers (data on file, Cephalon, Inc.). There were no changes in the prothrombin times from baseline or between the treatment groups. The most common AEs reported by the 13 patients receiving modafinil plus warfarin and the 12 patients receiving placebo plus warfarin were headache (N=5, N=4, respectively), fatigue (N=4, N=3), and nausea (N=3, N=2). All AEs reported were mild to moderate in nature.

Conclusions: Chronic administration of modafinil at 400 mg did not alter the single-dose PK of (R)- or (S)-warfarin in healthy volunteers. From all the evidence obtained to date, it appears unlikely that coadministration of modafinil would have any effect on the anti-clotting response to warfarin treatment. Administration of modafinil and warfarin or placebo and warfarin was generally well tolerated.

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1427.C

Induction of Nocturnal Panic by Pharmacological Challenge with CCK-4 During Different Sleep Stages in Healthy Volunteers

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Introduction: Sleep panic attacks are frequent in patients with panic disorder with estimates for lifetime prevalence ranging from 18 to 69 %. Epidemiological studies indicate that sleep-related panic occurs almost exclusively during delta sleep and during the transition from stage 2 to delta sleep, but almost never during REM sleep. The locus ceruleus (LC) is a particularly important brain region related to anxiety (e.g. Redmond et al. 1987) Evidence from lesions as well as electrical and pharmacological stimulation suggests that the LC might be implicated in arousal, the sleep-wake cycle, anxiety and fear. This study was designed to examine the relative contribution of different sleep stages to the induction of nocturnal panic attacks by CCK-4. The aminergic neurons in the LC are known to cease firing during REM sleep, so it might be expected that higher doses of CCK-4 would be necessary to provoke a panic awakening in REM as opposed to NREM sleep.

Methods: Subjects were volunteers between the ages of 18 and 33 years who were in good physical health and not pregnant. Medical assessment included a physical examination, EKG, blood chemistry and urine drug screening. Subjects agreed to refrain from use of beta-blockers and psychiatric medications 7 days and from alcohol and coffee 24 hours prior to the study. Subjects participated in a three-night protocol consisting of one accomodation night and two infusion nights. On the infusion nights, an intravenous catheter was inserted approximately 30 minutes prior to bedtime and kept open with a slow infusion of normal saline solution. During each night, doses of 50 and 100 mg of CCK-4 were administered during the first or second period of delta sleep or during the second and third period of REM sleep respectively. Blood samples were drawn 5

minutes before and 15 and 30 minutes after each injection of CCK-4. Subjects were randomly assigned to begin with either REM or NREM stimulation on the first night in a single-blind manner. Response to injection of CCK-4 was monitored using an infrared video system. If a subject awakened and appeared fully alert, the investigator entered the subject´s room from an adjacent laboratory and administered the Acute Panic Inventory (API).

Results: The study is still in progress. So far, eight healthy control volunteers have been included. All subjects awakened within a maximum of four minutes following injection of CCK-4. API scores tend to be higher for NREM as opposed to REM awakenings. Administration of CCK-4 resulted in a significant increase in heart rate from baseline without an apparent difference between either dose of the compound. Likewise, a statistical correlation between heart rate and panic symptomatology could not be found.

Conclusions: Our study shows that it is possible to provoke panic attacks during specific sleep stages. The differential sensitivity to cholecystokinin challenge during REM and Non-REM sleep might indicate that the LC plays an important role in mediating the panicogenic effects of cholecystokinin.

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1132.C

Effect of a Low Dose of Clonidine on Human Sleep

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Introduction: Noradrenergic system is considered to have a permissive role in the appearance of REM sleep. In other words, noradrenergic neuron needs to cease firing when REM starts. Clonidine, a noradrenalin (NA) alpha-2 receptor agonist, is thought mainly to act on autoreceptors in NA neuron, and to reduce the NA release. Previous studies in healthy man have shown that clonidine, at a dose of 0.1mg or higher, decreased REM sleep, and at 0.05mg, had no effect. But if clonidine reduces NA activities, REM sleep is likely to increase. Thus, we examined the effect of low dose clonidine on human sleep.

Methods: Six healthy volunteers, 22-24 years of age, took part in this study. The experiment was carried out in double-blind cross-over design. Each subject was recorded on consecutive 3 nights: 1st night (adaptation night, with placebo), 2nd night (placebo or drug night), 3rd night (withdrawal night, with placebo), and after 2 weeks intervals or more, participated in the following session: 4th night (adaptation placebo night), 5th night (drug or placebo night), 6th night (withdrawal placebo night). Twenty five microgram of clonidine was given at 10 p.m., and polygraphic recording was carried out from 11 p.m. to 7 a.m. Sleep stages were scored according to Rechtschaffen and Kales criteria.

Results: REM sleep increased in drug night and withdrawal night ($p<0.01$, $p<0.05$, respectively), and NREMsleep (stage2+3+4) decreased in drug night and withdrawal night ($p<0.01$, respectively).

Conclusions: Several studies on the effect of clonidine on sleep in healthy man has been reported. Kanno et al[2] reported that 225 microgram (high dose) of clonidine reduced REM sleep and increased NREM sleep. Gaillard et al[2] reported 0.4 microgram (low dose) of clonidine did not change REM sleep in drug night, but increase it in withdrawal night. In our experiment the dose of clonidine was mostly the same as in Gaillard et al [2], and is concordant with their result at the point that low dose of clonidine increase REM sleep in drug night or withdrawal night. As the results that low dose of clonidine increases REM sleep and high dose of clonidine reduces REM sleep. In locus coeruleus, relating with expression of REM sleep, low dose of clonidine might act on pre-synaptic alpha 2 autorecetor and reduces NA activity, but high dose of clonidine might act on post-synaptic alpha 2 receptor and increases NA activity.

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1156.C

Chronic IV Maternal Fluoxetine Causes Transient Changes in Sheep Fetal Behavioural State

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Introduction: Clinical depression is diagnosed in 10-15% of women during pregnancy increasing the risk of negative pregnancy outcomes including increased risk of low birth weight newborns and preterm delivery. Untreated depression exposes the mother and fetus to health risks such as poor self-care and nutrition, disturbed sleep patterns, lack of prenatal care, increased exposure to alcohol and drugs and increased risk of suicide. For these reasons, treatment of depression during pregnancy is crucial. Pharmacological interventions have a faster and more consistent onset of action that psychotherapy and thus are preferable. Fluoxetine (Fx), a selective serotonin reuptake inhibitor, is often prescribed due to its efficacy, high margin of safety and mild side effects. Fx treatment has been shown to alter sleep patterns in adults with single doses causing a decrease in total sleep time and REMS while chronic exposure decreased sleep efficiency, increased eye movements and increased arousals from NREMS. The effects of fluoxetine on sleep have not been studied in the fetus although 5-hydroxytrytophan (5-HTP), the precursor of serotonin has been studied in the sheep fetus. Fetal IV administration of 5-HTP resulted in a prolonged high voltage electrocortical (ECOG) activity, an increase in the incidence of fetal breathing movements (FBM) and an increase in blood pressure (1) while infusion into the cisterna magna increased FBM without affecting ECOG activity (2). Combined with the fact the Fx easily crosses the placenta, these results suggest that maternal treatment with Fx may result in changes in fetal behavioural state parameters such as electrocortical activity, eye movements and breathing movements.

Methods: Four pregnant sheep were surgically prepared for the measurement of blood gases, heart rate, blood pressure, ECOG activity, eye movement and FBM. After 3 days recovery from surgery, ewes received a 70 mg bolus IV infusion of Fx over 2 min in 10 ml of sterile water followed by continuous infusion at a rate of 0.08 mg/min for 8 days followedby a three day postinfusion period. Data is presented here as means ± SEM.

Results: The incidence of low voltage (LV) ECOG decreased from 55 ± 3% on the control day to 40 ± 5% on the day of Fx infusion returning to near normal values by infusion day 3. Eye movements decreased in incidence from 53 ± 1% on the control day to 35 ± 3% on the day of Fx infusion and remained low throughout the experimental period. High voltage (HV) ECOG increased from 44 ± 3% on the control day to 51 ± 5% on the day of Fx infusion and remained in this range throughout the infusion and post infusion periods. FBM decreased from 38 ± 4% on the control day to 27 ± 2% on the day of Fx infusion returning to normal values by infusion day 2.

Conclusions: These data show that although maternal treatment with Fx alters fetal behavioural state, these changes are relatively short lived. It is likely that these results are due to an increase in serotonin levels but it is not clear if they are due to a direct effect of serotonin on the central nervous system or indirectly due to the hypoxemia induced by reduced uterine artery blood flow.

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1500.C

Outpatient Prescription Patterns of Hypnotics, Anxiolytics, and Antidepressants

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Introduction: Over the past decade there has been a marked shift in prescribing patterns for the treatment of insomnia.[1] Insomnia is treated less frequently and nonhypnotics have replaced hypnotics as the more commonly used drugs. This study further assessed patient and prescription characteristics of the 10 most frequently mentioned drugs for treatment of insomnia.[1]

Methods: The outpatient pharmacy database of the Henry Ford Hospital, Health Alliance Plan, was searched over the 1/1/98 to 6/30/99 time period for mentions of the 10 most frequently used drugs for the treatment of insomnia in the National Disease and Therapeutic Index (NDTI) for 1987-1996.[1] The 10 drugs are: alprazolam, amitriptyline HCL, clonazepam, doxepin HCL, flurazepam HCL, lorazepam, temazepam, trazodone HCL, triazolam, and zolpidem tartrate. To qualify as a mention the prescription had to be written as 1 per day. The data base does not include information about the prescribing physician=s desired drug action (i.e., to promote sleep or other clinical effect). But with the exception of the 4 drugs with a hypnotic indication, all the remaining drugs specify divided daily dosing for their primary indication. Further, for those 6 non-hypnotic drugs the vast majority of prescriptions (80% and greater), with the one exception lorazepam (60%), were written for doses lower than the indicated minimal therapeutic dose. Thus dose and dose schedule suggest the desired drug action for the majority of these prescriptions is to promote sleep. These 10 drugs were classified by their indication as antidepressant (amitriptyline HCL, doxepine HCL, trazadone HCL), anxiolytic (alprazolam, clonazepam, lorazepam), and hypnotic (flurazepam HCL, temazepam, triazolam, zolpidem) and compared on patient and prescription characteristics.

Results: The total patient population covered over the 18 month period was 287,456 and 20, 014 (7%) patients received one or more prescriptions during the 18 mo. (25% antidepressant, 20% hypnotic, and 55% anxiolytic). Tabled below are the patient characteristics for the three drug indications.Females were most likely to receive antidepressants and least likely to receive hypnotics ($X2 = 152.6$, $p<.001$). Those receiving hypnotics were older than those receiving antidepressants or anxiolytics ($F=90.8$, $p<.001$). Of the 20,014 patients 89% had no diagnosis for the drug indication; 5% had a depression diagnosis, 6% anxiety, and .004% insomnia; none of these were primary diagnoses. Patients with a depression diagnosis were most likely to receive anxiolytics (56.6%) and least likely to receive hypnotics (17.8%), while those with anxiety received anxiolytics and with insomnia hypnotics ($X2 = 164.5$, $p<.001$). The prescription characteristics by drug indication are presented on the next table.The ratio of lowest to highest dose prescribed was narrow for hypnotics, whereas quite wide for antidepressants and anxiolytics. The mean number of pills per prescription differed among all three indications ($F=1158.9$, $p<.001$), as did the mean number of refills ($F=157.8$, $p<.001$), and the mean total number of pills per patient for the 18 mo ($F=2339.1$, $p<.001$) with hynotics prescribed the most conservatively.

Table 1

	% Pts Receiving Each Drug Indication		
	Depression	Anxiety	Insomnia
Antidepressant	25.6	15.2	26.9
Hypnotic	17.8	10.8	51.3
Anxiolytic	56.6	74.0	21.8

Table 2

	Num Refills	Total Pills
Antidepressant	4.32 (4.95)	133.2 (20.3)
Hypnotic	3.31 (4.24)	86.0 (52.8)
Anxiolytic	4.84 (5.47)	220.3 (151.3)

[1] Listed alphabetically for drugs within the indication (i.e. amitriptyline HCL, doxepin HCL, trazadone HCL)

Conclusions: Nonhypnotics account for the majority of prescriptions. Patients receiving hypnotics are more likely male and older and receive a narrower dose range, in smaller quantities, and with fewer refills.

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1848.C

Pharmacodynamic Evaluation of Single, Escalating Doses of (S)-Zopiclone Compared to Zolpidem

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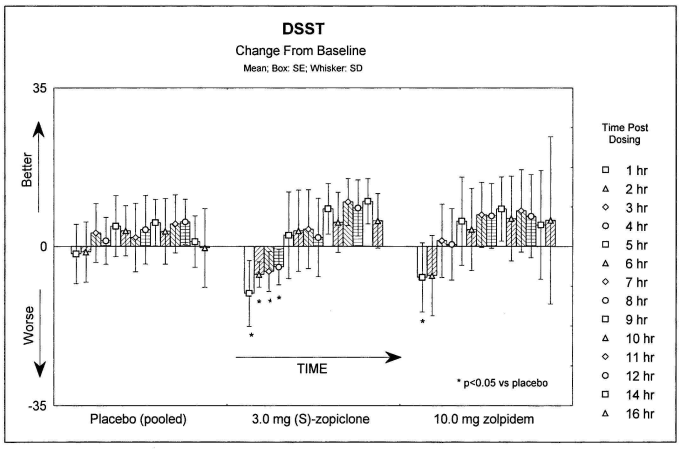
Introduction: (S)-Zopiclone is the active enantiomer of racemic zopiclone, a non-benzodiazepine hypnotic. Racemic zopiclone is marketed in Europe and many other countries. Recommended doses are 5 and 75 mg. (S)-Zopiclone may offer advantages over currently available therapies in terms of duration of steep. The present study describes the first evaluation of (S)-zopiclone in man.

Methods: Healthy male and female volunteers participated in this daytime, double blind, placebo-controlled, in-patient study. Single oral doses included 1, 2, 2.5, 3, 3.75, 5, 7.5 mg of (S)-zopiclone, 5 and 10 mg of zolpidem, and placebo. Dose escalation of (S)-zopiclone was accomplished by evaluating sequential cohorts of 9 subjects each, 3 of who were randomized to receive placebo. Subjects receiving zolpidem (5 mg, n=5 or 10 mg n=5 or placebo n=2) were studied as a separate group. Subsequent to screening over a 13-day period, subjects spent the night preceding dosing in the clinic with an obligatory 9 hrs in bed. After oral dosing in the morning, vital signs and adverse events (AE) were monitored for the following 24 hours. The Digit Symbol Substitution Test (DSST) was administered prior to dosing and post-dosing hourly for 12 hrs and at 14 and 16 hrs. DSST results were computed as change from baseline.

Results: Mean baseline DSST scores (± SD) were 59.7±1.0, 59.2±11.0 and 61.8±13.0 for the (S)-zopiclone, placebo, and zolpidem groups, respectively. Both (S)-zopiclone and zolpidem were well tolerated. At the higher doses of (S)-zopiclone (5 mg and 7.5 mg), the incidence of

sedation and dizziness were more frequent than with placebo. Diplopia was noted at the 10 mg zolpidem dose, but not at any zopiclone dose. Doses as low as 1 mg demonstrated an effect on the DSST. DSST data for 3 mg (S)-zopiclone, 10 mg zolpidem, and placebo are summarized in the figure. The effect of 3 mg (S)-zopiclone on the DSST was of comparable magnitude and onset to 10 mg zolpidem, but longer in duration. Significance of the effect on baseline DSST compared to placebo was tested using Tukey's HSD for unequal N. Placebo had no effect on post-dose DSST.

Figure 1



Conclusions: In confirmation of the preclinical observations, (S)-zopiclone was found to have sedative properties in man. These effects occurred at doses less than half of reported sedative/ hypnotic doses of racemic zopiclone. (S)-zopiclone was well tolerated. The effect on the DSST lasted for four hours with 3.0 mg (S)-zopiclone compared to 2 hours with zolpidem, suggesting a potential for a longer duration of sleep with nighttime administration of (S)-zopiclone. Lower doses of (S)-zopiclone may be useful in inducing sleep when a shorter duration of action is desired.

1212.C

Alcohol Ingestion at Bedtime Impairs Long Term Memory for Both a Cognitive Procedural and Motor Procedural Task

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Introduction: There is evidence to suggest that REM sleep deprivation following acquisition of cognitive procedural tasks impairs memory for these tasks days or weeks later. It has also been reported that interruption or deprivation of Stage 2 results in memory loss for motor procedural or skills tasks (Smith, 1995). Substantial alcohol ingestion at bedtime can interfere with normal sleep. Moderate ingestion of alcohol just prior to bedtime has been reported to result in marked memory impairment for a cognitive procedural task despite the fact that there were no significant differences between the groups in terms of amounts of sleep in any of the sleep stages (Sandys-Wunsch and Smith, 1991). The design of this last mentioned study did not allow us to conclude whether the memory loss was due to the effect of the alcohol directly on memory mechanisms or on the sleep architecture (possibly REM) of the participants. The present study was done to answer this question. As well, it was decided to use a skills task, which has been shown to be sensitive to Stage 2 sleep loss or interruption.

Methods: Thirteen college undergraduates were given an acclimatization night in the sleep lab. The following day they were asked to learn both a cognitive procedural (Tower of Hanoi) task and a skills task (Pursuit Rotor) between 4:00-5:30 PM in the afternoon. After task acquisition the members of the Afternoon group (5 females, 1 male) were asked to ingest 4-5 oz. of vodka in orange juice over a period of 2 hours. The Bedtime group members (6 females, 1 male) were asked to begin drinking the same amount of alcohol 2 hours before bedtime. All participants were retested on the two tasks between 4-5:30PM one week later.

Results: A t-test for independent groups revealed that the Afternoon group was superior to the Bedtime group on both the Tower of Hanoi ($t = 2.41$, $df=11$, $p < .04$) and the Pursuit Rotor ($t = 2.53$, $df = 11$, $p < .03$) task. An examination of the sleep values did not reveal any significant differences between the two groups on the number of minutes of each state of sleep.

Conclusions: This study shows that memory loss for both tasks occurred as a result of alcohol ingestion just prior to sleep onset. Combined with previous data, results suggest that it is the subtle effect of alcohol on sleep states which result in memory loss rather than alcohol directly affecting memory mechanisms. Results strengthen the hypothesis that alcohol ingestion at bedtime results in marked long term memory loss for a cognitive procedural task and indicate that memory for motor skills tasks are also impaired.

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1562.C

The Pharmacokinetics of Gamma-Hydroxybutyrate (GHB) Following Acute and Chronic Administration to Narcoleptic Patients

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Introduction: Previous clinical trials have documented the efficacy and safety of gamma-hydroxybutyrate (GHB) in the treatment of narcolepsy, particularly in the narcoleptic patient with cataplexy (Broughton and Mamelak, 1979; Scharf et al, 1985). Xyrem® is a 500 mg/mL oral solution of sodium gamma-hydroxybutyrate (sodium oxybate, GHB) currently undergoing clinical development as a treatment for cataplexy associated with narcolepsy. The present study was conducted to compare the plasma pharmacokinetics of GHB in narcoleptic patients following their first dose of Xyrem and after eight weeks of nightly treatment with Xyrem oral solution.

Methods: Thirteen patients with narcolepsy (including cataplexy) previously confirmed by standard polysomnography and Multiple Sleep Latency Testing were selected for participation. All patients were otherwise in generally good health as determined by medical history, physical examination, ECG and clinical laboratory measures. After giving written informed consent, the patients were administered a single bedtime dose of 4.5 g. of GHB. Blood samples (5 mL) were taken at the following times: Pre-Dose, 10, 20, 30 and 45 minutes, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5 and 7 hours after the dose. The blood was centrifuged and the plasma removed and stored frozen until taken for analysis of GHB content by a validated LC/MS/MS method with a lower limit

of quantification of 5.0 mc/mL. The patients were subsequently treated on an outpatient basis with Xyrem at the 4.5 g nightly dose (given as 2 x 2.25 g q4h) for eight weeks. Following chronic nightly treatment for eight weeks, the patients returned to the research laboratory and were again treated with the same 4.5 g GHB single dose given at bedtime. Blood samples were again collected at the same time-points as after the first dose and the plasma analyzed.

Results: The patients included 3 men and 10 women ranging in age from 24 to 52 years. Xyrem was well tolerated by all of the patients. No serious adverse events were reported and all 13 patients completed the study. The major pharmacokinetic indices are shown in Table 1. No statistically or clinically significant differences were present between acute and chronic dosing conditions for any of the kinetic measures.

Table 1. Pharmacokinetics of GHB After Acute and Chronic Dosing (Mean ± SD)

GHB	Lag T. (hr.)	Tmax (hr.)	Cmax (μg/mL)	T ½ (hr.)	AUC (μg/mL•hr)
Acute Dose	0.06 ± 0.04	0.87 ± 0.46	90.0 ± 30.8	0.72 ± 0.23	226.5 ± 74.9
Chronic Dose	0.03 ± 0.06	0.72 ± 0.44	103.6 ± 31.3	0.76 ± 0.34	255.5 ± 79.3

Conclusions: These results confirm that sodium oxybate (GHB) administered as an oral aqueous solution is very rapidly absorbed being discernable in the plasma of narcoleptic patients within 10 minutes after ingestion and reaching mean peak plasma concentration (Tmax) in 45 minutes. The elimination rate of GHB from plasma is also rapid in narcoleptics as shown by average half-lives (T½) of approximately 45 minutes. These findings are consistent with previous studies in healthy human volunteers and in narcoleptics (Scharf et al, 1998). These results also demonstrate for the first time that the pharmacokinetics of GHB do not differ significantly between acute and chronic dosing. Thus, chronic Xyrem treatment is not associated with the development of tolerance or changes in plasma elimination. These findings are consistent with the clinical observations of narcoleptic patients who have been maintained on constant GHB dosage for many years without any change in therapeutic benefit.

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1588.D

Nightmare Frequency Versus Nightmare Distress Among People with Frequent Nightmares

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Introduction: Studies have shown that nightmare frequency is only moderately related to the waking suffering or distress associated with nightmares.[1,2] Moreover, Belicki[2] reported that students' ratings of nightmare distress, but not of nightmare frequency, were significantly related to scores on both the Symptom Checklist 90 (SCL-90-R) and the Beck Depression Inventory (BDI). The aim of this study was to investigate whether this general pattern would be found among a non-student population presenting with frequent nightmares.

Methods: Subjects were 9 men and 24 women (mean age = 38.1 ± 14.2 yrs) who were recruited as part of a larger study on the psychophysiology and treatment of nightmares (NMs). NMs were defined as an "unpleasant dream that awakens you and for which you have clear recall" and were differentiated from bad dreams and night terrors. Subjects were selected on the basis of reporting 1 or more NMs per month for at least 1 year; 24 reported 1 or more NMs per week. Subjects completed a battery of questionnaires including the SCL-90-R, the BDI, the Beck Anxiety Inventory (BAI), and a standard measure of NM distress.

Results: The mean number of NMs reported by the 33 subjects was 2.4 ± 1.7 NMs per week. The correlation between NM frequency and NM distress was only .18. As shown in Table 1, when compared with NM frequency, NM distress had stronger correlations with the SCL-90-R but not with the BDI.

Table 1. Pearson correlations between NM frequency, NM distress and psychopathology.

	NM Frequency	NM Distress
SCL-90-R	.12	.51**
BDI	.39*	.30
BAI	.20	.21

Note: * = p < .05; ** = p < .005

Conclusions: These preliminary results provide mixed support for the hypothesis that psychopathology is related to NM distress but not NM frequency. However, they are consistent with the idea that NM frequency is only moderately related to the waking distress associated with NMs, even among people with very frequent nightmares. Understanding how waking levels of nightmare distress can influence or mediate the relation between nightmare frequency and psychopathology requires further study.

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1614.D

Are Frequent Nightmares a Form of Obsessive-Compulsive Mentation?

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Introduction: Belicki (1992) has shown that nightmare (NM) frequency and NM distress should be treated as separate constructs. The objec-

tive of the present study was to replicate this finding and assess psychological symptom patterns in relation to NM frequency, NM distress, and their effects on waking life (Krakow, 1998).

Methods: Subjects were recruited through media advertisement for a study on NMs. Forty-six NM sufferers (33F, 13M, 39.2 ± 15.1 yrs, range 18-74) completed mailed questionnaires on psychological symptom patterns (SCL-90-R), annual NM frequency, distress caused by NMs (5 point scales) and the negative effects of NMs on various aspects of waking life (5 point scales). NMs were defined as an "unpleasant dream that awakens you and for which you have clear recall" and were clearly differentiated from bad dreams and night terrors. Three stepwise multiple regressions were performed to determine which of the 9 dimensions of the SCL-90-R predicted each of the 3 NM variables.

Results: Sleep and mood were reported on the measure of NMeffects as being the variables most affected by NMs (58% and 13% respectively). The average number of NMs reported per year was 113 ± 99.4 (range: 1-364). Because of its skewed distribution, NMfrequency was normalized through square root transformation. NMdistress (average score: 38 ± 8.3) was significantly correlated with NMeffects ($r=.53$ $p<.01$) and with NMfrequency ($r=.37$ $p<.05$). NMeffects was positively correlated with NMfrequency ($r=.30$ $p=.058$). NMeffects was positively correlated with all of the SCL-90-R dimensions (all $ps<.05$) except obsessive-compulsive (O-C). NMdistress was significantly related to Interpersonal sensitivity, depression, phobic anxiety and paranoid ideation (all $ps<.05$). NMfrequency was significantly related only with the O-C dimension ($p<.05$). Multiple regression analyses indicated that the NM variables were predicted as follows:1. NMdistress: by depression only ($R2 = 0.21$, Beta = 0.45, $p=.002$); 2. NMeffects: by anxiety only ($R2 = 0.39$, Beta = 0.62, $p<.0005$);3. NMfrequency: by obsessive-compulsive only ($R2 =0.26$, Beta =0.51, $p=.012$).

Conclusions: The measure of NMeffects complements the NMdistress measure in revealing specific effects of NMs on waking function and appears to be related to more psychopathological indicators. The results replicate and extend the distinction between NM frequency and NMdistress including the moderate correlation between these variables (Belicki, 1985). More importantly, they indicate that these two factors are differentially associated with psychopathological symptoms. On the one hand, distress/effects are associated with mood disorders (depression, anxiety). On the other hand, the results raise the possibility that frequent nightmares are a form of obsessive (intrusive and persistent images that cause anxiety) and/or compulsive (repetitive behaviour or mental acts) mentation.

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1028.D

Non-Dreamers - Dream Reports on Awakening in the Sleep Lab From Individuals Reporting Non-Dreaming

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Introduction: It is generally accepted that everyone experiences dreaming. Multiple studies have shown a lack of correlation between REM Sleep and the presence or absence of cognitive reports of dreaming. An absence of reported dreaming has been shown to occur with several specific varieties of CNS damage in which REM Sleep is preserved (these studies do not assess whether dreaming is reported on awakening from sleep).[1] This study attempts to determine whether sleep laboratory patients reporting an absence of dreaming also report an absence of dreaming when awaken during polysomnographic evaluation.

Methods: Patients were queried by questionnaire as to whether they experienced dreaming [dreaming defined as the recall of any mental activity occurring during sleep]. Individuals responding negatively were further queried by interview as to when their last dream had occurred. Individuals reporting never having experienced a dream were classified as NON-DREAMERS. Individuals reporting dreaming in the past, but no dreaming for at least one year were included in the study classified as RARE DREAMERS. During clinically indicated polysomnography, each of these individuals were queried by the attending sleep technician when awaken for clinical reasons (toilet, c-pap application) as to whether they could recall any mental activity, color, emotion, or feeling from their sleep. Individuals having a late night REMS period (4-6 AM) were awaken after at least 10 minutes of the REMS period and queried as to whether dreaming had occurred. It is hypothesized that reported dreaming on awakening would be unusual in these groupings, and more likely to be reported in the RARE DREAMERS grouping.

Results: Among the NON-DREAMERS(N=5)(18 TOTAL AWAKENINGS), thirteen awakenings in the laboratory occured out of Sleep Stages 1 and 2, four awakenings out of REM sleep, and one out of Deep Sleep. Average age of NON DREAMERS was 45, 60 % were female, and 20 % were currently working. Associated diagnoses include OSA in 3/5 patients, obesity in 2/5, and epilepsy in 2/5. No dreams (0%) were reported on awakening in the sleep lab.. In the RARE DREAMERS grouping (N=7) (20 TOTAL AWAKENINGS), 12 awakenings were out of Sleep Stage 1 and 2 (one dream report - 8%) and eight awakenings were out of REM sleep (one dream report - 12.5%). Average age of RARE DREAMERS was 61, 28 % were female, average latency since experiencing a dream was 14.6 years (range 1.5-55), and 4/7 were currently working. Associated diagnoses included OSA (6/7),and PLMD (3/7). Of total awakenings for the RARE DREAMER grouping, dreams were reported in 10% of awakenings.

Conclusions: This study indicates that a subgroup of individuals (NON-DREAMERS) without known CNS damage do not report dreaming when awaken from REM and NREM sleep and queried as to the presence of dreaming. Do these individuals have dreams? Both subgroups (NON-DREAMERS and RARE DREAMERS) have much lower recall of dreams than the general population. Dreaming can occur without recall, ex. Behavioral correlates of dreaming in young children and animals, delayed recall of dreaming. In these NON-DREAMERS, if dreaming does occur, it occurs without cognitive or behavioral correlates.

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1078.D

Contextualizing Images in Content Obtained From Different Sleep and Waking States

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Introduction: A Contextualizing Image (CI) is the powerful, central image of a dream, hypothesized to "contextualize" or picture a dominant emotion or emotional concern of the dreamer. Thus, the dream image "I was overwhelmed by a tidal wave" contextualizes the emotion of terror or helplessness of someone who has recently experienced a severe trauma.A scoring system for CIs has been developed in which scorers examine a dream report on a blind basis, decide whether there is a CI, assign it an intensity of 0 (no CI) to 3 (a very powerful or intense CI), and then try to determine what emotion (from a list of 18) might be contextualized by this particular CI. The CI score - the 0 to 3 intensity score - shows good inter-rater reliability (r = .70 to .90). It has been shown that dreams score higher than daydreams, that series of dreams after an acute trauma score higher than ordinary students' dreams,[1] and that dreams of students who report any physical or sexual abuse score higher than dreams of those who do not.[2] The present study examines CI scores in four different physiologically defined conditions - REM sleep, NREM sleep, sleep onset and wakefulness.

Methods: From a sample of 1576 mentation reports obtained from students wearing a Nightcap device (details in (3)), a subsample of 563 reports were used in this study - about eleven reports from each of thirteen subjects for each of four states. Reports were all scored for CIs by a single trained scorer whose scoring had shown correlations of r = .80 with other trained scorers. The data was analyzed by ANOVA for the thirteen subjects times four states.

Results: Significant differences were found between states ($F = 41$, $p < .001$) but not between subjects. The mean CI scores were, for waking, .09 ± .30; for sleep onset, .10 ± .32; for NREM sleep, .38 ± . 62; and for REM sleep, .73 ± .83. By post-hoc analyses, REM sleep scores were significantly higher than NREM sleep scores which were significantly higher than scores in sleep onset and waking. The REM sleep reports were significantly longer than others. An ANCOVA , covarying for length (word count), produced no change in the ANOVA results above.The emotions most often judged as contextualized were 1) anger, frustration, 2) happiness, joy, excitement, and 3) power, mastery, pride. This was the case for REM sleep as well as NREM sleep. The other conditions had too few CIs to examine meaningfully.

Conclusions: CI scores are highest in REM sleep and next highest in NREM sleep with no significant differences between the other two conditions. (The sleep onset reports in this study, as opposed to some others, were predominantly short and mundane.) Overall, the study shows that CI scores do distinguish material according to state and in the direction which would be expected (highest in REM sleep). It is noteworthy that the CI score (intensity) differentiates the states well, whereas the type of emotion does not. The same findings - differentiation by CI intensity but not by type of emotion - were reported in comparing trauma and non-trauma dreams.[2]

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1113.D

Hypnagogic Images in Normals and Amnesiacs: Source, Synthesis, and Function

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Introduction: When people engage in novel physical or mental activity for extended periods of time, they often experience a hallucinatory replay of the activities as they are falling asleep. Individuals who become intensely involved in video games report intrusive images of the games as they are falling sleep, and similar phenomena have also been reported after periods of skiing, rock climbing and sailing. The nature, function, and source of these hypnagogic images has not been determined. In this study, the phenomenon was studied in novice and expert players of the game Tetris, as well as in a cohort of densely amnesic patients.

Methods: Twenty-seven subjects, including 12 novices, 10 experts, and 5 dense amnesiacs with no known prior Tetris experience, provided informed consent and then played the computer game Tetris for 7 hr over 3 days, 2 hr at the first exposure and 1 hr on each subsequent morning and evening. During the nights following play, subjects were automatically and repeatedly prompted for mentation reports during the first hour of attempted sleep. Experimental awakening were made using the Nightcap sleep monitoring system as described in Rowley et al. (1998). All reports were dictated into microcassette recorders and subsequently transcribed.

Results: Nine of 12 novices and 5 of 10 experts (63% of subjects) reported a total of 30 intrusive hypnagogic images of the game (7.2% of all reports). The 9 novices reporting Tetris images had mean game scores for the initial 2-hr session only half that of the subjects reporting no imagery (unpaired t-test: $df = 10$, $t = 3.69$, $p = 0.0004$), and those experts who reported Tetris imagery showed a strong negative correlation between initial game scores and the number of reports containing Tetris images (Pearson r-value = -0.92, $df = 3$, $p = 0.025$). Two of five experts reporting imagery reported that the imagery was consistently of their previous version of the game. Thus, one reported the imagery as being in color with music from her Nintendo version, while the version used in the study was in black and white and without music. All images were stereotyped, consisting of visual images of the Tetris pieces, usually "falling" in front of the subjects' eyes, sometimes rotating and fitting into place. Surprisingly, 3 of 5 dense non-Koraskoffs amnesiacs, with extensive bilateral medial temporal lobe damage including the hippocampus, reported a total of 8 hypnagogic Tetris images. The percent of subjects (60%) and percent of all reports (7.4%) were very similar to controls. Patients reported the images without recollection of playing the game. One reported, "I see images that are turned on their side. I don't know what they are from, I wish I could remember, but they are like blocks."

Conclusions: We conclude that amensiacs and normals alike create these hypnagogic Tetris images using cortical memory systems, without participation of the hippocampus or other medial temporal lobe structures. These findings further suggest that hypnagogic dream images arise in conjunction with a process of sleep-dependent memory consolidation and integration.

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POSTER PRESENTATIONS

1121.D

Autobiographical Memories That Go "Bump" in Your Dreams

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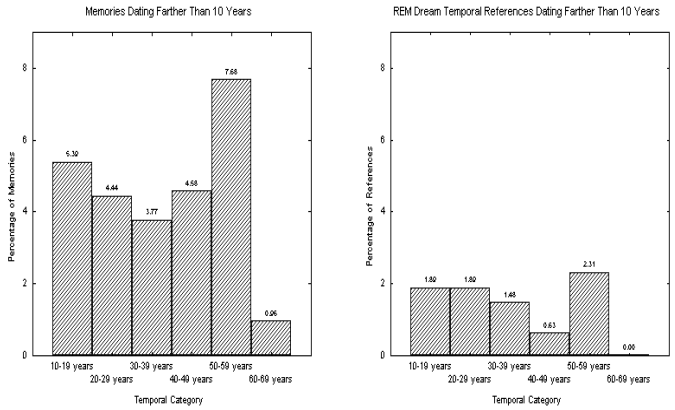
Introduction: Since the earliest times it has been believed that dreams are somehow related to memory in that they often incorporate bits and pieces of recent, and sometimes in a spectacular way, very remote and forgotten life experiences. It is still unknown, however, if there exists a pattern with which dream production mechanisms differentially draw elements from the brain's mnemonic repertoire. Rubin, Wetzler & Nebes (1986) explained that the temporal distribution of autobiographical memories (AM) in the elderly follow a cubic trend characteristic of three components: 1) a high frequency of AM for the most recent 10 to 20 years that declines with increasing remoteness; 2) a resurgence of AM or a "reminiscence bump" in the 30 to 50 years ago period; 3) a paucity of AM for the 60 plus years ago period. This study examined if the distribution of temporal references (TR) identified in dreams also fits such a cubic trend, typical of AM.

Methods: Thirty retired teachers/nurses (M age=65) were invited to spend one night in the laboratory and were awakened from all REM periods. In the morning, participants were asked to identify TR for every character, object, setting, event and activity in their dreams. A sample of AM was taken using the semantic cuing method. Only AM and REM dream TR reportedly non accessed by conscious awareness since time of original experience were classified in temporal bins.

Results: A total of 474 oneiric TR (from 68 dreams) and 742 AM were categorized using 7 temporal bins of 10 years. Frequency distributions revealed that 73.18% of waking AM and 91.89% of oneiric TR fell in the 0-10 years ago category. The remainder of AM and oneiric TR were distributed among the other six categories (see graph) and for both dreams and memories, there was a resurgence of references in the "50-59 years ago" category. Contrast analyses (1, 1, -1, -1, 1, -1) were conducted on the proportion of AM and oneiric TR distributed in the 6 temporal bins dating farther than 10 years. Results indicated that the AM did follow a significant cubic trend ($F(1, 29) = 8.75$, $p<.01$). Results further indicated that the oneiric TR also followed a cubic trend ($F(1, 29) = 6.47$, $p<.02$).

Figure 1



Conclusions: This is the first observation that the temporal distribution of oneiric TR closely matches that of the distribution of AM elicited in waking state. The observation that dream production mechanisms seem to differentially draw mnemonic elements in a pattern similar to that of autobiographical memories supports the notion of continuity between waking and dreaming memory and cognitive processes (Foulkes, 1985).

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1466.D

Enhancement of Subjective Intensity of Dream Features in Normal Subjects by the SSRIs Paroxetine and Fluvoxamine

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Introduction: Altered dreaming occurs during SSRI treatment and withdrawal[1,2] and rating scale data below shows that paroxetine and fluvoxamine intensify dreaming.

Methods: Fourteen normal, paid volunteers (4 Males, 10 Females; mean age 27.4 yr, range 22-39) free of medical or neuropsychiatric symptoms or psychotropic or sleep affecting drugs participated in a 31-day study consisting of 7 days drug-free baseline; 19 days on either 100 mg fluvoxamine (7 Ss) or 20mg paroxetine (7 Ss) in divided morning and evening doses; and 5 days acute withdrawal. Every morning, subjects completed eight 5-point Likert scales rating the past night's dreaming (if dreaming recalled) for: 1) memorability, 2) visual vividness, 3) amount of sound, 4) amount of movement, 5) emotional intensity, 6) emotional pleasantness, 7) meaningfulness, and 8) strangeness. Subject means were computed for each dimension during four "Study Phases" defined as: baseline (BA), days 1-7; increasing plasma drug levels (IN), days 8-17; steady state plasma levels (SS), days 18-26; and withdrawal (WD), days 27-31. Study phase and drug means were compared by: i. MANOVA of all 8 scales; ii. repeated measures 2-way (Drug X Study Phase) ANOVAs for each scale; iii. Bonferroni-corrected post-hoc Means Comparisons between Study Phases (when main effect significant).

Results: Dreams intensified during SS and WD compared to BA and IN. MANOVA revealed a significant Study Phase main effect ($p<0.05$). ANOVAs revealed significant Study Phase main effects for memorability, visual vividness, sound, meaningfulness ($p<0.05$) and emotional intensity ($p<0.01$) but not for movement, emotional pleasantness or strangeness. Neither MANOVA nor ANOVA showed significant Drug main effects or Drug X Study Phase interactions. Post-hoc comparisons showed SS dreams significantly ($p<0.0083$) more emotionally intense than BA dreams and more meaningful than IN while WD dreams had more sound than BA and more were more memorable than IN. Trends ($p<0.05$) appeared for other variables (SS>BA: memorable, vivid, sound, meaningful; SS>IN: memorable, emotionally intense; WD>BA: memorable, vivid, emotionally intense; WD>IN: vivid, sound). No scale showed increased intensity in opposing directions. Increased subjective dream intensity accompanied a decrease in dream recall frequency in SS compared to BA but paralleled an increase in dream bizarreness in WD compared to BA.[3]

Conclusions: Steady state treatment and acute withdrawal from paroxetine and fluvoxamine enhance subjective memorability, emotional intensity and perceptual vividness of dreaming. This is not due to better recall which decreased during SS. Rebound from serotonergic REM suppression may contribute to increased dream intensity within particular nights

(during SS) or after a prolonged suppression (during WD).

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1817.D

Nightmare Distress And Time Perspective

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Introduction: There has been much research on one's time perspective (i.e. past, present, future) and waking behavior. However, there has been very little research that has indicated a relationship between one's time perspective and dreams. Although, a recent study by Marquez et al (1999) has suggested that there is a correlation between present hedonistic, past negative, and present fatalistic time perspective and at least one type of nightmare (i.e. fantastic nightmares, post-traumatic nightmares, and night terrors). The purpose of the present study was to extend the previous research by Marquez et al on nightmares and time perspective by investigating the amount of nightmare distress that individuals with present hedonistic, past negative, future, past positive and present fatalistic time orientations experience. We hypothesized that present fatalistic and past negative individuals would report more nightmare distress than present hedonistic, future, or past positive individuals.

Methods: To do this, we asked 271 undergraduate students (100 male, 171 female) to complete a questionnaire that included the Zimbardo Time Perspective Inventory (1999) and Belicki's (1992) Nightmare Distress Questionnaire which measures the amount of waking distress associated with one's nightmares. We then converted each participants score on the Zimbardo Time Perspective Inventory to a standard score and assigned each participant to the time dimension group they scored the highest on. This resulted in the following number of individuals in each group: 42-Present Hedonistic, 51-Past Negative, 53-Future, 56-Past Positive, and 69-Present Fatalistic.

Results: A one way analysis of variance revealed that there was a significant difference among the Present Hedonistic, Past Positive, Future, Past Negative and Present Fatalistic time dimension groups in the amount of nightmare distress they reported, $F(4,270) = 3.87$, $p < .01$. A multiple comparison analysis showed that there was a significant difference in the amount of nightmare distress that was experienced by the Present Fatalistic group when compared to the Future and Past Positive groups, with the Present Fatalistic group (M=22.58, SD = 7.31) having more nightmare distress than the Past Positive (M=18.50, SD = 4.55) and the Future (M=19.43, SD =5.26) groups.

Conclusions: Thus, the data support the notion that there is a relationship between an individuals time orientation and nightmares. More specifically, that individuals with a present fatalistic time orientation have a more pronounced relationship with nightmare distress and more problems in their waking emotional adjustment because of their nightmares compared to individuals with other time orientations. Therefore, we concluded that time perpsective as measured by the Zimbardo Time Perspective Inverntory has implications for sleeping behavior as well as waking behavior.

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1170.D

Affect in REM Dreams: Exploration of a Time-of-Night Effect

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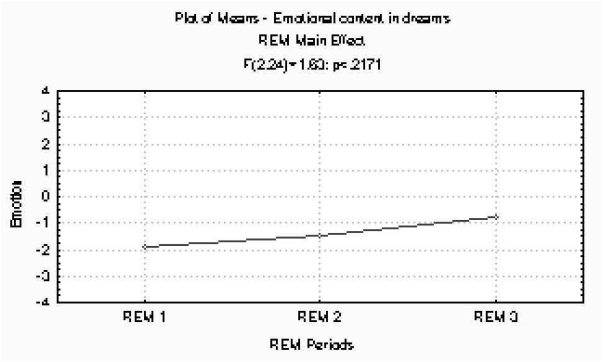
Introduction: Hall & Van de Castle (1966) focused on the coding of explicitly stated emotions in dreams. They found that surprisingly few emotions were included in dream reports, and when they were, 80% of emotions could be described as negative. Throughout the years, there has also been interest in the notion of processing emotion in dreams. Kramer (1993) summarizes the results of various studies and illustrates a theory in which negative affect is processed throughout the night resulting in improved morning mood. The present study was designed to examine the dreamer's subjective perception of affect in dreams and to explore the possibility of a time-of-night effect in dream content. It was hypothesized that an important level of negative emotions would be found in dreams, but that later REM dreams would become less negative.

Figure 1. Emotional Content in Dreams



Methods: Thirteen young-adult women spent four nights each in the laboratory. Awakenings for REM dream reports were made at 5 minutes for the first two REM periods and at 10, 15 and 20 for the remaining REM periods. After collecting three REM dream reports subjects were no longer awakened. Upon rising in the morning, participants were asked to identify the presence and intensity of 8 emotions in their dreams (joy, happiness, apprehension, anger, sadness, confusion, fear, and anxiety). The dreams were categorized according to their respective REM period and an average score per subject per REM period 1, 2 or 3 was calculated. The data from subsequent REM periods was not utilized since representive data was not always available for these later REM periods. The data was analysed by a judge who examined the dreamer's ratings of emotions and determined whether the prevailing emotion was either positive or negative. This decision was based on the intensity of the stated emotions. Each dream was then given a score which could vary from

most positive (4), neutral (0), to most negative (-4).

Results: Descriptively, 45 of the possible 156 dreams (29%) had no emotion and were therefore coded as neutral. Negative and positive emotions prevailed in 85 (54%) and 26 (17%) of the 156 dreams respectively. In total, 261 emotions were identified in the 111 dreams that did contain affect. Overwhelmingly, these emotions were negative in nature (82%). ANOVAs revealed that there was no significant difference in affective content for the dreams collected in different REM conditions, $F(2, 24) = 1.63$, $p < .22$. Planned comparisons indicated that there was no linear trend in REM dream emotions becoming more neutral or positive as the night progressed, $F(1, 12) = 2.07$, $p < .18$.

Conclusions: It therefore seems that subjective perception of affect in dreams reveals similar information than the explicit rating of affect in dreams: negative emotions tend to be more prominent than neutral or positive emotions in REM dreams. This study, however, indicates that emotion is perceived as present in dreams by the dreamer even when it is not explicitly stated as such. This is interesting since other aspects which are rarely found explicitly in dreams (such as pain) could perhaps benefit from a more subjective appraisal by the dreamer. Furthermore, the finding that there does not appear to be decreasing negativity of affect as the night progresses raises questions about the mood regulatory function of dreaming. A study which would be specifically constructed to examine this further would be useful in exploring this issue. This study should include ratings of mood before and after the sleep period which could then be compared to the affect in dreams.

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1835.D

Cognition in Stage 2 Sleep Parallels Neural Network State

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Introduction: By definition, Stage 2 sleep displays EEG spindling, K-complexes, and up to 6s of high amplitude slow waves (>75μV; ≤2Hz) per 30s epoch. Stage 2 is scored, however, not only during stage-defining events but also during intervals between them: up to three minutes of "relatively low voltage, mixed frequency EEG" (LVMF), similar to the EEG of Stage REM. During Stage REM, and presumably during LVMF in Stage 2, thalamic neurons discharge in depolarization-based single spikes. During spindling, thalamic neurons discharge in hyperpolarization-based bursts. If hyperpolarization is increased (if, for example, $GABA_B$ receptor activity increases), thalamocortical oscillation can assume the magnitude and regularity of "spike and wave" (absence) epilepsy, whose symptoms include interruption of consciousness and a blank countenance. It is hypothesized that cognition in Stage 2 sleep reflects the binary brain state of Stage 2: Some Stage 2 mentation reports will be dreamlike, and others will be absencelike.

Methods: A classic set of 73 Stage REM awakenings and 73 Stage 2 awakenings was reanalyzed. First, Total Recall Count (TRC) was redefined as "number of words that describe remembered experience." (When TRC is defined as the *informative content* of a sleep mentation report, TRC in Stage 2 reports—in sharp contrast to REM reports—is often judged to be zero. As a consequence, studies of this REM-Stage 2 corpus have deleted as many as 45% of Stage 2 reports.) Second, using accepted criteria of dreamlikeness and a detailed symptomatology of absence, (a) Stage 2 reports (TRC>0) and Stage REM reports (TRC>0) were classified as either dreamlike or absencelike, and (b) Stage 2 reports and Stage REM reports (Stage 2 TRC=Stage REM TRC) were classified as either dreamlike or absencelike.

Results: Two reports were deleted as unscorable; two as misclassified; six as "thoughtlike"; and three as contentless (TRC=0). In the remaining instances (Table 1), subjects related (a) dreamlike imagery or narrative of more or less complexity, with or without bizarre elements; or (b) some version of "I can't remember" or "Nothing"; or (c) (despite all Stage 2 EEGs' meeting formal scoring criteria) some version of "I did not fall asleep" or "I did not feel asleep." For independent observations (no REM-Stage 2 pairs) equated for TRC ($F = .454$; $p = .763$), dreamlike reports still significantly outnumber absencelike reports in Stage REM; in Stage 2 the ratio is about the same as for all reports (Table 2; $\chi^2 = 10.0624$, χ^2 critical for 1 $df = 7.88$; proportion in critical region = .005).

Table 1. All Scorable REM-Stage 2 Report Pairs: Dreaming vs. Absence

	Dreamlike	Absencelike	Total
REM	**68** M_{log}TRC=1.61	**1** M_{log}TRC=0.70	**69**
Stage 2	**27** M_{log}TRC=1.32	**37** M_{log}TRC= 0.84	**64**
Total	**95**	**38**	**133**

Table 2. REM-Stage 2 Report Pairs (Equal TRC): Dreaming vs. Absence

	Dreamlike	Absencelike	Total
REM	**12** M_{log}TRC=0.95	**1** M_{log}TRC=0.70	**13**
Stage 2	**12** M_{log}TRC=0.94	**18** M_{log}TRC= 0.98	**30**
Total	**24**	**19**	**43**

Conclusions: The hypothesis that cognition in Stage 2 sleep is binary—paralleling the binary neurophysiology of Stage 2—cannot be rejected. Whether dreamlike reports in Stage 2 are elicited chiefly from intercurrent LVMF, and absencelike reports chiefly from "true" Stage 2, remains to be discovered.

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1196.D

Children's Dreaming: A Study Based on Questionnaire Compiled by Parents

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Introduction: Classical methodologies to collect children's dream reports (upon REM awakenings or upon final morning awakenings at home) even though guarantee the maximum proximity between dream

report and its experience, involve considerable costs and several methodological problems. For these reasons, at present days, empirical data on young children's dreams derive from few studies on small groups of subjects. The purpose of the present study was to collect data on dreaming in developmental age through a questionnaire compiled by parents. Using this method we expect to collect in a more easy and economic way data on larger groups to compare their congruence with known data in literature. In this paper we present some preliminary data.

Methods: The questionnaires were distributed to parents in several Italian schools. The questionnaire (QSEE) used considers three groups of questions: A. Questions about parents'dreams compliance; B. Questions about dreaming on children in particular on the last dreams they have had; C. Questions about children's sleep habits. Here we analyze the answers of the first 210 parents of children from 2 to 7 years of age (125 male / 85 female).

Results: Parents who have answered at questionnaire were more frequently mothers (83%) than fathers (17%). Their mean age was 34 years old. Generally their "believed that dreams may have a meaning" (79%). In reference to last dream report from their children parent answer that this had happened at morning awakening (65%) and spontaneously (81%) rather than on application (14 %). During the narration of this dream children appear tranquil or satisfied (74%), anxious (21%), gloomy (5%). In tables we summarize other results.

Table 1. Dreams recalled by children in the previous month and length of the last dream report

Dreams recalled	2-5 years–olds	6-7years-olds
	N 100	*N 87*
None	41% (41)	32% (28)
1-3 dreams	46% (46)	48% (42)
4-6 dreams	10% (10)	8% (7)
7 or + dreams	3% (3)	11% (10)
Dream Length	*N 76*	*N 76*
Dream as: "Brief sentence"	21% (16)	17% (13)
"Long sentence"	9.% (7)	8% (6)
"Brief story"	62% (47)	64% (49)
"Long story"	5% (4)	7% (5)
"Long and articulate story"	3% (2)	4% (3)

Table 2. General contents of the last dream report by children

Contents	2-5 years –olds	6-7yeras-olds
	N 74	*N 74*
Settings		
Home	19% (14)	27% (20)
School	16% (12)	4% (3)
Recreational	7% (5)	8% (6)
Other	23% 17)	31% (23)
Vague	35% (26)	30% (22)
Character		
Animals	51% (39/76)	40% (30/76)
Family	59% (44/74)	50% (36/72)
TV characters	21% (16/75)	24% (18/74)
Known child	46% (33/72)	37% (27/73)
Social interactions	69% (48/70)	67% (48/72)

Conclusions: These results are mainly congruent with those of previous studies based on interviewing children on their dreams directly (home and school settings) (Resnick et al 1994; Colace e Tuci, 1995). Some features (e.g. dream length, percentage of animals character, home setting and vague setting) are also in agreement also respect to children's REM dreams (Foulkes, 1982). This study shows that through parents'answers it is possible to have reliable indications on the characteristics of young children's dream reports.

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1198.D

Self-Representation in Young Children's Dream Reports

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Introduction: Studies on children's dreams can help to understand dreaming and psychological aspect of child development. While several children's dreams collected by Freud and by Piaget shown an active self-representation in their scenario, systematic studies on children's dream reports remains divided about the possibility that young children represent themselves actively in their dreams. In two extensive studies Foulkes and co-workers (e.g. Foulkes et al 1990) observed that there was a lack of active self–representation in REM dreams of young children (3-7 years-old). By contrast, Resnick et al (1994) reported that in home-dreams an active self-representation was present in 85% of young children (4-5 years-old). This result was confirmed in a second study where an active self-representation was observed in 72% of children's dreams collected in school setting (4-6 years-old) (Colace et al 1995). Here we report a further analysis of self-representation based on larger group of young children's dreams.

Methods: We analyzed three sets of dream reports. Set A. 44 dream reports from 44 children 3-7 years old (mean age 5;7 years) collected by researcher in school setting in individual session. The question "please tell me the last dream you have had" was made. Set B. 64 dream reports from 64 children 3-7 years old (mean age 5;6 years) collected as in Set A. Here, however a series of questions to elicit additional details on self-representation and other aspects (e.g. settings, characters) was made. Set C. 25 dream reports from 9 children 3-5 years old (mean age 4;3 years) collected in home setting. Parents interviewed their children at morning awakenings using the same questions of Set B. Tape recordings of dream reports were transcribed and self-representation was scored as in previous studies: "Active-participant" when there was an explicit statement of presence and/or action in the dream scene (e.g. "I have dreamed that I ski with dad, with mama and my sister.."), "Passive-observer" when the children report that stay in dream's scenario but merely as observer (e.g. "I have dreamed that I was seeing the film .."), "Absent" when in dream there is not present the dreamer (e.g. "I have dreamed a cow that eat..")

Results: Active self-representation was present in 68% of dream reports. Only in 23% of dreams the dreamer was not present.

Table 1. Self-representation in children's dream reports

Dream Reports	Age Years	Dreams N	Absent	Passive/ Observer	Active/ Participant
Set A	3-7	44	11 (25%)	4 (9%)	29 (66%)
Set B	3-7	64	14 (22%)	6 (9%)	44 (69%)
Set C	3-5	25	6 (24%)	2 (8%)	17 (68%)
Total		133	31 (23%)	12 (9%)	90 (68%)

Conclusions: Frequently young children have dreams with an active participation of the self. These results confirm previous investigation

based on children's dreams collected in home and school settings. Our results together with previous data (Resnick et al.; Colace et al) do not support the hypothesis that young children do not have the cognitive skills to represent themselves actively in their dreams (Foulkes). The discrepancy remains between dreams recalled after a rather long interval (school and home setting) and those recalled directly upon REM awakenings (sleep laboratory setting). It is possible, but not demonstrate, that also for self-representation the differences between laboratory-collected (L) and home-collected (H) dreams are due to differential L vs. H selectivity in attentional/memory processes.

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1203.D

Life Satisfaction and Emotions in Dreams of Elderly and Young Women

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Introduction: Blick & Howe observed that the dreams of elderly women contained more joy-enjoyment emotions than those of college women, who in turn had more anger-rage and fear-terror emotions in their dreams. Interestingly, a study of elderly women by Schredl, Schröder & Löw observed that the negative emotionality of dreams was correlated inversely to life satisfaction of their participants. We attempted to further examine this relation in two age groups, using both laboratory and home dreams and analysing eight different dream emotions. Following the continuity hypothesis between waking and dreaming, we predicted that positive emotions would be more related to life satisfaction than negative emotions.

Methods: Thirty retired women , aged between 60-77, and 28 undergraduate psychology students, aged between 20-33, spent a single night in the laboratory for dream collections from each REM periods. Participants were asked to spontaneously report their dreams. In the morning, they were asked to judge the presence and intensity (1 = very little to 4 = a lot) of the following eight emotions in their dreams: happiness, contentment, quietness and cheerfulness as positive emotions, and anger, sadness, uncertainty, and anxiety as negative emotions. Prior to the night in the laboratory, each participant kept a morning dream diary at home for one week and fill in a questionnaire on the presence and intensity of the same emotions. At the initial interview, participants were asked to fill in 5-items using a 7-point rating scale of Life Satisfaction.

Results: For each participant, the mean score for each emotion was calculated separately for REM and home dreams. A series of t-tests conducted on the intensity of emotions revealed that in REM dreams, young women had more anxiety ($t(56) = 2.6$, $p = 0.012$) and uncertainty ($t(56) = 2.01$, $p = 0.05$) than the elderly. In home dreams, young women had more uncertainty ($t(56) = 2.42$, $p = 0.02$) than the elderly which had more calm ($t(56) = 2.72$, $p = 0.02$) and contentment ($t(56)=2.13$, $p=0.04$). Life satisfaction did not differ between the young (M = 25.5/35) and elderly women (M = 26.3/35). Multiple Regression using life satisfaction as dependent variable and the positive and negative emotions as a independent variables were calculated separately for REM and home dreams and for each age group. Only in REM dreams of young women was life satisfaction related to positive emotions ($beta=0.43$, $p=0.03$).

Conclusions: This study suggests that generally young women have more negative emotion in their dreams than elderly women. Although there is no difference in life satisfaction between groups, the young women who had greater life satisfaction experienced a higher intensity of positive emotions in their dreams. The fact that both groups did not show the same pattern needs further exploration.

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1851.D

REM Mentation in Narcoleptics and Normal Controls: A Test of Two Neurocognitive Theories

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Introduction: A major dispute in dream science concerns what sorts of brain mechanisms are crucial for the universal characteristics of dreaming. The "activation-only" view predicts that sleep mentation reflects overall brain activation levels combined with blockade of external stimuli (Antrobus 1986). The AIM model (Hobson 1992) suggests additional specific effects upon mentation of phasic activation and neurochernical brain modulation. REM mentation data from narcoleptics and normals could not be accounted for by the activation only view but were in line with the AIM model.

Methods: 244 reports of REM mentation (from 3 to 15 minutes into stage) were derived from (1) early (n=43) and late night (n=40) sleep in 15 narcoleptics off medication, (2) early (n=37) and late night (n=61) sleep in 9 matched normal controls, and (3) from sleep onset (SOREM) during daytime naps (n=43) and at the onset of night time sleep (n=20) in the narcoleptics. The study was performed in a home-setting using ambulatory polysomnographic techniques and instrumental awakenings. Subjects scored their REM mentation for (1) level of reflective consciousness and (2) visual vividness (photo response scale). Judges rated mentation reports for (3) bizarre improbabilities (excluding paralysis, flying, falling), (4) improbability density (controlled for report length), (5) bizarre discontinuities, and (6) report length (total recall count, TRC). Visual vividness and TRC were applied as "activation measures". Variables were transformed (log, dichotomized, rank) to cope with skewdness and tested with ANOVA and accompanying post hoc tests, and with rank sum tests (visual vividness).

Results: The following findings argue for a heterogeneity of sleep mentation and thus against the activation-only models: (A) The prevalence of reflective consciousness was higher ($p < .001$) but the prevalence of improbabilities ($p < .002$) and improbability densities ($p < .05$) were lower for both SOREM and nocturnal REM in narcoleptics as compared to nocturnal REM in normals (Fig. 1). (B) Comparing reports from the second half of night, narcoleptics scored lower than normals on both TRC ($p = .018$) and visual vividness ($p < .01$) (Fig. 2), in spite of possibly higher circadian activation levels in narcoleptics (Broughton & Mullington, 1994). (C) Compared with nocturnal REM in normals, both SOREM and nocturnal REM in narcoleptics had fewer discontinuous characters, objects, and actions ($p < .05$), again in spite of (i) assumed

higher circadian activation levels and (ii) for SOREM - similar levels of TRC and visual vividness.

Figure 1

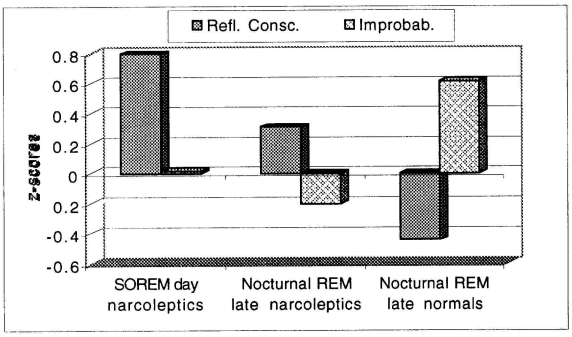

Figure 1. Refl. consc. and improb. in three central states

Figure 2

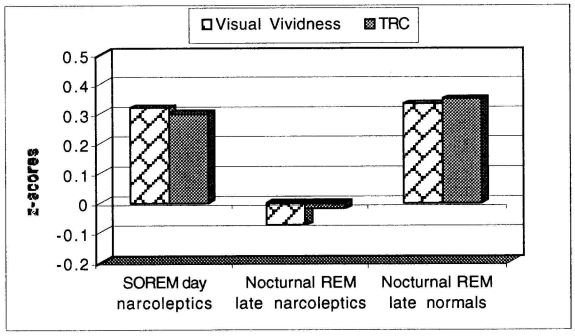

Figure 2. Visual viv. and TRC in three central states

Conclusions: The heterogeneous variation in the cognitive variables are contrary to the activation-only hypothesis but consistent with the AIM model. To account for the findings, I hypothesize that REM sleep in narcoleptics is associated with frequent, intermittent elevations in aminergic brain modulation and perhaps also with reductions in tonic and phasic cholinergic activity.

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1852.D

Reciprocal Variations in Thoughts and Hallucinations Across Wake-Sleep States

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Introduction: The relative exclusion of thinking from recent studies of sleep mentation may have skewed our understanding of how mental activity differs across brain-mind states. We present data on internal deliberation (thinking) and endogenously generated imagery (hallucinations) derived from an extensive field study of cognitive activity in 16 normal subjects (Stickgold et al, 1998). We asked whether thinking and hallucinatory experiences have (1) different prevalences and (2) different incidences when they occur, in active waking, quiet waking, sleep onset, NREM, and REM.

Methods: Sixteen subjects carried a pager during 14 days and wore the Nightcap (Ajilore et al. 1995) during 14 nights. Dictated mentation reports were provided 4 times each day when paged and from sleep when awakened. 1576 reports with content were obtained, of which 881 were from active waking, 57 from quiet waking (lights off, lying in bed with eyes closed), 244 from the sleep onset period, 165 from NREM, and 229 from REM. About one-third of the NREM and REM reports were derived from computerized awakenings, the remaining from spontaneous awakenings. All sleep stages were identified using the Nightcap. Reports were scored for (1) the prevalence of endogenously generated imagery (hallucinations), (2) the prevalence of deliberate thoughts, defined as continued mental effort or occupation such as contemplating, brooding, decisions, and planning, that lacked images, and (3) for the presence of multiple, non-concurrent hallucinations or thoughts (either sequences or multiple incidents).

Figure 1

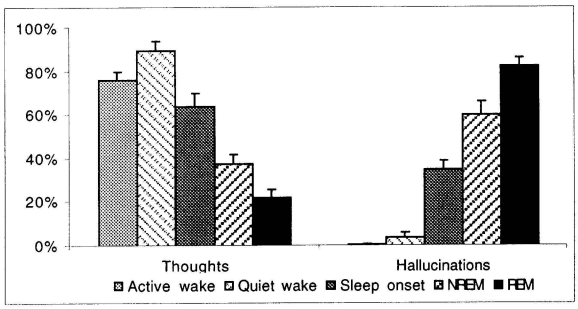

Figure 1. Prevalence of thoughts and hallucinations

Figure 2

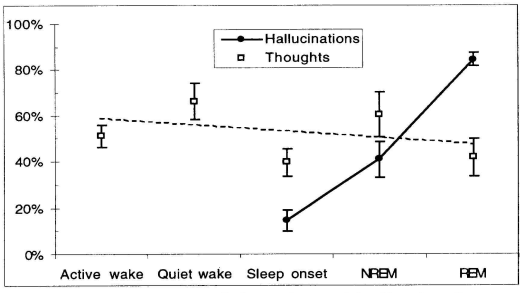

Figure 2. Percentage of thought and hallucination *reports with sequence development*

Results: Thoughts and hallucinations fluctuated in an inverse, reciprocal manner across active waking, quiet waking, sleep onset, NREM, and REM. The prevalence of hallucinations increased across the states (ANOVA, df = 4, F = 87.13, p < .0001), while thoughts decreased in parallel (ANOVA, df = 4, F = 44.97, p < .0001; Fig. 1). Similarly, the prevalence of hallucinations in conjunction with sequential development increased across states (ANOVA, df = 4, F = 54.57, p < .0001). But in contrast to their overall prevalence, the frequency of reports of thoughts

with sequential development declined only gradually across states (ANOVA, df = 4, F = 1.65, p = .18, Fig. 2).

Conclusions: The results demonstrate prominent differences in the modal pattern of mental activity across the wake-sleep states, and cannot be accounted for by "activation-only" models. Based upon the AIM model (Hobson et al., 2000), we suggest that the decrements in thinking and increments in hallucinations across waking, sleep onset, NREM, and REM reflect, first, a change in input-output gating and, second, a progressive shift from a high to low aminergic to cholinergic neuromodulatory ratio which is accompanied by changes in regional brain activation patterns.

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1563.D

Trait Anxiety and its Relationship to Dream Content

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Introduction: Many studies have investigated relationships between nightmare frequency and various measures of anxiety.[1] Taken together, the data indicate a weak to moderate relationship between anxiety and retrospective as well as sleep log-based estimates of nightmare frequency. Little is known, however, about the relationship between anxiety and the content of every day dreams. One preliminary study[2] of 46 women found that scores on a measure of trait anxiety were significantly negatively correlated with ratios of positive to negative affect in everyday dreams. The goal of the present study was to obtain more detailed information on the relation of dream content to anxiety.

Methods: Seventy-four women and 18 men with a mean age of 39.8 years (SD = 12.5, range 19-81) completed the trait version of Spielberger's State-Trait Anxiety Inventory (STAI-T) and recorded the dreams they remembered on awakening for 14-21 consecutive days. For each dream reported, participants were asked to describe the overall emotion and its intensity on a 5-point scale ranging from very weak to intense. The first 10 dream reports from each subject were first scored using the participants' self-reports to determine a) the proportion of dreams containing intense or very strong negative emotions (e.g., nightmares or bad dreams), b) the ratio of positive to negative affect reported irrespective of intensity, and c) dream report length (number of words). In addition, the dream content analyses instrument of Hall and Van de Castle was used to determine: a) the ratio of friendly to aggressive interactions, and b) the ratio of success and good fortune experiences to failure and misfortune experiences. Since men and women did not differ significantly in age, scores on the STAI-T, or on dream content variables, their data were combined for all analyses.

Results: There was no significant association between levels of self-reported anxiety and the length of dream reports. Anxiety was significantly correlated with the proportion of dreams containing intense or very strong negative affect ($r = .30$, $p < .005$) and with the ratio of positive to negative dream content ($r = -35$, $p < .001$). Scores on the STAI-T did not correlate significantly with any other of the dream content variables.

Conclusions: Consistent with past studies, the data indicate a small but statistically significant relation between anxiety and the occurrence of highly unpleasant dreams. The results also confirm preliminary findings showing that people's scores on a measure of trait anxiety are negatively correlated with the proportion of their dreams containing positive affect. However, no relation was found between anxiety and more refined quantitative measures of positive and negative dream content.

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1579.E

Lack of Sleep/Wake Circadian Rhythms in Narcoleptic Patients Submitted to a 4 Hour Ultradian Regimen

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Introduction: In narcolepsy the disruption of the sleep /wake pattern by intrusion of sleep during the day and of wakefulness during the night suggests that sleepiness could be caused by a disorder of the rhythmic sleep organiza-tion resulting from the interaction of the sleep processes (homeostatic, circadian, ultradian). It has been shown that there was no solid evidence for a disorder of NREM sleep homeostatic regulation in narcolepsy (Tafti et al 1992). Furthermore a 4 hour rhythmicity of slow wave activity (SWA) has been evidenced in narcolepsy (Nobili et al 1995). Finally the sleep wake circadian pattern was persistent but dramatically attenuated in narcoleptics subjected to an ultradian regimen of 90 minutes (Dantz et al 1994). Thus in narcolepsy the ultradian component should be stronger than the circadian component and the sleep wake cycle could be organized according to an ultradian pattern of 4 hours. In order to confirm this hypothesis we submitted 8 narcoleptic subjects and 8 control subjects to a 4 hour ultra-dian regimen

Methods: Following a 16 hour sleep deprivation and a baseline night recording, 8 narcoleptics, 5 male and 3 female aged 18 to 28 years, mean 23.8 years ± 3.40 and 8 sex and age matched controls were maintained on a 4 hour sleep wake schedule for 48 hours. Each cycle (n=12) consisted of a 90 minute sleep period in which subjects were asked to sleep, followed by 150 minutes of enforced wakefulness out of bed. Timing of the beginning (08h30 to 10h00) of the first cycle was mathematically extrapolated from the SWA rhythmicity assessed during the baseline night. Poly-graphic recordings were performed during sleep periods only. In addition EEG power spectra and sleep microstruc-ture were assessed by means of fast Fourier transform and by digital filtering analysis. Body core temperature (BCT) was sampled every 5 minutes during the whole study. Circadian rhythms were assessed by means of cosinor proce-dure.

Results: Mean cycle sleep latency (SL) was significantly (p<.01) shorter and mean cycle total sleep time (TST) significantly (p<.01) longer in narcoleptics than in controls (SL=4.73 ± 1.23 min versus 27.60 ± 9.34 min, TST =77.48 ± 12.32 min versus 57.77 ± 11.43 min). Thus narcoleptics slept 249 minutes more than controls during the 48 hours. Mean slow wave sleep (SWS) cycle and REM sleep cycle were significantly increased (p<.01) in nar-coleptics in comparison with controls (SWS = 26.48 ± 5.42 min versus 22.85 ± 4.98 min, REM sleep = 16.03 ± 3.91 min versus 7.91 ± 3.12 min). Significant (p<.01) circadian rhythms of SL and TST were observed in controls but not in narcoleptics while significant (p<.01) circadian rhythms of BCT and REM sleep were observed in both groups. However REM sleep rhythm was stronger in controls than in narcoleptics.

Conclusions: When subjected to a 4 hour ultradian sleep wake regimen during 48 hours, narcoleptic patients did not exhibit anymore circadian rhythms of sleep wake patterns (SL and TST). These data suggest that an alteration of the circadian sleep wake process might be responsible for the occurrence of an ultradian (4 hours) sleep wake pattern specific of narcolepsy. However the preservation of the BCT circadian rhythm was in favor of the func-tionality of the circadian biologic clock.

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1876.E

Fixed Spectrum Light Field for the Treatment of Seasonal Affective Disorder (SAD)

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Introduction: The present study was conducted in order to determine if subjects with seasonal affective disorder (SAD) respond to three weeks of treatment with a fixed spectrum (red, green, blue) light source administered through fiber optic cables embedded in a pair of clear lenses mounted in conventional eyeglass frames.

Methods: Subjects were five males and 12 females between the ages of 18 and 60. In order to be included in the study, subjects were required to meet DSM IV criteria for recurrent major depression with seasonal pattern. They were required to obtain a baseline score on the Hamiltion Depression Rating Scale - Seasonal Affective Disorders Version (SIGH-SAD) of 20 or greater, with a Hamilton Depression Rating Scale score of 10 or greater, and an Atypical score of 5 or greater. Subjects also were evaluated using the Hypomania Interview Guide (HIGH-C), and SIGH-SAD-SR, HIGH-C-SR, the Zung Self-Rating Depression Scale, and sleep logs. Nine subjects were randomized into a high intensity light group (HIGH), and eight subjects were randomized into a low intensity light group (LOW). Subjects and raters were blinded to the light condition, as light devices were dispensed by a third party. Subjects used light devices at home, obtaining daily light exposure for a period of one hour between 06:00 and 08:00 AM. Subjects returned to the investigator's laboratory once each week for a period of three weeks at which time evaluations were repeated.

Results: T-tests were used to determine between group differences in the change scores (between baseline and visit three) following three consecutive weeks of treatment. Overall, highly significant differences (p< 0.0001) were observed in the mean scores obtained on all measures (except the HIGH-C instruments) between baseline and visit three, indicating significant improvement with treatment. There were no signifcant differences between baseline and visit three between the HIGH and LOW treatment groups, although a non-signficiant trend indicates greater improvement in the HIGH group (p< 0.10). Notably, subjects in the HIGH group were more likely to demonstrate a 70% decline in SIGH-SAD scores between visits two and three than those in the LOW group (p< 0.05). No significant difference were detected in the sleep log data, but these data were incomplete and considered unreliable.

Conclusions: The results of this study indicate that SAD subjects in both the HIGH and LOW treatment groups had statistically significant improvement in assessment scores following three weeks of treatment. No differrences were observed between the HIGH and LOW light conditions at these times. However, subjects in the HIGH group were more likely to demonstrate 70% or greater decline in SIGH-SAD scores than those in the LOW group between visits two and three. This finding is important because a 70% decline in scores has been used as a criterion of improvement in previous studies. Sleep logs did not contribute meaningful data to this study. Additional research using larger sample sizes, longer periods of assessment, and more reliable measures of sleep and wakefulness (e.g., actigraphy) is needed.

1242.E

Prevalence and Consequences of Circadian Abnormalities in Older Adults

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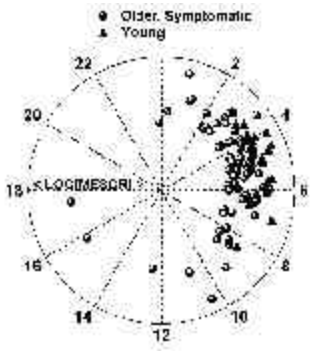
Introduction: The aims of this experiment were: (1) to establish the prevalence of circadian phase abnormality in older, symptomatic adults compared with young, healthy adults; (2) to compare the relative association of sleep disturbance in older adults with circadian malsynchronization, depression, sleep apnea, nocturnal myoclonus, age, gender and medication usage.

Methods: Seventy-two volunteers ages 60-79 with complaints of insomnia or depression were assessed for 5-7 days at home. A group of 30 young, good sleepers ages 20-40 years was also assessed. Sleep was assessed via an Actillume wrist monitor and a sleep diary. Objective and subjective measures of sleep onset latency (SOL), total sleep time (TST), and wakefulness after sleep onset (WASO) were averaged across all available nights of recording. Urine was collected over two 24-hr periods and radioimmunoassayed for 6-sulphatoxymelatonin (6-SMT). Volunteers completed the Center for Epidemiologic Studies Depression scale (CES-D) on days 3 and 6. It was also determined whether the volunteer had consumed any analgesic, cardiac drug, melatonin, antihypertensive, or antidepressant during the previous month. Following home recording, the volunteers spent 5 nights and 4 days in the laboratory. Sleep periods were fixed at 8 hours corresponding to volunteers' usual sleep habits. Using standard polysomnographic procedures, mean nightly SOL, TST, WASO, apnea-hypopnea index (AHI), and myoclonus index (MI) were determined. The sleep diary was maintained. On days 1 and 4, urinary 6-SMT and CES-D were assessed. Cosine fitting of 6-SMT data (ng/hr) across both days at home and, separately, across both laboratory collections estimated the acrophases (peak times) of 6-SMT excretion. Phase abnormality among the older, symptomatic group was

defined by the percentage of volunteers whose 6-SMT acrophases were outside the range established for the young volunteers. Circadian malsynchronization was defined as the absolute number of hours (advance or delay) between the 6-SMT acrophase and the middle of the sleep period. Stepwise multiple regressions were calculated associating sleep dependent variables with the predictors of sleep disturbance, both for home and laboratory data (circadian malsynchronization, AHI, MI, CES-D, age, gender, drug usage).

Results: Median 6-SMT acrophase for the young volunteers was 0412 hr (range: 0148-0612 hr) at home and 0436 hr (range: 0248-0824 hr) in the laboratory. Median 6-SMT acrophase for the older volunteers was 0358 hr (range: 2031-1335 hr) at home and 0447 hr (range: 2354-1731 hr) in the laboratory. The distributions of laboratory 6-SMT for the young and older volunteers are displayed in the Figure. Among the older volunteers, 26% of the home acrophases and 28% of the laboratory acrophases were outside of the range for young volunteers. Stepwise multiple regression of home data established the following independent associations: myoclonus index with TST (b=-0.26, p=0.045), circadian malsynchronization with WASO (b=0.29, p=0.018), and drug usage with subjective TST (b=-0.30, p=0.023). Stepwise multiple regression of laboratory data established that MI was independently associated with TST (b=-0.30, p=0.016), WASO (b=0.37, p=0.004), subjective SOL (b=0.30, p=0.025), and subjective TST (b=-0.28, p=0.039). Circadian malsynchronization was independently associated with SOL (b=0.37, p=0.002).

Figure 1. 6-SMT Acrophases



Conclusions: These data suggest that circadian malsynchronization is a common and significant cause of disturbed sleep in older adults.

Research supported by AG12364, HL61280

1591.E

Modeling Habitual Bed and Wake-up Times as a Function of Age: Circadian and Homeostatic Regulation in the 90 Min Day

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Introduction: The physiologic basis for early bed and rise times in aging often has been assumed to reflect a phase advance of circadian timing. In a companion Abstract,[1] we describe how such habitual patterns, as assessed via sleep diary, are reflected in BT, subjective sleepiness, and timing of maximal REM/sleep propensity recorded during 32 90-min "days." Here we report how habitual schedule may differentially reflect interactive components of both circadian and homeostatic regulation.

Methods: Subjects were 19 M & 29 W, ages 18-73. Full details regarding the current 90 min day protocol and derivation of phase markers have been described previously.[2] We employed an increase in SWS (Stg 3/4) on Recovery (relative to Baseline) as a marker of homeostatic drive. In order to take into account varying levels of sleep duration within subjects on Baseline and Recovery nights, both nights were truncated at the minimum TST for the shortest of the two nights (X= 373 mins). Stg 3/4% was then expressed as function of TST for each night.

Results: For all subjects Stg 3/4% increased significantly on Recovery (17.6%) relative to Baseline (13.9%) (t=3.50, p < .002) indicating that the 32 30/60 cycles induced mild sleep debt. Computation of median % increase in SWS resulted in low (< 5.0%) and high SWS drive (>/= 5.0%) groups. High and low drive subjects did not differ in age nor in gender composition. In men, older age was correlated with earlier bedtimes (rho = -.73, p < .0005) and wake up times (rho = -.79, p < .0001). Age was uncorrelated with any marker of circadian phase (timing of BT min/max, SSS min/max, BT/SSS phase diff, and 30 min nap with max TST/REM). In men, low SWS drive was associated with earlier SSS max (p < .02), earlier time of max TST on 30 min naps (p < .001), and a trend towards earlier habitual bedtime (p < .12). In women, older age was also correlated with earlier bedtimes (rho = -.57, p < .002) and wake-up times (rho = -.58, p < .001), as well as several markers of circadian phase, including timing of BT min (p < .07), SSS max (p < .07), phase difference between max SSS and BT (p < .05). In women, SWS drive was unrelated to bedtime/wakeup time, BT min/max, SSS min/max, BT/SSS phase diff, and timing of max REM. The timing of max TST on 30 min naps tended to occur later in low SWS drive women (p < .07).

Conclusions: These results show that although both older men and women go to bed and wake up earlier than younger persons, they may do so for very different reasons. In women the relationships described suggest a relative phase advance of various circadian markers with age. In men no such relationships were shown with age but lower SWS rebound was associated with these putative markers of phase advance. These results can be explained if the increase in SWS in males seen under mild sleep loss reflects a customary compensatory response to sustained wakefulness in the habitual situation. The data suggest that age-dependent changes in habitual sleep-wake schedule may reflect a complex gender-dependent interaction involving both circadian and homeostatic components.

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1601.E

Habitual Sleep Schedule Changes with Age and is Reflected in Rhythms of Body Temperature, Sleepiness and Sleep Propensity in a 90-Min Day

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Introduction: We have instituted the 90-min day to investigate age-dependent changes in circadian rhythms. Although the protocol does not eliminate the possibility of masking effects on body temperature and subjective sleepiness due to intermittent sleep episodes, the short, regular sleep opportunities may minimize effects of prolonged waking periods on circadian markers. Additionally, the protocol may be easier for infirm, elderly subjects to tolerate than the constant routine.

Methods: Subjects were 48 adults (19 M, 29 F) (X age = 34.4, SD =16.4, range 18-73). All were in excellent health and used no psychoactive or cardiovascular medications. Five elderly women used hormone replacement. Subjects were relatively good sleepers (X PSQI = 3.5, SD=1.8). Prospective subjects underwent a screening polysomnogram on a night noncontiguous to the Baseline night to eliminate sleep apnea, upper airway induced arousals, and periodic leg movements. Premenopausal women were studied during the follicular phase of their menstrual cycle. Baseline night started at 2000. Duration of protocol was approximately 84 hours. Subjects maintained a sleep diary for approximately one week prior to entry into the protocol that was brought to the lab on the Baseline night. Bedtime and wake-up time for Baseline night were set to approximate these hours. Beginning at 2000 on Nt 2, subjects entered the 90 minute day portion of the protocol (30 minutes scheduled for sleep, 60 minutes scheduled for wake) for a total of 32 cycles, until 2000 on Nt 4 (Recovery). Meals were provided ad lib. No attempt was made to time isolate subjects. All remained in indoor light in a facility without windows. Subjects were free to sit up and leave bed. Oral BT's and Stanford Sleepiness Scale (SSS) ratings were taken every 30 minutes during the 48 hrs of the 30/60 portion of the protocol. BT's were subjected to a 5-point moving average and then curve fit visually for the best single cycle during the 30/60 portion of the protocol; times of BT min/max were based on this cycle. Min/max SSS ratings were normalized within subjects, also subjected to 5-point moving average, and curve fit for min/max to match the targeted BT cycle from the 30/60 portion of the protocol.

Results: Older age was highly related to earlier bedtimes (rho = -.67, $p < .0001$) and wake-up times (rho= -.70, $p < .0001$) in the sleep logs. During the 30/60 portion of the protocol, age was also associated with an earlier BT min (rho = -.34, $p < .03$; mean time of BT min = 0540). Both earlier min and max SSS in the 30/60 portion of the protocol were also related to age (for min, rho = -.31, $p < .04$; for max, rho = -.36, $p < .02$). Mean phase angle difference (in minutes) between BT max and maximal alertness (SSS) was + 24.8 (SD = 193.6) mins; the large SD suggested appreciable individual differences in the offset of timing of maximal alertness and timing of the BT max. This difference was associated with age (rho = -.31, $p < .04$). A final set of markers of relative phase position, time of 30 min sleep period with maximal total sleep/REM sleep occurrence (calculated to the nearest half hour based on start of each 30 min period), appeared earlier in older people as well (rho's = -.25, $p < .09$ and -.29, $p < .05$, respectively).

Conclusions: These results confirm the utility of measurements of BT and subjective sleepiness recorded during the 90 minute day as putative markers of circadian phase position in normal subjects relative to habitual sleep/wake schedule occurring under entrained conditions. The fact that older subjects show a greater phase angle difference between subjective alertness and BT max (i.e., subjective alertness anticipating BT max) implies change in coupling of these two phenomena as a function of age and/or the impact of other factors (e.g., age-dependent changes in homeostatic sleep regulation) in producing the relatively earlier peak of alertness seen in the elderly.

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1608.E

On-Duty Alertness in Regular Shift Work and On-Call Schedules

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Introduction: On-duty alertness is a concern in many different industrial settings. One industry where on-duty alertness is of interest is in railroad operations. Because of the round-the-clock demands for railroad operations in the United States, locomotive engineers are often required to work at all times of the day and night. The actual schedule that they work under varies with the type of work being completed. Some engineers work under relatively regular shift work schedules where they go to work at about the same time during a 24-hour day. Many other engineers work under much less predictable schedules, where they are literally on-call 24 hours a day, 7 days a week. Furthermore, in the railroad industry in the United States, it is much more common for locomotive engineers to work under on-call conditions than under more predictable shift work schedules. Unfortunately, little research has addressed the effect of such different scheduling practices on alertness. One previous study (Pilcher & Coplen, 1999) has shown that on-duty alertness is best predicted by the duration of the off-duty period, however, no research has specifically addressed how on-duty alertness differs between the very different working conditions that exist in the railroad industry. The purpose of the current study is to examine how regular shift work and on-call schedules differentially impact on-duty alertness in the railroad industry.

Methods: The data used to complete this study were gathered as part of the Federal Railroad Administration's fatigue program by the Volpe National Transportation Systems Center (Pollard, 1996). A sample of 198 railroad engineers (195 males, 3 females; mean age: 44 ± 6.7) completed a 14-day activity log resulting in a total of 1547 work days where on-duty alertness was reported. As part of the activity log, the participants provided information about self-report on-duty alertness (scale of 1: fully alert to 4: fighting sleep) and their type of work schedule. On-duty alertness was recorded at the beginning of each work shift and then every two hours while at work. For analysis, self-report alertness was averaged across each work shift. A one-way ANOVA, accounting for individual differences, was completed using type of work schedule as the factor.

Results: As expected, there were unequal numbers of engineers who reported working under regular shift work conditions versus on-call conditions. In the current sample, 36 engineers reported working under regular shift work conditions, whereas 162 engineers reported working under on-call conditions. The engineers working under regular shift work conditions reported an average self-report alertness rating of 1.86 (SD=0.80). The on-call locomotive engineers reported an average alertness rating of 1.95 (SD=0.85). The ANOVA indicated that locomotive engineers working under on-call conditions reported significantly less on-duty alertness than locomotive engineers working under regular shift work conditions ($F1,1351=3.81$, $p<.05$).

Conclusions: Although a wide range of studies have been completed examining the effects of shift work schedules, few studies have directly compared shift work schedules with on-call schedules in similar working environments. The current study allowed one such comparison to be made. The present data indicate that on-call schedules result in less self-reported on-duty alertness than more regularly scheduled shift work in locomotive engineers. This difference between the much more commonly used on-call scheduling and more regularly scheduled work times in on-duty alertness could have an important impact on scheduling decisions currently being made within the railroad industry.

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The views of the authors do not intend to reflect the position of the Federal Railroad Administration or the Department of Transportation.

1320.E

Age-Related Differences in Urinary 6-Sulphatoxymelatonin Excretion

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Introduction: Numerous reports suggest age-related declines in the amplitude of circadian melatonin secretion, but this hypothesis has recently been challenged by a constant routine study (Zeitzer et al 1999). In that study, elders were selected who had the health status of much younger people and were quite atypical of the American population over age 60 years. While causes for sleep complaints are many and not well understood, we have been interested in testing whether age-related declines in circadian amplitude or deviations of circadian phase timing may contribute to poorer sleep. We previously reported an alarming prevalence of abnormal acrophases of 6-sulphatoxymelatonin (6SMT, the main urinary metabolite of melatonin) in elderly San Diegans (Kripke et al 1998). Here we report preliminary results from a study to verify our findings using an ultra-short sleep wake cycle to minimize sleep masking.

Methods: Elderly subjects (age 60-78) were selected for insomnia complaints, but those taking beta blockers and other drugs thought to influence melatonin were excluded, as were elders suffering acute medical illnesses. For comparison, we selected a control group of 10 young healthy subjects (age 20-39) free of all medicines, active medical illness, unusual sleep habits or more than minimal sleep complaints. Volunteers followed an ultra-short sleep-wake cycle of 60-min wake (50 lux) and 30 min sleep for 72+ hours. Urine samples were collected during each wake period and assayed for 6SMT using the Arendt RIA (ALPCO, Windham, NH). The current data are from the first year of a planned 5-year study.

Table 1

		N	Mean	Std Error	Mean Diff
Mesor	Old	15	170	28	419*
	Young	10	588	114	
Amplitude	Old	15	185	31	536*
	Young	10	720	141	
Acrophase	Old	15	4.0	.47	0.6
	Young	10	4.6	.38	
Goodness of fit	Old	15	.63	.035	.07
	Young	10	.70	.024	

*p < .001 T-Test comparing means of Elderly and Young

Results: Cosine fitting showed significant age-related differences between elderly and young volunteers. Mean mesor and amplitude 6SMT values were reduced by 3.5 and 3.9 fold, respectively, in elderly compared to young ($p < .001$). In this small sample, there were no significant differences between elderly and young in 6SMT acrophases ($p = .335$) or goodness of fit ($p = .153$). Mesor range was 1081 (71-1152) for young and 421 (38-459) for the elderly sample. Amplitude ranges were 1287 (67-1354) for young and 487 (44-530) for elders. Six of 15 elderly displayed a 6SMT acrophase outside the range of the 10 young.

Conclusions: In the present sample average daily 6SMT excretion and circadian amplitude were greatly reduced in elderly as compared to young healthy subjects. Our elder volunteers were selected for sleep complaints, unlike the young, but elders with many medical conditions and medications were excluded. These results suggest reduced melatonin secretion in the large population of elderly with sleep complaints, but do not suggest melatonin amplitude is causal.

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1338.E

Circadian Phases of Melatonin and Body Temperature are Associated

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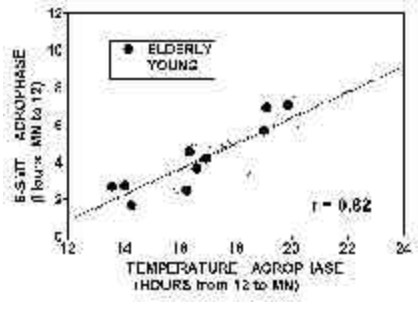
Introduction: Recently, our group examined excretion patterns of the urinary metabolite of melatonin, 6-sulphatoxymelatonin (6-SMT), in over 220 aging men and women between the ages of 60 and 79 years.[1] Many older volunteers demonstrated circadian phase abnormalities that fell well outside the normal range for 6-SMT excretion of healthy adults ages 18-40. Although unlikely, it is possible that the phase abnormalities observed in the aging do not reflect a true malsynchronization of the circadian system, but can be explained by other factors such as sample collection and assay errors, abnormal melatonin metabolism, or an uncoupling of melatonin secretion from the superchiasmatic nuclei. Therefore, a primary aim of this investigation is to verify that the observed circadian 6-SMT deviations in the aging are indicative of functionally significant phase abnormalities in the circadian pacemaker by measuring 6-SMT in conjunction with other circadian markers, in this case, body temperature.

Figure 1



Methods: Ten elderly (mean age 66.6± 6.6 yrs) and seven younger (mean age 26.8± 8.1 yrs) volunteers entered the Circadian Pacemaker Laboratory and followed an ultra-short sleep-wake cycle of 60 min wake and 30 min sleep for 72 hours. Volunteers both provided a urine sample and assessed oral body temperature (BT) every 90 minutes. Urinary con-

POSTER PRESENTATIONS

centrations of 6-SMT were assayed using an Arendt RIA assay (American Laboratory Products, Wyndham, NH). The acrophases of 6-SMT excretion rate (ng/hr) and BT were determined by cosine fitting across all available days.

Results: Adequate acrophase fits (Q > 0.5) were available for 10 elderly and 7 young adults, providing a total N of 17. An excellent correlation was found between 6-SMT acrophase and BT acrophase (r =0.82, p = 0.001). Although greater acrophase dispersion was observed among the elderly, the difference was not significant in the current sample size.

Conclusions: Though more subjects must be studied to be conclusive, the strong correlation between the phase variables 6-SMT and BT suggest that urinary 6-SMT secretion patterns are not misleading indicators of the central circadian system in the elderly. Furthermore, this correlation argues that it is unlikely that circadian phase abnormalities determined by analysis of urinary 6-SMT can be explained by measurement errors or metabolic factors.

References:
(1) Kripke D, Elliott, J, Youngstedt, S: Melatonin: marvel or marker? Ann Med 1998;30: 81-87.

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1033.E

The Effects of Age on Human Circadian Period

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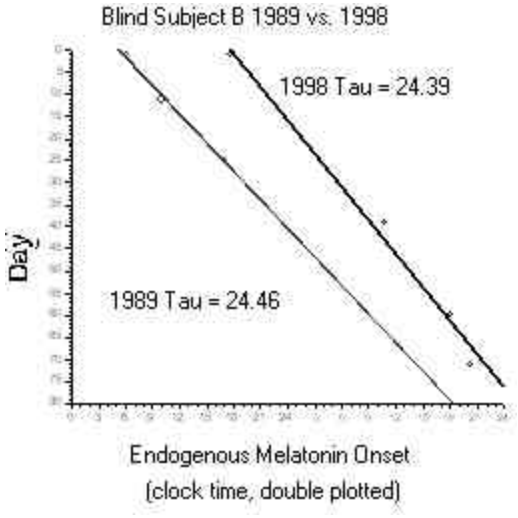
Introduction: A variety of animal and human studies suggest that circadian period (tau) shortens with age.[1,2] Recently, a between-subject study indicated that tau is not significantly different between older and younger subjects.[3] Few studies, however, offer the opportunity to employ a longitudinal study design.

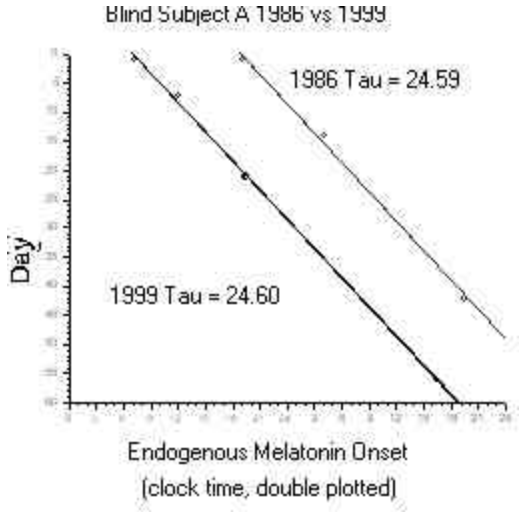
Methods: Two totally blind human subjects with free running rhythms were studied at two time points separated by 13 and 9 years. Subject A was studied at ages 33 and 46. Subject B was studied at ages 39 and 48. Their circadian periods were estimated by measuring the timing of daily endogenous melatonin secretion over several weeks. Their melatonin onsets were defined as the 10 pg/ml threshold of plasma melatonin, assayed from hourly blood samples. These onsets were then fitted to linear regressions to reveal their taus.

Figure 1



Results: Subject B revealed a slight change in tau (24.5 h to 24.4 h) (Fig. 1). Subject A, however, had a tau which appears to be unchanged (24.6 h) (Fig. 2).

Figure 2



Conclusions: This study shows that the circadian period of these individuals did not significantly change during the given time intervals. A possible explanation for this may be that circadian period changes so slightly over time that a 10 year interval will not detect a significant change. Alternatively, circadian period may be relatively stable between ages 30 and 50. Additional subjects are similarly being evaluated.

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1692.E

Changes in Plasma Melatonin Secretion Following Chronic Sleep Restriction

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Introduction: Previous studies examining one night of sleep deprivation or sleep restriction have reported no change in melatonin secretion relative to baseline sleep conditions.[1] The aim of the present experiment was to investigate the effect of chronically reduced nocturnal sleep duration, with and without a daytime nap on plasma melatonin profiles.

Methods: A total of 13 subjects (8m; 5f; mean age ± sd: 28.5 ± 4.9) attended the sleep laboratory for a 14-day protocol (ambient light <50 lux). Following 2 nights of baseline sleep (8.2h between 2154h-0606h) subjects were randomly assigned to a sleep restriction condition, that was maintained for 10 consecutive days, followed by 2 recovery days (14h sleep). For the 10 day experimental periods, in condition A [control condition] (N=5) subjects were allowed an 8.2h anchor sleep between

2154h-0606h; in condition B (N=4) subjects were allowed a 4.2h anchor sleep between 2354h-0406h; and in condition C (N=4) subjects were allowed a 4.2h anchor sleep between 2354h-0406h and a daily 1.2h nap sleep between 1324h-1440h. On the first baseline day (day 1) and the final condition day (day 12), starting at 1630h subjects were maintained in a quasi-constant routine paradigm for twenty-six hours. During this time subjects were near-supine in bed, and allowed to sleep at the allocated times, with blood samples collected at 15 minute intervals via an indwelling non-thrombogenic venous catheter. From these samples plasma melatonin concentrations were determined at hourly intervals, using an RIA (Melatonindirect, DiagnosTech Int, Inc, WI). Melatonin secretion was analyzed using within-subjects repeated-measures ANOVA comparing day 1 with day 12 across conditions.

Results: For all three conditions there was a significant time of day variation, reflecting circadian changes in melatonin levels ($p<0.001$). As expected, in condition A there were no significant differences in melatonin secretion between days 1 and 12. In sleep-restriction conditions B (4.2h) and C (4.2h + 1.2h), however, the phase of the melatonin curve appeared to be delayed. In both conditions the timing of melatonin offset was delayed, with continued elevation of melatonin levels at the end of the nocturnal secretory phase (0930h-1230h). This extension of the melatonin curve was evident for up to 5 hours following the termination of melatonin secretion in the baseline (day 1) condition.

Conclusions: The findings from the present study suggest that sleep restriction was able to alter the organization of the circadian system, as evidenced by changes in the timing of melatonin secretion. This effect may result from changes in light-dark exposure associated with the reduced sleep period, or may be due to the reduced sleep period itself. It is interesting to note that following the restricted sleep periods there appeared to be an increase in melatonin secretion towards the end of the normal nocturnal secretory period. It has previously been reported in rats that REM sleep deprivation produces an increase in melatonin secretion.[2] Conversely, it has also been reported that exogenous melatonin administration increases the amount of REM sleep.[3] In the present study, the elevation in melatonin levels may reflect increased REM pressure, resulting from sleep restriction. Polysomnographic data from the present study are currently being analyzed, and may serve to clarify this issue.

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(2) Peder M, Porkka-Heiskanen T, Alila A, Laakso ML, Johansson G. REM sleep deprivation increases early morning pineal melatonin in castrated rats. Behav Neural Biol, 1989, 51:237-246.
(3) James, S. P., Mendelson, W. B., Sack, D. A., Rosenthal, N. E., & Wehr, T. A. (1987). The effect of melatonin on normal sleep. Neuropsychopharmacol, 1, 41-44.

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1375.E

When is Your DLMO?

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Introduction: The dim light melatonin onset (DLMO) has become a popular marker of human circadian phase in both clinical and research settings.[1] Relationships between the DLMO and sleep/wake times of day-active adults have been roughly described: for example, the DLMO measured in plasma occurred "about 14h after lights on in the morning" among adults whose lights on time was about 07:00.[2] However, there has been little effort to document the DLMOs of normal healthy adults who are not following study-imposed sleep schedules, and whose self-selected sleep times are naturally more variable. One study found the average DLMO of 7 day-active adults was 21:34, 2.2h before the average time of sleep onset, 23:46, and 13.4h after the average wake time, 08:12.[3] The current study seeks to determine the best way to use the times of sleep and of light exposure to predict the DLMO of normal, healthy, day-active adults.

Table 1. Pearson correlations

		DLMO
Sleep Onset Averages	Last 5 Days[a]	+0.87***
	Last 7 Days[b]	+0.84**
Wake Time Averages	Last 5 Days[a]	+0.75**
	Last 7 Days[b]	+0.71*
Morningness-Eveningness Score		-0.78**

* $p<0.05$, two-tailed
** $p<0.01$, two-tailed
*** $p<0.001$, two-tailed
[a] weekdays only
[b] weekdays and weekend

Methods: To date, 11 normal subjects (10 females, 1 male) aged 23.2 ± 7.4 years (mean ± SD) have been studied. All subjects maintained day-active schedules; none had worked night shifts or had traveled across more than 2 time zones in the month preceding the study. Subjects completed the Horne-Ostberg Morningness-Eveningness Questionnaire. For 14 days, subjects kept daily sleep logs, which were verified with wrist activity monitors (Mini Mitter Co, Inc), and daily outdoor light exposure logs, which were verified with photosensors (Mini Mitter Co, Inc.) worn on the chest. There were no restrictions on the subjects' sleep schedules or outdoor light exposure. On Day 14 (Friday), subjects were admitted to the lab for determination of the DLMO. Between 1930 and 0730, subjects sat in a reclined position and saliva samples were collected with salivettes in dim light (<20 lux) at 30 minute intervals. Melatonin assays were performed by DiagnosTech (Osceola, WI). Each subject's DLMO was defined as the first time that melatonin levels exceeded and remained higher than the threshold melatonin concentration, which was 20% of the maximum melatonin value. For this analysis, DLMO estimates were correlated with times of sleep onset and wake reported by subjects on sleep logs, and with Morningness-Eveningness scores.

Results: The mean DLMO, at 21:57±1:24, was 13.7 h after the mean wake time (08:15±1:04) and 2.6 h before the mean time of sleep onset (00:36±1:22). As shown in the Table, the DLMO was significantly correlated with times of sleep onset, wake times, and the Morningness-Eveningness score, but the correlations with sleep onset times were the best.

Conclusions: These preliminary data show that the DLMOs of day-active adults can be fairly accurately predicted simply using the times of sleep onset recorded on sleep logs. Furthermore, the times of sleep onset appear to be better predictors of the DLMO than are wake times. However, data from additional subjects are needed to verify the strength of these relationships, and we have yet to analyze the relationships between the DLMO and patterns of light exposure.

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(2) Lewy AJ, Bauer VK, Ahmed S, Thomas KH, Cutler NL, Singer CM, Moffit MT, Sack RL. The human phase response curve (PRC) to mela-

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(3) Sack RL, Blood ML, Lewy AJ. Melatonin rhythms in night shift workers. Sleep 1992, 15, 434-41.

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1084.E

Homeostatic and Circadian Factors in Improving Adaptation of Rapidly Rotating Night Shift Workers

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Introduction: Night-shift workers are known to suffer from desynchronization between endogenous circadian and sleep-wake rhythms. As a phase-shifting method to synchronize the two rhythms, a light exposure treatment during the night shift has been very popular. However, previous studies have problems when practically applied: too high intensity of light; limited applicability because of being from laboratory setting rather than from real workplace setting; and too large phase-shift, possibly causing phase disturbance on returning to normal routines. With clinical applicability in mind, the specific aims of this study were set as follows. First, we planned to observe whether and to what extent phase-shift would occur by light exposure of tolerable intensity in real workplace. Second, we intended to evaluate whether a method based on homeostatic principle would be effective in improving night-shift adaptation even if no phase-shift was induced.

Methods: Twelve night-shift nurses working at a private mental hospital participated in this study. The study protocol consisted of three different treatment procedures: baseline (Baseline), in which there was no light exposure during the night-shift; light exposure treatment 1 (Light-1), in which 4-hour light exposure of 4,000-6,000 lux was done during the night-shift followed by 1- hour exposure to sunlight or 10,000 lux light next morning to inhibit phase delay possibly induced by nocturnal light exposure; light exposure treatment 2 (Light-2), in which the same light exposure as in Light-1 during the night-shift was followed by no light exposure next morning to maintain phase delay possibly induced by nocturnal light exposure. Each treatment went on for 4 days in a repeated measures crossover design. Phase-shift was monitored with measuring saliva melatonin by radioimmunoassay. Nocturnal alertness and daytime sleep were measured with actigraphy and visual analogue scale.

Results: During Light-2, total phase delay of 1.7 hours per 3 days was observed based on change of melatonin acrophase time. In Baseline and Light-1, no phase delay was noted. Comparing daytime sleep among the 3 treatments on such sleep variables as sleep latency, sleep period time, total sleep time, and sleep efficiency, the most significant overall improvement of sleep was noted in Light-2. Light-1 showed less improvement than Light-2 but more than Baseline. Comparison of nocturnal alertness among the 3 treatments produced the same results; during Light-2, the subjects were most alert, followed by Light-1 and then by Baseline.

Conclusions: Since only 1.7 hours per 3 days were phase-delayed by light exposure in this real workplace study, it is least likely that our way of exposing night-shift workers to light may induce a large phase shift sufficient to cause a phase disturbance. Application of homeostatic principle (Light-1) improved daytime sleep and nocturnal alertness, but more improvement was observed with partial circadian synchronization (Light-2). We suggest that it may be helpful for night-shift workers to get light exposure in workplace during the night-shift and to avoid light on the way home. Facilitated adaptation to the night-shift could be obtained without large phase shift and consequent phase disturbances.

1742.E

Sleep Deprivation in the Clock Mutant Mouse

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Introduction: The timing of daily sleep episodes is thought to be regulated through the coordination between the circadian and sleep homeostatic systems. To better understand these systems we examined the sleep patterns following sleep deprivation in male homozygous Clock mutant mice. Clock is a semi-dominant mutation causing behavioral circadian abnormalities. Under 12:12 light-dark conditions, homozygous Clock mice are capable of entraining but show increased activity in the lights-on period. In constant darkness, Clock homozygotes have a lengthened tau of 27-28 hours for approximately three weeks before becoming arrhythmic (Vitaterna et al, 1994). Since previous research has shown that normal sleep is affected in Clock mice (Naylor et al, 1998), the focus of this study was to determine how Clock mutant mice respond to six hours of sleep deprivation during the lights-on period.

Figure 1

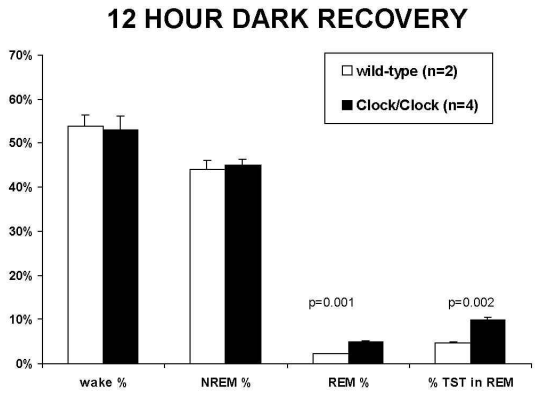
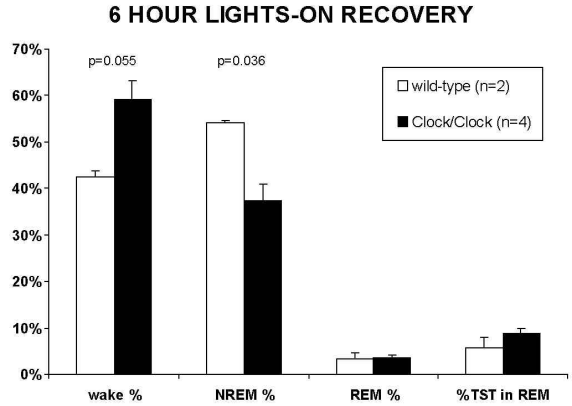


Figure 2



Methods: Following surgerical implantation of electroencephalograph and electromyograph recording electrodes, two wild-type and four Clock homozygous C57BL/6J male mice were entrained for 7-10 days to a 12:12 light-dark (LD) cycle with lights on at 1000. The mice were connected to a head tether and allowed two days to acclimate to the sleep recording chamber before recording commenced. Baseline records were

collected over a continuous 48 hour period. Sleep deprivation was performed from 1000-1600 (ZT0-6), during the lights-on phase. Recovery sleep after the deprivation was also recorded for the remainder of the light phase and for the 12 hour dark phase immediately following for a total of 18 hours. Data were hand scored in 10 second epochs of wakefulness, NREM sleep, and REM sleep.

Results: Analysis of the sleep patterns in response to six hours of deprivation revealed that Clock homozygotes spend more time awake and less time in NREM sleep when compared to wild-type mice for the 6 hour lights-on recovery period. The 12 hour dark recovery period revealed that the Clock homozygotes experience more time in REM sleep than the wild-type mice.

Conclusions: The preliminary results from this experiment continue to support the idea that the Clock mutation can influence sleep. The continued decrease in NREM recovery sleep during the lights-on period suggests that the sleep homeostatic process may be lowered in these animals, while REM rebound seems to be occurring during the 12 hour dark recovery period.

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(2) Naylor E, Vitaterna MH, Takahashi JS, Turek FW. Sleep in the Clock mutant mouse. Sleep, 1998, 21(3 [Supplement]): 9.

1409.E

Circadian Rhythms in the Human Retina

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Introduction: The retina has been demonstrated to contain an oscillator which is a good model to study circadian function (Herzog and Block 1999). In humans, reports that show circadian variability in the eye are still scanty and somewhat inconsistent. We used a strictly controlled design and clinical electrophysiologic techniques to evaluate circadian patterns of human retinal function.

Methods: Twelve healthy subjects (10 M, 2 F; mean age 26.3 years, range 19-40) were studied for 36 hours in the chronobiology laboratory using an ultra-short sleep-wake cycle (30 minutes sleep, 60 minutes wake). We recorded horizontal electrooculography (EOG), electroretinography (ERG), and oral temperature every 90 minutes throughout the study. The subjects also wore an Actillume to determine sleep and wake. For both eye measurements, we used skin electrodes below the eyes. The EOG was performed in 50 lux light, produced by tracking movements of 60 degrees, and defined as the median peak-to-peak amplitude of 11 consecutive potentials. The ERG was performed in the dark, being the average evoked response to a series of 50 flashes. For the ERG, we determined the a-wave and b-wave implicit time (the latency to the peak of the wave), and the peak-to-peak amplitude of the b-wave. The acrophases for the measurements were estimated by a cosine curve-fitting technique applied to each 36-hour data set. Directionality in the group acrophases was assessed by the Rayleigh test (Rayleigh's z).

Results: We found that the EOG followed a circadian rhythm ($z = 4.728$, $p < 0.01$), with a nocturnal nadir (about 02:00h - 03:00h) and a peak of the amplitude after noon (acrophase 12:22h, 95% CI 09:48h - 14:57h). In the ERG, the b-wave implicit time showed a circadian rhythm ($z = 5.679$, $p < 0.01$), with increase in the latency in the early morning (acrophase 06:46h, 95% CI 04:31h - 09:02h). No circadian rhythms could be demonstrated in the a-wave implicit time ($z = 2.764$, N.S.) and the b-wave amplitude ($z = 1.612$, N.S.). Temperature data were available for 11 subjects, showing a significant circadian rhythm ($z = 10.291$, $p < 0.001$), with a nadir early in the morning (about 05:30h - 06:30h) and a peak late in the afternoon (acrophase 17:38h, 95% CI 16:56h - 18:20h). The circadian rhythm of sleep ($z = 9.057$, $p < 0.001$) occurred with a peak in the morning (acrophase 06:32h, 95% CI 05:12h - 07:52h).

Conclusions: We were able to demonstrate circadian rhythms of EOG and ERG of different acrophases in the human eye. Strictly controlled study design based on the ultra-short sleep-wake cycle allowed us to get frequent and regular recordings throughout the day and night, and monitor rhythms with minimized interference from sleep masking.

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1410.E

Effects of Early Morning Melatonin (MT) Administration on Daytime Sleepiness and Cognitive Functioning

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Introduction: Studies have demonstrated the effectiveness of Melatonin (MT) as a hypnotic and as a means to adapt to jetlag. The sleepiness produced by MT is a positive effect when MT is used as a treatment for sleep onset insomnia. However, when MT is used to phase shift circadian rhythms it is most effective when administered hours before sleep and hours after sleep (Lewy, et al., 1998). Therefore, sleepiness is a negative unwanted side effect of MT when used as a chronobiotic. The effects of MT on sleepiness and performance have been studied at mid-day and in the evening. We examined the effects of MT in the morning on sleep latency, performance and subjective sleepiness.

Methods: This study was a within subjects design, comparing three conditions: placebo, 0.3 mg MT and 5.0 mg MT ingested at the habitual wake-up time. Drug administration was double-blind. All subjects (3 male, 6 female) were screened for medical and psychiatric disorders and had a polysomnographic recording to rule out sleep disorders. Order of conditions were counterbalanced by a Latin Square design (one subject's data not yet analyzed). MT was administered 45 minutes after habitual wake-up time. A nap opportunity (modified MSLT) and performance assessment battery (PAB) were conducted every hour for five hours starting 30 minutes after pill administration. Subjects were awakened after three consecutive epochs of any stage of sleep to terminate the nap opportunities. PAB sessions occurred 30 minutes offset from the naps. The PAB consisted of five individual tests which measure reaction time and cognitive functioning. Finally, subjects rated their sleepiness, fatigue and alertness (on a scale 1=very little to 10=very much) every 30 minutes, immediately prior to each of the MSLT and PAB sessions.

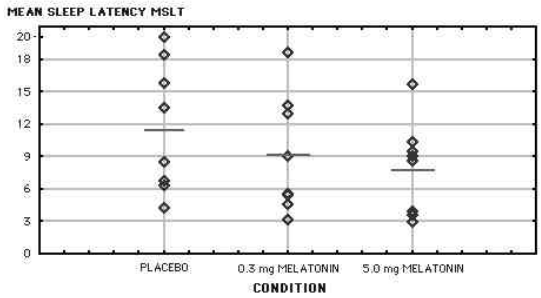
Results: As seen in Table 1 and Figure 1, in comparison to the placebo condition the 5.0 mg MT dose increased sleepiness ($p < 0.01$) while the 0.3 mg MT dose showed a borderline increase in sleepiness ($p < 0.07$). Similarly, the 5.0 mg MT dose produced an increase in the number of errors on the choice reaction time test ($p < 0.05$) compared to placebo, while the 0.3 mg MT dose did not effect number of errors (NS). No other performance measures approached significance. Compared to placebo,

subjective sleepiness and fatigue were substantially increased following the 5.0 mg MT ($p < 0.1 \times 10\text{-}5$; $p < 0.00005$, respectively) and also increased with the 0.3 mg MT dose ($p < 0.00002$; $p < 0.005$, respectively).

Table 1

VARIABLE by CONDITION	Mean MSLT Sleep Latency	Choice Reaction Time #	Sleepiness	Fatigue
Placebo (P)	11.7 (6.31)	0.6 (0.92)	3.7 (1.99)	3.8 (2.11)
0.3 mg MT (Low)	9.1 (6.08)	0.7 (0.97)	5.1 (2.19)	4.7 (2.13)
5.0 mg MT (High)	7.9 (6.03)	1.1 (1.60)	5.4 (2.04)	5.1 (2.03)
Placebo vs. Low	$p < 0.07$	NS	$p < 0.00002$	$p < 0.005$
Placebo vs. High	$p < 0.01$	$p < 0.05$	$p < 0.000001$	$p < 0.00005$

Figure 1



Conclusions: Even after a full night's sleep, a high dose of MT in the morning produces a robust sedating effect while a physiological dose of MT is not without similar effects. These findings are consistent with previous studies showing that MT produced sleepiness in the afternoon. Therefore, the use of MT to treat circadian rhythm disorders must be accompanied by careful consideration of patient safety.

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(1) Lewy AJ, Bauer VK, Ahmed S, et al. The human phase response curve (PRC) to melatonin is about 12 hours out of phase with the PRC to light. Chronobiology International 1998;15:71-83.

1756.E

Later Circadian Phase of Plasma Melatonin Relative to Usual Waketime in Older Subjects

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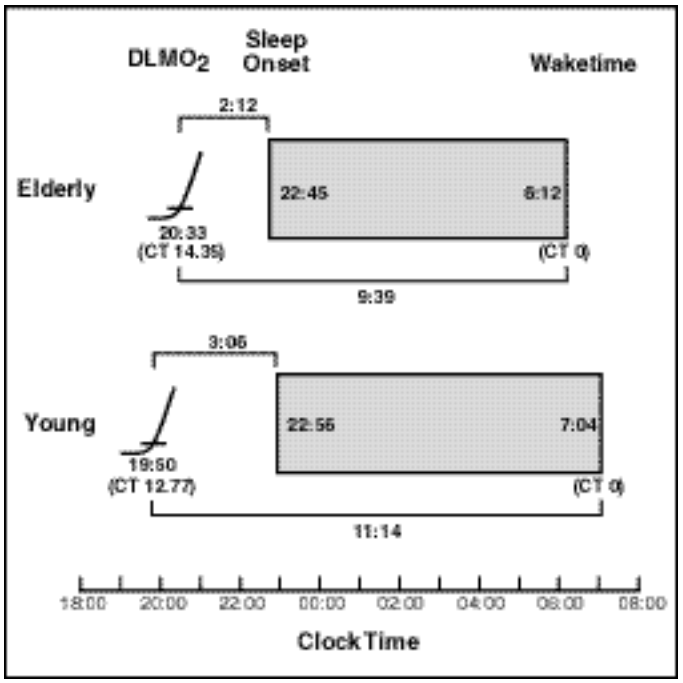
Introduction: It has been hypothesized that many elderly people who go to bed early and wake up early are phase advanced, and, if they were to free-run, they would have a relatively short intrinsic circadian period (tau). However, replicating the finding of a later melatonin midpoint relative to usual waketime in older men and women compared to younger men[1], we now report statistically significant results using age groups balanced for gender ratio and sample size. Also, we used the dim light melatonin onset ($DLMO_2$), operationally defined at the 2 pg/ml threshold, which minimizes artifactual delays of the melatonin onset in people who are low melatonin producers, which can occur in the elderly[2].

Methods: Fourteen elderly [mean age (years): 75.5±4.7 (SD)] subjects (four males) and fourteen young (31.1±8.1) subjects (five males), who were healthy volunteers not taking any medications that could affect melatonin production, collected sleep diary data for one week prior to determination of the $DLMO_2$.

Results: Statistically significant clock time results were: 1) the average waketime was earlier in the older group compared to the younger group ($p<.02$); and 2) the $DLMO_2$/waketime interval was significantly shorter in the elderly ($p<.02$).

Figure 1



Conclusions: As previously reported[1], we found that healthy elderly people have an earlier usual waketime than younger individuals. More importantly, we have replicated the finding[2] that the time interval between the melatonin phase marker and usual waketime was significantly shorter in older subjects. Therefore, it is unlikely that older people have a shorter tau, because the circadian time (CT) of a phase marker relative to the light/dark cycle (that is, the phase angle of entrainment) predicts tau[3], and older subjects clearly are not phase advanced relative to the light/dark cycle. We conclude that the elderly probably would not have relatively short taus when studied under free-running or forced desynchrony conditions.We recommend the following use of the terms "clock time" and "CT." By established convention[3], usual wake-up time ("lights on") in diurnal animals (such as humans) is designated CT 0. Accordingly, our elderly subjects have a $DLMO_2$ at a significantly ($p<.02$) later CT (14.35) than our younger individuals (CT 12.77). Normalizing phase based on an internal circadian marker, i.e., stating that older subjects, relative to their melatonin rhythm, "wake at an earlier internal circadian time[1]" is technically correct; that is, the elderly have a phase-advanced waketime relative to an internal circadian phase marker: however, this also means that these people are experiencing an earlier light/dark cycle relative to an internal circadian phase marker. On the other hand, it is also correct to interpret the same finding conversely: the internal circadian rhythms of older subjects are phase delayed relative to the light/dark cycle. We think the latter is less confusing. That is, the clock time of sleep (preferably waketime) is generally used to diagnose advanced and delayed sleep phase syndromes. We further suggest that waketime (lights on) be designated CT 0 and that this be the frame of reference for calculating the CT of the internal phase marker that indi-

cates the phase angle of entrainment which is known to predict tau. One other point is that the clock time of an internal circadian phase marker can be used to assess the phase positions of other internal circadian rhythms, including the light and melatonin phase response curves.

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Research supported by M01 RR00334 (OHSU GCRC), R01 MH55703 (AJL), R01 AG15140 (AJL) and an Established Investigator Award from the National Alliance for Research on Schizophrenia and Depression (AJL).

1424.E

Recovery of Circadian Rhythm in EEG Slow-Wave Activity in NREM Sleep by a Change in Photoperiod

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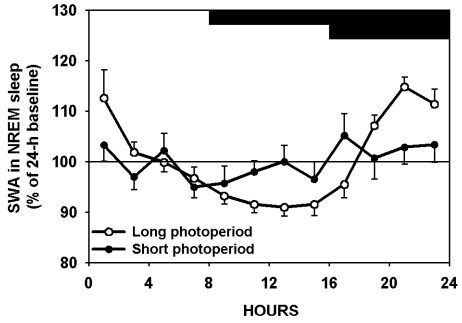
Introduction: Photoperiod is a reliable predictor of seasonal changes. The Djungarian hamster shows strong behavioral and physiological adaptations from a long (LP) to a short photoperiod (SP). These adaptations are accompanied by a redistribution of sleep and waking, but the total amount of sleep over 24-h is unchanged (Deboer and Tobler, 1996, 1997). Combining the shift to SP with a decrease in ambient temperature (TA) reduces the circadian amplitude of sleep and waking and the daily changes in the time-course of SWA (EEG power density between 0.75-4.0 Hz) in NREM sleep disappear (Deboer and Tobler 1997). This suggests that low TA reduces the influence of the circadian clock on sleep-wake behavior. Here we show that the disappearance is not related to TA alone, but is a combined effect of low TA and photoperiod.

Methods: EEG, EMG and EEG spectral data were obtained for 24 h in 8 Djungarian hamsters (Phodopus sungorus) well adapted to SP (L:D 8:16 h) and low TA (14.4 ± 0.1 °C ±SEM). At the end of the winter season (March) the animals were transferred to LP (L:D 16:8 h), at the same TA (14.9 ± 0.1 °C, $p>0.05$). After at least two months adaptation another day was recorded. Vigilance states were scored according to criteria described previously (Deboer and Tobler 1996).

Figure 1



Results: The most prominent effect of the shift from LP to SP was the recovery of the circadian time course of SWA (Fig. 1. Black bars: LP and SP dark period; ANOVA factor '2-h interval' LP: $p<0.0001$; SP: $p>0.3$) and a redistribution of vigilance states. In SP the difference in the percentage of sleep and waking between light and dark period was lower compared to LP (waking difference SP: 6.1 ± 1.5, LP: 20.5 ± 5.0, $p<0.05$), whereas the total amount of sleep and waking over 24 h did not differ (waking SP: 40.3 ± 1.7, LP: 40.1 ± 1.8).

Conclusions: The time course of SWA in NREM sleep in SP at low TA resembles its time course in the Guinea pig and in SCN lesioned rats, which have the same level of motor activity in the light and dark period (Tobler et al, 1993). The data show that in the Djungarian hamster a return to LP enhances the sleep-wake amplitude and restores the circadian rhythm in SWA in NREM sleep, indicating that its loss is not due to the low TA alone. The data support the notion that the time course of SWA in NREM sleep is determined by the distribution of sleep and waking (Tobler et al, 1993).

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1449.E

Masking Effect of Rest-Activity Cycle on Heart Rate Daily Variation in Depressed In-Patients

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Introduction: Studies have demonstrated that circadian rhythms in depressed patients were disturbed. The circadian abnormalities were either a phase advance, a reduction of amplitude or a circadian instability (poorly entrained to 24-hour day). In this studies , masking effects, especially rest-activity, were not controlled. In a previous study we demonstrated that in depressed patient sleep problems were not responsible to the reduction of the amplitude and the goodness of fit of heart rate daily variation (Taillard 1993). Like it was very difficult to maintain drug free depressed patients during constant routines protocol, the purpose of this work was to determine the effect of rest-activity cycle on the circadian parameters of ambulatory heart rate data.

Methods: Activity and heart rate were recorded simultaneously for 48 hours in 12 in-patients suffering from nonseasonal major depression (according to the DSMIII-R criteria). These patients (7 men and 5 women, 48±10 years) were drug free and scored 31± 4.5 on the MADRS when the recordings were performed. Circadian parameters were assessed by a traditional Cosinor analysis. Relation between activity and heart rate circadian parameters were analyzed by Spearman correlation. In second step, we used demasking techniques for estimated the circadian parameters of heart rate (Reynolds 1995). Heart rate data were corrected by masking effect of activity recorded by wrist accelerometer. 8 categories of activity were chosen in this study. Circadian parameters of raw data and purified data were compared by the Wilcoxon test.

Results: We found just a significant correlation between the phases of rest-activity rhythm and the heart rate daily variation only for the first

day (rho=0.664, p=0.018). Amplitude, mesor and goodness of fit were not correlated. As expected, purified amplitude was lower than raw amplitude (z=-3.05, p=0.002), but mesor, phase and goodness of fit were not different.

Conclusions: This is the first report in literature trying to quantify the effects of rest-activity cycle on circadian parameters in depressed patients. This preliminary results tended to demonstrated that circadian parameters of heart rate was not entirely depended to rest-activity cycle in depressed patients.

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1145.E

Effect of Melatonin on Slow Wave Sleep Distribution in Delayed Sleep Phase Syndrome Patients with Elevated Depressive Indices

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Introduction: Abnormal distribution of slow wave sleep (SWS) across the night is a common finding both in depression and delayed sleep phase syndrome (DSPS). In depression, SWS predominates in the second and sometimes in the third sleep cycle. In DSPS, SWS is shifted even further - towards early morning hours when the propensity for non-rapid eye movement (NREM) sleep is minimal. In healthy people circadian modulation of SWS is known to be closely associated with the endogenous circadian rhythm of melatonin. The aim of the present study was to investigate SWS distribution in different sleep cycles in DSPS patients treated with exogenous melatonin.

Methods: Twenty patients (13 males, aged 35.6±14.0 and 7 females, aged 30.8±12.4) with an established diagnosis of DSPS according to standard criteria of the International Classification of Sleep Disorders were investigated in the study. The patients had elevated scores on the depression scales (HAM-D =13.8 ± 6.3 and CES-D =23.5 ± 9.5 at baseline assessment. For the baseline polysomnographic recordings, patients chose their own retiring (from 2:00 h to 5:00 h) and wake up (from 10:00 h to 14:00 h) times as consistent with their normal routine. At the end of the fourth week of either placebo or melatonin (5 mg) treatment, polysomnographic recordings were done during the imposed sleep period from 24:00 h to 8:00 h. There was a washout period of one week between two treatment limbs. A single scorer who was blind to the condition of the treatment scored the polysomnograms according to standardized criteria. Duration of SWS in different sleep cycles was determined at baseline, and during melatonin and placebo conditions. Statistical analysis was performed using SPSS.

Results: The repeated measures procedure did not reveal any significant differences in the overall SWS percentage (stage 3 and stage 4 sleep) on the baseline, melatonin and placebo limbs of the trial (15.4 ± 9.1; 16.8 ± 10.6; 15.5 ± 9.9; F=0.26, p>0.05). However the duration of SWS in the 1st sleep cycle was significantly longer at baseline as compared to both melatonin and placebo conditions (44.2 ± 34.2; 33.7 ± 21.6; 29.7 ± 15.4; F= 3.5, p=0.04). There were no differences in the duration of SWS in subsequent sleep cycles in each phase of the clinical trial. There was statistically significant decrease of SWS duration from the 1st to the last (5th) sleep cycle (F=10.8, p= 0.0001) on melatonin treatment. Similar trend of SWS distribution (i.e. decrease in the amount of SWS towards the end of the night) was observed on placebo. However, 8 out of 20 DSPS patients had a reversal amount of SWS in the 1st and in the 2nd sleep cycles. This finding is commonly seen in depression.

Conclusions: Abnormal distribution of SWS with its highest amount in the early morning hours at baseline supports the diagnosis of DSPS. Exogenous melatonin administration normalizes SWS distribution with the shift to the beginning of the conventional sleep period.

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1146.E

Effect of Melatonin on REM Sleep in Patients with Delayed Sleep Phase Syndrome and Comorbid Depression

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Introduction: Many patients with delayed sleep phase syndrome (DSPS) have depressive features. Research indicates that DSPS may lead to symptoms of depression and treating this circadian rhythm disorder often alleviates these symptoms. It is well recognized that depression is associated with altered REM sleep. Although administration of exogenous melatonin usually does not change sleep architecture, some reports have suggested that the quality of REM sleep might be different when circulating melatonin levels are increased. Patients with insomnia described an increase in dreaming, even after ingesting physiological doses (0.3 mg) of melatonin.[1] In DSPS patients REM sleep parameters have not been studied. The aim of this study was to investigate the effect of melatonin on REM sleep distribution and REM density in different sleep cycles under treatment conditions.

Methods: Twenty patients (13 males, aged 35.6±14.0 and 7 females, aged 30.8±12.4) with an established diagnosis of the DSPS were investigated in the study. The patients had elevated depression indices at baseline assessment (HAM-D =13.8 ± 6.3 and CES-D =23.5 ± 9.5). Two consecutive overnight polysomnographic studies were performed at baseline and at the end of four weeks on melatonin (5 mg) and at the end of four weeks on placebo treatment. Polysomnograms were analysed according to international criteria. REM sleep latency was defined as the time from sleep onset (stage 2). Duration of REM sleep in different cycles was determined at baseline and during melatonin and placebo conditions. The 1st sleep cycle was estimated as sleep duration from sleep onset until the end of the first REM sleep period. The subsequent sleep cycles were estimated as sleep duration from the end of the previous REM sleep period until the end of the subsequent REM sleep period. Eye movements (EM) in REM sleep were counted visually; the criterion for EM detection was a minimum of 25 μV. We counted all simultaneous fluctuations on both channels of electrooculogram. The EM density was counted as EM frequency per minute in REM sleep in every cycle. In addition, we also counted in REM sleep a frequency of 5-second intervals, which contained at least one eye movement. Statistical analysis was performed using SPSS.

Results: REM sleep latencies on the baseline, melatonin and placebo limbs of the trial were within the normal range and the repeated measures procedure did not reveal any significant differences (83.4 ± 38.9; 72.4 ± 21.7 and 71.7 ± 26.6 respectively; F=1.0, p>0.05). There were also no significant differences of REM sleep percentage in each phase of the study (20.3 ± 5.1; 18.3 ± 6.9 and 18.6 ± 4.3; F=2.1, p>0.05). However there was a significant increase of REM sleep duration in the

4th sleep cycle on melatonin as compared to both baseline and placebo conditions (42.33 ± 11.3; 22.7 ± 8.2; 22.5 ± 13.1; F=7.8, p<0.0001). Interestingly, the patients showed normal distribution of REM sleep on melatonin treatment, i.e. increase of REM sleep duration and increase of REM density from the 1st sleep cycle towards the end of the night (F=10.9, p=0.005). On the baseline and placebo conditions the duration of REM sleep did not differ statistically in sleep cycles across the night. There was a significant increase of REM density on melatonin in the 3rd and 4th sleep cycles as compared to the baseline and placebo (F=4.6, p=0.03 and F=4.5, p=0.03 respectively). On the baseline and placebo conditions REM density was flattened across the night.

Conclusions: A high prevalence of depressive symptoms in DSPS patients is commonly reported and our data confirm this finding. The common polysomnographic markers for depression such as short REM sleep latency and increased duration of REM sleep were not observed in DSPS patients with depressive features. However, on the baseline and placebo conditions the patients displayed a flattened distribution of REM density, which is another characteristic finding in depression. There was normalization of REM sleep distribution and REM density pattern on melatonin treatment.

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1811.E

Variation in Self-Rating of Performance and Motivation to Perform During a 28-hr Forced Desynchrony Protocol

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Introduction: Research studies have demonstrated that performance and alertness vary as a function of circadian phase and time awake (e.g., Dijk et al 1992). Few of these studies have examined the degree to which subjects can accurately evaluate their performance. We used a 28-hr forced desynchrony protocol to investigate whether subjects can accurately evaluate changes in their performance due to circadian and homeostatic pressures. We were also interested in whether changes in motivation to perform co-varied with changes in alertness and performance.

Methods: Seven healthy subjects, six males and one female ages 20-38, were studied as part of a 55-day inpatient protocol on circadian entrainment. Following 35 days of the entrainment protocol (Wright et al 1999), subjects were scheduled to a 28-hr day (18.66 hours awake and 9.33 asleep) for 12 consecutive days. The forced desynchrony data were used to examine the contribution of circadian and of time awake changes in neurobehavioral function. Subjects performed a battery of tests every 2 hours during wakefulness. Performance on a mathematical test, a self-rating of performance from a scale of 1 (very good) to 7 (very poor), and a rating of alertness and motivation using visual analog scales were analyzed. Data were transformed into deviation from the mean and then analyzed in 60 degree (4 hour) bins with the temperature minimum assigned to 0 degrees for the circadian component, and analyzed in 2 hour bins for time awake. Significance of circadian and wake-dependent components in the dependent variables were analyzed with repeated measure ANOVA techniques.

Results: Results from the alertness scale showed significant effects of circadian phase (P<0.001) and hours awake (P<0.0001). Performance data also showed a significant effect of circadian phase (P<0.0001). Although performance levels declined throughout the waking day, the effect was not significant (P>0.05). Self-ratings of performance and motivation also showed significant variation by circadian phase (P<0.05) and hours awake (P<0.001). Performance and self-ratings of performance, alertness and motivation were lowest near the core body temperature minimum and decreased throughout the waking day (Figures 1-2). The magnitude of circadian and homeostatic variation in alertness, performance, rating of performance and motivation were similar.

Figure 1

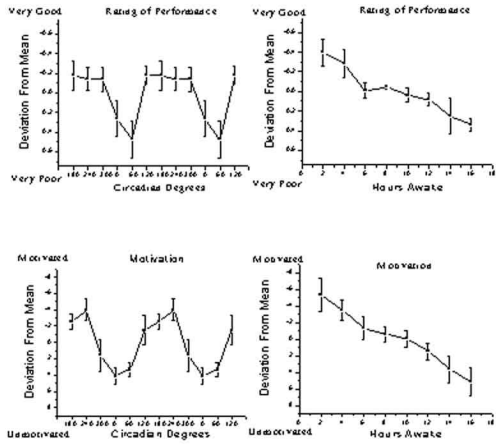
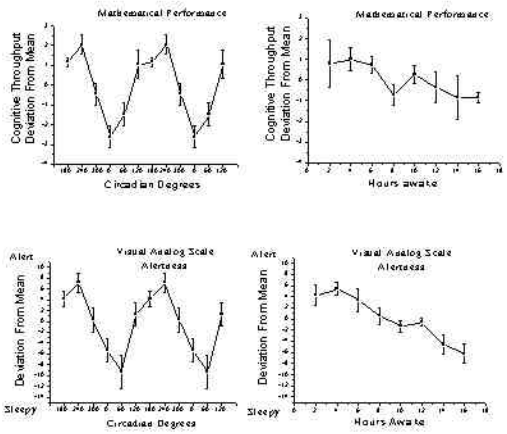


Figure 2



Conclusions: We found subject performance ratings to vary as a function of circadian phase and time awake and that these self assessments of performance were consistent with their actual performance. We also found that motivation levels varied as a function of circadian phase and time awake. The results of this study suggest that changes in motivation should be considered when interpreting the results of sleep and circadian rhythm studies of performance.

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supported in part by NIH T32-DK07529, the Medical Foundation and Harold Witworth Pierce Charitable Trust.

1833.E

Exogenous Melatonin Increases REM-Sleep and Improves Daytime Well-Being in REM Sleep Deficient Patients

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Introduction: Some five years after the beginning of the "Melatonin Madness" followed by the biggest uncontrolled drug-trial ever, the precise role of melatonin in human physiology and particularly in the sleep-wake cycle remains poorly understood. We treated earlier in open labelled trials patients with RBD, PLMD and other sleep related disorders with melatonin. Besides an improvement of clinical symptoms and a reduction in sleep motor activity in most of the patients, there was a restoration of REM sleep muscle atonia in RBD patients and an increase of REM sleep percentage in patients with a quantitative REM sleep deficit. The aim of the presented study was to confirm the hypothesis that exogenous melatonin, administered at the time of the maximal rise of endogenous melatonin, increases the output amplitude of the circadian pacemaker and thereby restores circadian rhythms, one of them being the circadian modulation of REM sleep.

Methods: Sixteen consecutive outpatients (6 women, 10 men; mean age 48 yrs, range 26-68 yrs) with a quantitative REM sleep deficit of 25 percent below age-norm (Williams et al. 1974) shown in diagnostic laboratory PSG, were treated with 3 mg melatonin (Helsinn Chemicals SA - Switzerland) over a 3 to 4 week period in a double-blind, placebo-controlled, cross-over design. Concomitant diagnoses were RLS (4), PLMD (6), idiopathic insomma (7), RBD (6) and narcolepsy (3). Patients were either free of medication or medication was unchanged during all study procedures. None of the patients were taking any medication known to interfere with melatonin production/secretion or REM sleep. Special care was taken with respect to sleep hygiene, which was controlled by continuous actigraphy and sleep log. Patients were asked to administer melatonin within 30 minutes prior to bedtime in the time interval of 10 to 12 p.m.. One narcoleptic patient was excluded during phase one taking placebo, because he was unable to meet appointed bedtimes. Polysomnographic recordings, including one adaptation night, clinical global impression (CGI) and PSQ1 were performed in all patients, both at baseline and at the end of each treatment period.

Results: 12 of the 15 patients who completed the study correctly identified melatonin and placebo conditions and reported clear improvement of symptoms. Three patients did not experience differences between both conditions. Except for a significant reduction of sleep onset latency, there was no placebo effect. Relating placebo to melatonin condition, there was a significant increase of sleep-efficiency, total sleep time, NREM 2-and REM sleep percentage as well as a significant improvement of subjective sleep quality (item 1 PSQI), of daytime dysftmction (item 7 PSQI) and of clinical global impression (CGI) during melatonin treatment. Moreover, by relating changes between baseline vs. placebo in phase 2 (after melatonin) to baseline vs. placebo in phase 1 (prior to melatonin), only the increase of REM sleep percentage and the improvement of clinical global impression (CGI) in the placebo condition after melatonin treatment were significant, indicating a carry-over effect.

Conclusions: This confirmatory study proves for the first time that melatonin administered to patients with a quantitative REM sleep deficit, regardless of underlying pathology increases REM sleep percentage and improves daytime well-being. Secondly, we confirmed that there was a carry-over effect of melatonin treatment on REM sleep, ruling out an acute effect. Although REM sleep primarily exhibits an ultradian rhythm, it is circadian modulated. As expected from the phase-response-curve of melatonin, there was no sign of a phase shift in our patients (e.g. shortening of REM latency). Further analysis of our data, including the circadian rhythmicity of temperature and melatonin, will clarify whether the effect seen in our study was due to an increase of output amplitude of the circadian timing system.

1850.E

Examination of the Relationship Between Sleep Timing and Free - Running Period Length

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Introduction: The spontaneous period of the human circadian clock has been reported to range from about 24 to 25 hours, depending on the conditions under which rhythms are assessed.[1,2] Such variability in the estimation of tau may be due to differences in experimental protocols, the number of sleep periods taken per circadian day (i.e., presence or absence of napping), ambient light levels, or a combination of such factors. Recently, it has been suggested that differences in tau may occur as a consequence of differential timing of exposure to ambient illumination relative to the human phase response curve (PRC) to light, resulting in circadian phase advances or delays.[3] The aim of this study was to examine that hypothesis with two case studies of subjects in temporal isolation.

Methods: Data were analyzed from two healthy male subjects who lived in a time – free environment for 21 days on two separate occasions. Each subject participated in a Traditional (TFR) session in which he was allowed only one major sleep period per subjective day, and an Unstructured (UFR) Free – Run session in which he was specifically instructed to eat and sleep whenever inclined to do so. Room lighting by floor lamps was at the subjects' discretion and did not exceed 100 lux. For each experimental condition, tau was calculated by periodogram analysis of the rest/activity cycle. Core body temperature data from all free – running days were divided into periods of the calculated tau, and upturn of the temperature curve (Tup) was identified for each circadian day. Phase angles between bedtime (BT) and Tup, as well as Tup and wake up time (WT) were calculated for each free – running day and compared across experimental conditions.

Results: The first subject had a mean (±SD) Tup - WT interval of 5.8±2.9 h associated with a tau of 25.4 h in TFR, compared with an interval of 2.7±2.3 h associated with a tau of 24.8 h in UFR. The same subject had BT - Tup intervals that were highly variable and not significantly different between conditions (4.0±2.1 h in TFR; 3.7±2.5 h in UFR; n.s.). A Wilcoxon Signed Rank Test indicated that this subject had a significantly shorter Tup - WT in UFR than TFR (p=.003). This result would mean that this individual awakened at different points on the phase advance portion of the PRC. The second subject showed no significant difference in tau between the two conditions (24.5 h in TFR; 24.7 h in UFR; n.s.). Similarly, mean Tup - WT intervals across conditions were not significantly different (4.8±3.0 h in TFR; 4.8±2.2 h in UFR; n.s.). BT - Tup intervals were also not significantly different between conditions in this subject (2.7±2.4 h in TFR; 2.8±1.9 h in UFR; n.s.). Preliminary analyses that included two additional subjects (1M, 1F) revealed a significant correlation between wake time relative to Tup and period length (R=0.83); the shorter the interval, the shorter the period length.

Conclusions: These results are consistent with the hypothesis that dif-

ferential light exposure is related to period length. In our first subject, waking earlier relative to Tup was associated with a shorter tau. It is possible that the shorter period observed in this subject occurred because he was exposed to light during a portion of the PRC more sensitive to phase advances. In contrast, there is no indication that differential exposure to the delay portion of the PRC lengthened tau, since BT - Tup interval did not differ in the two conditions. Other factors may interact with light exposure or act alone to affect tau. Additional analyses are underway to further assess these relationships.

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1560.E

Altered Phase Shifting Response to Light in the Elderly

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Introduction: Older adults commonly report sleep maintenance insomnia and early morning awakening. These disruptions may be related to an advance in the phase of circadian rhythms, as evidenced by an earlier core body temperature (CBT) minimum in the elderly as compared to young adults. While the cause of this advance in phase is unknown, it may result from altered responsiveness to light, the primary synchronizing stimulus of the circadian timing system. A decrease in the phase shifting response to light has been observed in rodent models of aging.[1,2] In the present report we assessed the response of the clock to light in older humans.

Methods: Six healthy young (3 M, 3 F, 30.3 + 2.2 years) and elderly (3 M, 3 F, 66.2 + 1.8 years) subject volunteers were admitted for a 4 night/3 day stay in the Clinical Research Center at Northwestern University. Self-selected bedtimes ranged from 21:00 to 24:00, and all elderly subjects were within normal limits on neuropsychological and opthalmologic exams. Subjects remained under constant conditions (light < 50 lux and semi-recumbent in bed) during wake periods and slept for 8 h in dark at their usual bedtime. Following a habituation and baseline night, subjects were exposed to light (4,000 lux for 3 h, bracketed by ½ h of intermediate illuminance) beginning 4 h before the baseline CBT minimum (estimated by cosine analysis with demasking). Blood samples, collected from 19:30 to 9:30 on the nights before and after light exposure, were analyzed by radioimmunoassay for melatonin levels in plasma. The rising and declining phases of the melatonin profiles were defined as the first samples to exceed 50% of the peak. Treatment induced changes in the rising and declining phases were compared by t-test.

Results: The baseline CBT minimum averaged 5.17 + 0.81 h in young subjects and 3.63 + 0.95 h in the elderly group. Exposure to light prior to the CBT minimum in young subjects resulted in consistent delays in both the rising (1.28 + 0.21 h, $p < 0.001$) and declining (1.75 + 0.32 h, $p < 0.01$) phases of the melatonin profile. In contrast, exposure to light prior to the CBT minimum in elderly subjects did not significantly delay either the rising (0.98 + 0.81 h) or declining (0.50 + 0.55 h) phase of melatonin. Only 2 of the elderly subjects showed delays in both the rising and declining melatonin phases, while 3 elderly subjects exhibited advances in either the rising or the declining phase.

Conclusions: These results indicate that age alters the responsiveness of the circadian timing system to light. Given that both delays and advances in phase were observed in the elderly group, it is possible that age may affect the phase response curve to light as well as the magnitude of the response to light. While additional data are required to distinguish between these two possibilities, these preliminary results indicate that an altered response to light contributes to the advance in circadian phase and disruption of sleep in older adults.

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1863.E

Nocturnal Sleep Pattern in Native Brazilian Terena Adults

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Introduction: Social-economic and cultural factors play a relevant role determinig nocturnal sleep habits, including sleep duration, regular sleep onset time and morning wake up time. Several sleep disorders and treatments are also influenced by these factors, including the disorders of initiating and maintaining sleep and the use of hypnotic. This research is part of a larger project that we have been systematically conducting to describe and understand ethnic influences on sleep, with emphasis on the Native Brazilian. The present study characterizes Terena adult nocturnal sleep habits, insomnia and the use of hypnotic. Literature focusing on nocturnal sleep in Native Brazilian adults is unknown to us.

Methods: The Brazilian Native Terena belongs to the Aruak-speaking Native branch. The group in this study are agriculturally oriented, peaceful and well-adapted to the fertile lands and tropical climate of the central region of Mato Grosso do Sul. We studied the Corrego do Meio (CM) village, in the municipality of Sidrolandia. CM is located on an Indian Reservation; 40 krn from the nearest town. The interviews were conducted from house to house, encopassing all homes in this age range. Sixty-four Native Terena adults with ages ranging from 18 to 75 years (mean age 37.0 years) were evaluated (31 M; 33 F). Mean ages was 36.8 years, ranging from 18 to 75 years. Mean age of females was 37.2 years, ranging from 18 to 66 years. Sleep characteristics were investigated through interviews during the summer of January 1999. Interviews were conducted personally by the authors. Three male adults were excluded because they worked out of the Indian Reservation, on an irregular sleep-wake schedule. Ten yes/no multiple choice questions were employed focusing primarily on nocturnal sleep habits, the presence of insomnia and the use of medications to induce sleep. This is part of a larger sleep questionnaire data set that will be presented elsewhere.

Results: The reported Total Time in Bed (TIB) was mean of 8.5 h or more in every age bracket during weekdays and week ends. There were

no clear tendencies between sexes or age groups. Even in the 60-69 year group the mean TTB, was remarkably long of 9.5 h. The mean nocturnal sleep onset time was 20.8 h in males, and 19.7 in females. There was a mild tendency to sleep earlier in the 20 to 60 year olds, as the 20 year old group had a mean nocturnal sleep onset time of 2 1.0 h and the 60 year old group a mean of 19.2 h. The eldest group (>70 years) was composed of only one individual precluding conclusions. The mean mornig wake up time was 5.7 h in males and 5.1 h in females. There was a slight trend to wake up earlier in the 20 to 50 year old group, as the 20 year old group had a mean morning wake up time of 6.3 h and the 60 year old group a mean of 5.1 h. In the entire sample of 64 adults, only 3 referred present insomnia, so that seven-day prevalence rate of insomnia was 4.6%. All these 3 cases were females, ages 21, 22 and 44. Only one of them (44 years old) had ever reported the insomnia to a health care provider, and regularly takes hypnotic (diazepam); the two others had never used hypnotic, including Folk Medicine sleep inducing substances and alcohol. In the entire sample of 64 adults, only one subject used hypnotic, so that seven-day prevalence rate of hypnotic use was 1.5%.

Conclusions: The present report showed that nocturnal sleep in Terena adults was characterized by longer TIB, earlier sleep onset time, and earlier morning wake-up time than that described in urban populations. The prevalence of insomnia and the prevalence of hypnotic use were remarkably less than described in urban populations,

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1224.E

Entrainment of Circadian Rhythms in a Totally Blind Subject Using Low Dose Melatonin

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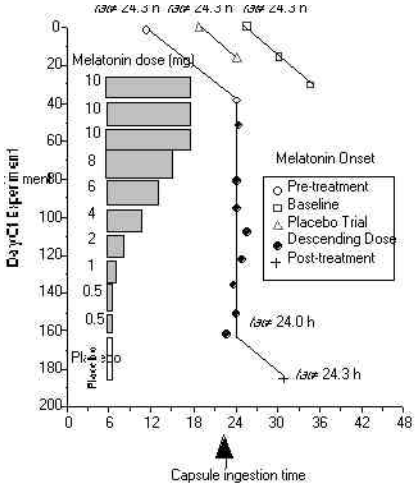
Introduction: In most totally blind people, circadian rhythms of hormonal secretion and body temperature free-run on a non-24-h cycle, even if a conventional sleep/wake schedule is maintained. Periodic insomnia and daytime sleepiness occur as circadian rhythms drift out of phase with desired sleep times. We have recently shown that melatonin given orally, approximately one hour prior to habitual bedtime, can entrain most totally blind subjects with free-running rhythms. However, the dose we used (10 mg) produces blood levels that are far above the physiological range. In order to determine the minimally effective dose, we re-treated a subject (who had been previously entrained to 10 mg) using a "step down" dosing regimen. We hypothesized that, as the dose was reduced, the subject's circadian rhythms would "escape" from the influence of treatment and resume a free-running pattern, thereby revealing the threshold dose for entrainment.

Methods: Melatonin onsets (MO) were assessed about every two weeks by serial 24-h plasma sampling and used as markers for circadian phase. (Melatonin treatment was omitted on the days when melatonin plasma levels were measured.) The subject was a 47 y.o.man who had been shown to have a free-running rhythm (tau = 24.3 h) during a previous baseline assessment (open squares in Fig) and during the placebo arm of the treatment protocol (open triangles in Fig). A previous trial with melatonin (10 mg nightly at 23:00) resulted in entrainment (tau = 24.0 h; data not shown). Prior to the step-down trial, he was given no treatment for several months and his free-running rhythm (tau = 24.3 h) was re-established (open circles in Fig). Melatonin treatment was then given nightly at 23:00 starting on Day 23. After it was demonstrated that his rhythm was again entrained with 10 mg, the dose was reduced every two weeks using the schedule shown (see Fig).

Results: Contrary to our prediction, circadian rhythms did not escape (free-run) as the dose was reduced. Instead, MOs during treatment (filled circles in Fig) remained consistently at about 24:00 for over 100 days, indicating stable entrainment, even with the lowest dose (0.5 mg). Furthermore, sleep quality and quantity showed no decline as the dose was reduced (data not shown). After melatonin was discontinued, the free-running pattern resumed and sleep deteriorated.

Figure 1



Conclusions: In this totally blind person with previously documented free-running circadian rhythms, a nightly dose of melatonin in the physiological range (0.5 mg) maintained entrainment, thereby substituting for photic input to the circadian pacemaker. It remains to be determined whether the 0.5 mg dose is sufficient to entrain circadian rhythms if used as an initial treatment (not maintenance), and whether other subjects will respond similarly. Sack RL, Brandes RW, de Jongh E, Pen S, Nordstrom S, Lewy AJ. Melatonin entrains free-running circadian rhythms in a totally blind person. Sleep 1999; 22 (Supplement):S138-139.

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1230.G

Prevalence of Key Clinical Features of Sleep-Disordered Breathing in a Community-Based Sample of 8-10 Year Old U.S. Children

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Introduction: Sleep-disordered breathing (SDB), characterized by recurrent apnea, hypopnea, and sleep disruption is a common problem in pediatrics. In clinical practice, SDB is diagnosed if clinical assessment includes key clinical features of loud snoring with difficulty breathing or witnessed apnea and physical findings of nasal obstruction and/or tonsillar enlargement. Daytime symptoms such as sleepiness, inattentiveness, or poor school performance are often factored into a decision to

treat SDB in light of increasing awareness of potential neurocognitive and behavioral sequelae. In this study, we assessed the prevalence of the key clinical features of SDB in an unreferred, community-based sample of 8-10 year old children.

Methods: A stratified random sample of 229 full term and pre-term children, born between 1988-1991 in Greater Cleveland area hospitals, participated in this study. Parents completed a standardized health and sleep questionnaire that included both nocturnal and daytime SDB symptoms. Symptom reports were dichotomized to "NO" for responses of "never or rarely" and "YES" for responses of "sometimes, frequently or always". All children were studied with overnight in-home sleep monitoring (Sensormedics PT-2). An obstructive apnea hypopnea index (OAHI) was computed based on the number of obstructive apneas and hypopneas (resulting in a > 50% reduction in the summed rib and abdominal respiratory inductive plethysmography (RIP) signals, or a lesser reduction in RIP associated with a >3% desaturation) per estimated sleep hour.

Table 1

	All Children N=229	OAHI > 3 N=17	OAHI ≤ 3 N=212
Snores	13%	30%	12%
Snores Loudly	13%	24%	12%
Daytime Sleepiness	8%	13%	8%
Falls Asleep in School	4%	0	4%
Inattentive in School	16%	24%	15%
ADDH Diagnosis	10%	0	11%
Misbehaves in School	6%	6%	6%

Results: The sample included 51% females, 7% African Americans, and 41% pre-term children. In this sample, 6 to 16% of children were reported to have symptoms of snoring, daytime sleepiness, and school problems. Boys as compared to girls were more frequently reported to experience snoring (19% vs. 7%, p=.007), behavioral problems at school (11% vs. 1%, p=.001), and attention deficit disorder or hyperactivity (ADDH) (17% vs. 3%, p=.001). No differences in clinical symptoms were observed for former pre-term as compared to term children. The overall OAHI was 1.33 ± 1.38 (SD) (range: 0-8.6). 7.4% of the sample had an OAHI > 3 which was chosen as a cut-off value for recognition of SDB by "objective" respiratory criteria. Approximately twice the proportion of children with OAHI > 3 were reported to have symptoms of snoring and daytime sleepiness, but these differences did not reach statistical significance. In this sample, a large proportion (8-13%) of children with OAHI ≤ 3 also had these symptoms. The nocturnal symptom "stops breathing" was reported in only one child (OAHI ≤ 3) and "struggles to breathe" in no child. Differences in school behavior and ADDH did not discriminate between those with and without elevated OAHI values.

Conclusions: In a population based sample of unreferred children with a wide range (but generally low levels) of SDB, symptoms of snoring, daytime sleepiness, and school problems were reported relatively frequently. However, these symptoms did not clearly differentiate between children with and without elevated OAHI values. These findings suggest that parental symptom reports without other clinical or physiologic data have limited diagnostic or predictive value, especially for children with mild SDB.

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1241.G

Prevalence of Symptoms of Obstructive Sleep Apnea in Children—Preliminary Report of the Tucson Children Assessment of Sleep Apnea Study (TuCASA)

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Introduction: There is increasing recognition that obstructive sleep apnea (OSA) and more broadly, sleep disordered breathing (SDB), may be important factors in childhood development with potentially adverse neurobehavioral and cardiopulmonary consequences.[1] Nevertheless, an accurate prevalence rate of OSA/SDB in children is not known, in part because there have been no large epidemiologic studies employing polysomnography (PSG) which have provided normative data. The TuCASA study which began recruiting in November 1999 intends to use home PSG to determine the prevalence rate of objectively documented OSA/SDB in children and determine its relationship to symptoms, performance on neurobehavioral measures and physiologic/anatomic risk factors. This is a preliminary report of OSA/SDB symptom prevalence in the initial cohort of children recruited.

Methods: Parents of all children in 3 Tucson elementary schools were asked to complete a 15 item survey inquiring about symptoms attributable to OSA/SDB. Parents were asked whether or not their child stopped breathing or struggled to breathe during sleep, turned "blue" while sleeping, snored, was sleepy during the daytime, fell asleep at school or while watching television, or had learning problems (LP). They also were asked whether they ever awakened their child because they stopped breathing. Additionally, information regarding age, height, weight and ethnicity were obtained. Excessive daytime sleepiness (EDS) was defined as being sleepy in the daytime, falling asleep at school or while watching television either "frequently" or "almost always". Witnessed apnea (WA) was defined as stopping breathing or struggling to breathe during sleep, turning blue while sleeping or waking the child because of stopping breathing either "occasionally", "frequently" or "almost always". Snoring (SN) was considered present if it occurred more often than "occasionally" and habitual snoring (HS) was defined as occurring "frequently" or "almost always". Obesity was defined as a body mass index (BMI) in the 95th percentile of the child's age/gender category.

Results: Of 1325 surveys distributed, 266 have been returned to date (20.1%). The mean age of the respondents was 8 years (range 5-12). 53.4% were boys and 46.6% were girls. Ethnic distribution was 39.1% White/Anglo, 41.7% Hispanics, 17.6% Other. The prevalence of WA was 8.8% and was not different by age, gender or ethnicity. However, WA was more common in obese children (19.2% vs 7.6%, p<.05). EDS occurred in 9.2% of children and was not affected by age, gender or BMI. EDS was more common among those with WA (39.1% vs 6.3%, p<.0001). EDS also may be higher among Hispanics (15.5% vs 5.0%, p<.10). The prevalence rates of SN and HS were 30.5% and 11.5% respectively. SN and HS were more common in obese children (SN: 53.8% vs 28.0%, p<.01; HS: 34.6% vs 8.9%, p<.0001), but were not affected by age, gender or ethnicity. LP were noted in 13.7% of the cohort and were not related to age, gender, BMI or ethnicity. However, LP occurred more commonly in children who had WA (38.1% vs 11.5%, p<.001) and EDS (20.0% vs 7.3%, p<.05). The clinical syndrome of WA and either EDS or LP was observed in 14.5% of the cohort and was unrelated to age, gender, ethnicity or BMI.

Conclusions: This preliminary analysis of recruitment for TuCASA indicates that symptoms suggestive of OSA/SDB occur commonly in

children, especially those who are obese. The prevalence of HS is similar to that reported from other studies[2,3] although the prevalence of EDS appears slightly greater.[1] The relationship between LP and both WA and EDS suggests that OSA/SDB may have significant neurobehavioral consequences in children. Objective PSG data which will be forthcoming in TuCASA will be very useful in further defining this impact.

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1247.G

Cosleeping in Korean Young Children

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Introduction: Many child health professionals in western society emphasize the adverse effects of the cosleeeping. However, patterns of child rearing reflect cultural values and contemporary circumstances and cosleeping is still very common practice in non-western cultures including Korea. This study was undertaken to examine[1] how often Korean young children are cosleeping with their parents,[2] whether there are any characteristics of cosleeping children,[3] whether there are any relationships between cosleeping and sleep problems.

Methods: Subjects consisted of 427 Korean young children of 12 - 84 months old. Information on child's and parents' basic demographic characteristics, sleep arrangements and sleep-related problems etc were gathered by concentration on the month preceding the interview. Considering Korean peculiar sleeping environments, bedsharing and roomsharing were defined as cosleeping. Five categories of conflictual sleep related behaviors were investigated and sleep problems were defined as problematic behaviors occurred regularly three or more nights a week at bedtime or during the night.

Results: 1. The rate of cosleeping was 377(88.2%) of 427 which consisted of 192(50.9%) bedsharing and 185(49.1%) roomsharing. Cosleeping was decreased with age.2. The mean age of cosleeping children was significantly younger(¥ö2=49.20, p<0.001). Only children and first-born children were more common in cosleeping group. Otherwise, first-born and later-born children were more common in noncosleeping group(¥ö2=16.67, p<0.001).3. The parental mean age of cosleeping group was significantly younger(¥ö2=16.2, p=0.001) and they were using significantly more separate bed than their counterpart(¥ö2=10.03, p<0.005). There were no significant intergroup differences with regard to socioeconomic status, the numbers of family member, family structure and room density.4. Cosleeping was significantly associated with all five categories of sleep problems(¥ö2=17.49, p<0.001). But Korean parents were more accepting of their children's sleep behaviors.5. Cosleeping mothers had significantly more acceptable attitude for cosleeping than non-cosleeping mothers(¥ö2=30.32, p<0.001).

Conclusions: We suggests that the practice of cosleeping in Korean young children is very common and reflects Korean cultural values such as strong family bonds and a large societal value of interpersonal interdependency. Most Korean parents seem to consider cosleeping as a normal part of child rearing. However, cosleeping is significantly associated with sleep-related problems.

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1668.G

Prevalence of Infant Sleep Problems in Pediatric Settings

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Introduction: Most infants exhibit regular sleep-wake and feeding schedules, are able to self-soothe or are effectively soothed by their familiar caregiver, and do not have prolonged periods of crying or fussiness by the time they reach six months of age. A disturbance in the early social regulatory or attachment system with the primary caregiver is hypothesized to cause infant regulatory disturbances, such as difficulties regulating sleep. This study examined how prevalent sleep difficulties are among infants and whether parents typically discuss their questions regarding sleep difficulties with their child's physician during periodic infant health exams. Further, it measured how stable difficulties with sleep are in young infants and whether sleep problems are more common than difficulties with crying, irritability, or feeding.

Methods: This research examined the prevalence and stability of sleeping, crying, and/or feeding difficulties in infants as they were brought to well-child pediatric visits. Maternal psychological well being was also assessed. Interviews and questionnaires were conducted with 70 mothers with 6-month-old infants (36 females) as they waited in Pediatric Clinics for well-baby check-ups. Mothers were contacted again at the next three well-baby visits, for a total of four interviews over nine months. Questionnaires included a demographic form, a Beck Depression Inventory and a Parenting Events Scale to measure daily hassles and stress (from the work of Crnic & Greenberg, 1990). Infant behaviors were reported by the mother with a semi- structured interview form and the Infant-Toddler Symptom Checklist (DeGangi et al., 1995). A medical chart review was also completed to document physician notes about concerns with the infant's sleeping, crying, or feeding behavior.

Results: Preliminary analyses showed that parents reported more sleeping difficulties (60% at 6 months, 88% at 9 months, 75% at 12 months, 75% at 15 months) than crying or feeding difficulties (both average 40%). However, while sleep difficulties were reported on the questionnaires, it was often not noted in the medical chart for the corresponding well child visit. There was no significant stability of sleep difficulties as reported by parents from one well child visit to the next even though a majority of the infants continued to have difficulties with waking their parents during the night by vocalizing or crying. In contrast, behavior at the beginning of the night in bed (either awake or asleep) was highly stable across measurements. Interestingly, it was not until 12 months of age that a majority of the infants started the night in their beds awake (63%). Infant sleep problems were associated with parenting hassle scores.

Conclusions: Problems with infants and toddlers' sleep are commonly reported by mothers however sleep difficulties are less frequently noted by physicians as complaints in the medical charts. For a small minority of mother-infant dyads, persistent difficulties are evident at repeated

well child care visits. Sleep problems were more common than difficulties with irritability, crying or feeding. Stable patterns of difficult sleep in infants may involve a regulatory disturbance in the attachment relationship and suggests a need to examine parent-child relationship assessment and treatment in health care settings.

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1366.G

Childhood Nocturnal Asthma: Chronobiology and Sleep

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Introduction: Sleep-related asthma occurs in 61-74% of asthmatics. The consequences of nocturnal asthma are frequent arousals and hypoxemia which may contribute to poor sleep, daytime sleepiness and fatigue, and impaired cognitive functioning. Episodes tend to occur in the later part of sleep in the early morning. This apparent circadian fluctuation and the impact of nocturnal asthma (NA) have been studied in adults but not in children. We report the findings of a retrospective study of overnight polysomnography (PSG) and a prospective study of variations over 24 hrs of plasma cytokines, blood eosinophils, and exhaled nitric oxide (NOe) in children with NA and controls.

Methods: (1) We reviewed the sleep history , overnight PSG, and MSLT studies performed in 18 boys and 2 girls (ages 1.7-17.3 years) with asthma and determined the character of sleep and sleep related breathing dysfunction, and tendency for daytime sleepiness. (2) We prospectively evaluated 5 children with NA and 5 control children (ages 9-15 yrs) during an admission to General Clinical Research Center of Texas Children's Hospital. These children underwent pulmonary function testing (PFT) and measurement of eosinophil counts (EOS), NOe, and plasma cytokines determined at time points 19:00, 22:00, 02:00, 04:00, 08:00, 12:00, and 16:00. Comparisons were made for these values for the NA group vs the controls.

Results: Study 1: The 20 children comprised 2 groups: (a) 5 young asthmatics (1.7-3.8 yrs). The reason for PSG was nighttime breathing problems; 4 had had been observed to snore and to have possible cessation of breathing during sleep. In 4 there were PSG findings of sleep-related breathing dysfunction; 2 had findings of obstructive sleep apnea/hypopnea (OSAH) with oxygen desaturation to 77-88%: 4 had elevated end tidal pCO2 values during sleep (range 50-56 mmHg): 2 had central apnea with oxygen desaturation to 86-88%. (b) 15 older asthmatics (5.3-17.3 yrs). The reasons for were nighttime breathing problems including 8 with observed snoring and cessation of breathing during sleep and 3 with nighttime cough and wheezing; and excessive daytime sleepiness in 6. Six were obese and 8 were receiving bronchodilators. PSG revealed 6 had findings of OSAH with oxygen desaturation to 73-80%; 11 had elevated ETpCO2 (51-69 mmHg) during sleep. Three children s/p Tonsilectomy/Adenoidectomy had findings of OSAH and elevated ETpCO2. Eight had > 10 arousals during sleep. Six had MSLTs and 2 had MSLT latencies <5 minutes. Study 2: PFT in NA children showed a decreased baseline (from % predicted) at 20:00 and 16:00 and a further decrease at 04:00 (FEV1, p=0.01; FEF 25-75, p=0.005). In the NA group EOS (p=0.03), NOe (p=0.03), IL-13 (p=0.08), and TNF alpha (p=0.08) showed elevated group differences and further EOS and NOe elevation at 04:00.

Conclusions: These studies, though performed in a small number of NA children, support the hypothesis that inflammatory markers in children with NA are elevated in the later part of the sleep cycle and cause additional immunologic problems, such as migration of eosinophils, macrophages, and neutrophils into pulmonary airways and tissue. NA children and adolescents frequently were found to have sleep-related breathing dysfunction including OSAH, significant oxygen desaturation and elevation of ETpCO2 during sleep, and may experience arousal with fragmentation of nocturnal sleep. Circadian variations in inflammatory markers in lower airways may contribute to increased CO2 retention during sleep and also impact on the patency of the upper airway especially in the context of preexisting factors such as obesity and tonsillar hypertrophy, and result in disturbed nocturnal sleep. The consequences may include daytime problems with attention, concentration and memory resulting in poor school performance and behavioral difficulties.

1064.G

Sleep and Rhythms in Tenth vs. Third Graders

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Introduction: Studies have suggested that as children grow older, their rhythms become delayed. Delayed sleep phase syndrome (DSPS) has been shown to lead to poor performance in school, behavioral problems, and sleep problems. The DSPS is believed to be a result of changes in the biological clock rather than a result of the environment. If so, sleep in teenagers should be more disturbed than that of younger children. To test this hypothesis, this study examined whether tenth graders would rate themselves as "evening" more often than third graders and compared both subjective reports and objective sleep/wake rhythms and light exposure in these two groups

Methods: The Carskadon Morningness/Eveningness questionnaire[1] and a sleep questionnaire were given to 50 third graders (26 girls, 24 boys; mean age=8.3 years; SD=0.5; range=8-9 years) and 86 tenth graders (45 girls, 41 boys; mean age=15.2 years; SD=0.4; range 14-16 years). All questionnaires were filled out in class and collected by the teachers. A sub-group of 5 tenth graders and 7 third graders also had their sleep/wake recorded with Actillume recorders (Ambulatory Monitoring Inc, Ardsley, New York). All subjects wore the Actillumes on either weekends or vacations when they wouldn't be required to wake up early but rather could sleep on their own rhythm. Each subject wore the Actillume for 72 continuous hours. Actillumes were removed only for bathing and sports. All subjects recorded the times the Actillume was removed, time to bed and time of final waking. Questionnaire data, sleep/wake data and light exposure data were analyzed using Kruskal-Wallis analyses of variance. Rhythm data were computed using cosinor analyses (Action 3; Ambulatory Monitoring Inc, Ardsley, New York).

Results: As expected, on school nights, the tenth graders compared to the third graders, reported going to bed significantly later (22:29h vs.20:33h; $p<0.0001$) and sleeping less (7.48 hours vs 9.24 hrs; $p<0.0001$). On weekends, tenth graders reported going to bed about 1.5 hours later than third graders (2355h vs. 2220h; $p<0.0001$)) and waking up about two hours later (0903h vs. 0710h; $p<0.0001$). There was no significant difference in reported total sleep time. On the morningness/eveningness scale, tenth graders scored more toward eveningness (mean=25.6; SD=5.8; range=10-37) while the third graders scored more toward morningness (mean=30.7; SD=5.6; range=15-40)($p<0.0001$). There were no significant differences between the third

grade boys and girls. However, tenth grade girls rated themselves as being less "evening" (mean=27;SD=5.5; range=16-37) than tenth grade boys (mean=24;SD5.7; range=10-35) (p=0.034). Based on Actillume recordings, there was a trend (p=0.069) for the tenth graders to sleep 67 minutes longer than the third graders (611 vs. 544 minutes). Actillume recordings indicated that the tenth graders were more delayed than the third graders by about an hour (mean acrophase= 1449h vs. 1350h; p<0.055), but had lower amplitudes (15.8 vs. 23.1; p<0.055) and lower mesors (13.8 vs. 23.5; p<0.011), also indicating less robust rhythms. There were no differences in mean lux levels of exposure, however, tenth graders had significantly lower maximum levels of exposure than the third graders (7943 vs. 19953 lux; p=0.054).

Conclusions: Tenth graders reported being more delayed than third graders. They not only reported going to bed later and sleeping later, but scored as eveningness while the third graders scored as morningness. Objective data also confirmed the subjective reports. Acrophase for the tenth graders was an hour later than that of the third graders. Tenth graders also had weaker rhythms (lower mesor, lower amplitude) possibly because they recieved less bright light exposure during the day

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This study was conducted as a seventh grade science fair project and won first place in the County of San Diego.

1392.G

A Comparison of Sleep Patterns Between Cosleeping and Solitary Sleeping Infants

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Introduction: Infants' sleep patterns differ depending on their sleeping environments. Infants who sleep in the same beds as their mothers have the extra stimuli of their mothers' movements, body temperature, and CO2 exchange. One study found that mothers and their 11-15 week old infants spend 55-68% of the time sleeping face-to-face when cosleeping (Richard et al., 1996). Another study found that cosleeping infants spend more time sleeping in a more aroused state than solitary sleeping infants (Mosko et al., 1996). These researchers propose that the CO2 exchange that occurs during face-to-face sleep keeps infants aroused during sleep. From these prior data, it was hypothesized that cosleeping infants would spend more time in active sleep, have more nighttime arousals, and spend the majority of the night sleeping face-to-face with their mothers. This study tested these hypotheses on a sample of 3-15 month old cosleeping infants.

Methods: Nine healthy, full-term cosleeping infants (7 males) were selected from a larger sample of infants who were recruited from the local community for a developmental sleep study. Nine solitary sleeping infants were chosen as controls from the same sample by matching on age, gender, ethnicity, maternal age, and family SES. The infants' sleep was recorded using videosomnography and then coded for sleep states using an established coding procedure (Anders & Sostek, 1976). The following variables were used for this analysis: percentage of time spent in active sleep, quiet sleep, awake, the number of nighttime awakenings, and the percentage of time the infants and their mothers spent sleeping face-to-face.

Results: No significant differences were found between cosleeping and solitary sleeping infants for the amount of active sleep, quiet sleep, or wakefulness. Significant differences were found, however, in the number of awakenings between cosleeping and solitary sleeping infants. Cosleeping infants had a mean of 5.8 (SD=1.50) awakenings per night while solitary sleeping infants had a mean of 3.2 (SD=1.95) awakenings per night (t=3.159, p=.006). In addition, infants in this study displayed face-to-face positioning with their mothers 40% of the time.

Conclusions: The average percentage of time spent in active sleep, quiet sleep, and awake was similar between cosleeping and solitary sleeping infants. However, the number of nighttime awakenings was significantly higher for cosleeping infants. Although cosleeping infants were waking up more, on average they remained awake for shorter durations per awakening. Perhaps higher percentages of active sleep were not seen in this study because these infants did not spend the majority of the night sleeping face-to-face with their mothers. This difference in sleep positioning could be due to the differences in age between the infants in the prior study and the infants in this study.

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1074.G

Young Children Who are Late Sleepers Sleep Less than Early Sleepers

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Introduction: According to the Ministry of Health and Welfare of Japan, the percentage of young children who fall asleep at 22:00 or later has been increasing in recent years, now being more than 40%. In addition, infants of 10 and 13 months of age living in Tokyo were reported to fall to sleep later at night than those living in rural parts of Japan.[1] Their living environments, including the life styles of their parents, were considered to cause this phenomenon.[1] Some researchers commented that the delayed nocturnal sleep onset time in young children is permissible because no obvious adverse effects of this delay were found among them. However, this speculation has not yet been confirmed. The present study aimed to determine the sleep-wakefulness rhythm of young children currently living in Tokyo.

Methods: Guardians were asked about the sleep habits of their children at regular health checks performed for 18 and 36-month-old children (18-month exam. and 36-month exam.). In Japan, this health check system for children was established by the government, and is widely utilized by almost all guardians. From July to September 1999, a questionnaire was mailed in advance to the guardian(s) who were scheduled to visit 2 (Hikarigaoka and Kita) of the 6 regional public health centers in the Nerima district of Tokyo. At another 2 public health centers (Sakuradai and Seki), the questionnaire was handed out directly at the time of the visit. We analyzed the answers to the following 6 questions: 1. What time does your child fall into sleep? 2. What time does your child wake up? 3. Does your child take naps? (Answers: not at all, sometimes, often, every day) 4. What time does your child start to take a nap? 5. How long does your child take a nap? 6. What are your concerns about the sleep of your children? The questionnaire sheets were collected after the health check at each center. Student's t-test and analysis of variance (ANOVA) were performed when necessary.

Results: The answers from 649 guardians (319, 18-M-C; 330, 36-M-C) were valid and thus analyzed. The average nocturnal sleep onset time and wake-up time in the morning were 21:38 and 7:22 in 18-M-C, and 21:39 and 7:31 in 36-M-C, respectively. Forty-three percent of the children fell asleep at 22:00 or later. Among regular nap takers (97.5% in 18-M-C and 46.1% in 36-M-C), the mean wake-up time in the morning and the average wake-up time from naps became later, and the average daily total sleep time became shorter, as the nocturnal sleep onset time became later. This daily total sleep time difference between children who fell asleep before 21:00 and those who fell asleep at 23:00 or later was 1.2 hours in 18-M-C and 0.9 hours in 36-M-C, respectively.

Conclusions: According to Roffwarg et al.,[2] the daily total sleep time in infants aged between 6 to 23 months was 12.8 hours, and in children aged between 2 to 3 years 11.8 hours, respectively. Recently, Louis et al. reported the mean total daily sleep time in 1.6-year-old children was 718 minutes (12.0 hours).[3] In the present study, the daily total sleep time in the regular nap-takers was 11.8 hours for 18-M-C, and 11.3 hours for 36-M-C, respectively. The total daily sleep times for the early sleepers in the current study (21:00>; 18-M-C, 12.4 hours; 36-M-C, 11.7 hours) are identical to those in the previous descriptions.[2,3] Although it is difficult to determine the ideal or normal sleep-wakefulness pattern in young children, we believe that few researchers would accept the present results as ideal ones. The late sleepers were found to fail to compensate for their reduced sleep time by means of a delayed wake-up time and a longer nap duration. The sleep in the late sleepers was interpreted to be deprived.

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1093.G

Cosleeping in Childhood: Native Brazilian Terena and Bororo, and African-Brazilian

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Introduction: Sleep habits in childhood vary due to physiological factors. They also adjust to social, economical and cultural influences. Cosleeping (bedsharing, in the same bed) with family members is uncommon and even culturally dissuaded in the present Anglo-Saxon culture. This research is part of a larger study we have been conducting in order to determine ethnic factors on sleep, in Native Brazilian (Terena, Bororo) and African-Brazilian children. In the present paper we compare our previous findings of cosleeping in these ethnic groups.

Methods: a) Terena. Sleep characteristics of 87 children (50M;37F) from 0 to 10 year olds, were evaluated in interviews with their mothers. Two villages, Terere and Corrego do Meio, were studied, both in Reservations, in the state of Mato Grosso do Sul. The same standardized interview was applied in the two other populations, the Bororo and the African-Brazilians.b) Bororo. Sleep characteristics of 44 children (24M;20F) from 0 to 10 year olds in Meruri Reservation in the state of Mato Grosso were evaluated.c) African-Brazilian. Sleep characteristics of 57 children (36M; 21F), from 0 to 10 year olds, in the isolated rural African-Brazilian community of Furnas do Dionisio, in the state of Mato Grosso were evaluated.

Results: a) Terena. A most remarkable finding was that cosleeping, in the same bed with family members is the standard Terena pattern present in every evaluated child.b) Bororo. Cosleeping was present in every child 0-1 year olds; in 81.5% of the 2-9 year olds; in 40.0% of the 10 year olds. c) African-Brazilian. Cosleeping, in the same bed with family members was present in every child 0-1 year olds; in 80.0% of the 2-3 year olds; in 75.0% of the 4-5 year olds; 66.7% of the 6-7 year olds; decreasing to 25.0% of the 8-10 year olds.

Conclusions: It was observed that cosleeping (bedsharing, in the same bed) with family members is the standard pattern in Native Terena children. Cosleeping was also found in every Bororo and African-Brazilian child in the first two years of life and reduces markedly by the end of the first decade.

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1108.G

Adolescent Sleep and Daytime Functioning: A National Study

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Introduction: There are many negative effects of severe sleep deprivation on mental and physical health, but it is less clear what the effects of mild but chronic sleep deprivation are. Adolescents are an ideal population to study the effects of mild sleep deprivation on daytime functioning because they stay up progressively later through high school and they almost always have early school start times (Manber et al 1995). Thus, there is growing evidence that adolescents do not typically get enough sleep to function optimally (Wolfson & Carskadon 1998). However, much of this evidence has been collected from small convenience samples and ties sleep habits to single outcomes such as school performance or daytime sleepiness. The following presentation is based on analyses of a large database on adolescent health and behavior with explicit focus on the relations between sleep habits and various indices of daytime functioning.

Methods: The National Longitudinal Study of Adolescent Health, which began in 1994 with a large nationally-representative sample of 7th - 12th grade students, has produced a wealth of data on the health-risk behaviors of adolescents, as well as their family, school, and social contexts. The data reported here are based on analyses of in-home interviews conducted in 1995 with 20,745 adolescents. Information about sleep habits was identified and then five scales were created to associate with self-reported hours of sleep. These scales were as follows: a 15-item delinquency scale, a 5-item anxiety scale, a 7-item depression scale, a 4-item problems-during-school scale, and a 12-item somatic-complaints scale.

Results: The delinquency scale had an alpha reliability of .84 with 3 factors. The other scales all had a single factor with alphas of .69, .70, .79, and .84 for the problems, anxiety, somatic-complaints, and depression scales, respectively. A 4-course most recent GPA was also computed, and students were categorized on the basis of how much they worked

after school and how much they smoked and exercised. Results include the following: 1. Average self-reported sleep per weeknight drops from 8.4 hours to 7.3 hours from 7th grade to 12th grade. 2. The percentage of students who get 9 or more hours of sleep per night drops from 42% in grade 7 to 15% in grade 12. 3. When students are categorized as Low (<= 6 hours) vs. High (>= 9 hours) Sleepers, Low Sleepers get lower grades and score higher on measures of depression, anxiety, trouble with others, delinquency, and somatic complaints (all Fs > 25 and Ps <.001). 4. Overall, girls sleep less than do boys (F=9.8, P<.002) and this difference holds at every grade level. 5. Those who work more than 10 hours per week sleep significantly less than do those who work less than 10 hours per week (F=28.4, P<.001). 6. Smokers sleep less than do nonsmokers (F=41.4, P<.001). 7. Those who are physically active get more sleep (F=39.1, P<.001), have better grades (F=26.3, P<.001), and score lower on measures of depresssion (F=49.9, P<.001) and anxiety (F=37.5, P<.001).

Conclusions: These findings confirm at a national level what sleep researchers, teachers, and parents have long suspected, namely, most adolescents do not get enough sleep during the week to function well during the day and those who get the least sleep are more likely to have academic, health, and behavioral problems.

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POSTER PRESENTATIONS

1763.G

Children's Sleep and Parental Practice: Timing, Order, and Composition of Bedtime Routines

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Introduction: This study investigated the relationship between consistency of bedtime routines in terms of timing, order, and bed place, routine composition, and sleep in 2- to 5-year-old children. There is anecdotal evidence that regular bedtimes and routines aid children in transitioning from wakefulness to sleep, however, this relationship has not been sufficiently examined. Existing studies have found regular routines to be extremely common but not related to settling difficulties and night waking.[1] Routine consistency rather than composition has been suggested important in helping a child get ready to go to bed and fall asleep.[2]

Methods: Data were collected on 30 children (12 male, 18 female), ages 2 to 5 years (mean = 3.3, SD = 1.15) attending a University Child Development Center. Seventy percent of the children were Caucasian and 30% were African American, Asian American, and Hispanic. Parents completed a general information questionnaire and The Sleep-Wake Scale for Children (SWSC). The SWSC was used to obtain parental report about sleep difficulty in children along five behavioral dimensions: Going to Bed, Falling Asleep, Arousals/Awakenings, Reinitiating Sleep, and Returning to Wakefulness. This instrument also assessed sleep-related routines that parents employed with their children.

Results: Table 1 shows the relationship between bedtime routine factors and sleep and waking difficulties. Parents overwhelmingly reported having a bedtime routine (96%), but sleep difficulties were unrelated to the presence or absence of this routine. Children of parents that executed the routine at the same time in the evening and consistently enforced bedtime had fewer problems with going to bed, falling asleep, waking at night, reinitiating sleep, and waking in the morning. Similarly, parents who varied the order of the routine were more likely to have children who resisted bedtime, had sleep onset delay, and were unable to reinitiate sleep independently following an awakening. Putting a child to bed in the same place was related to fewer sleep difficulties and less difficulty in the morning. Individual routine components (e.g., putting on nighttime clothes, brushing teeth, using the bathroom, drinking liquids, reading, and watching TV) were not related to sleep problems. Children who had less difficulty returning to wakefulness were read to by their parents more often (r=-.374, p=.042) or watched TV less often before bedtime (r=.447, p=.013).

Table 1. Relationship Between Bedtime Routine Factors and Sleep/Waking Difficulties

Bedtime Routine Factors	Going to Bed	Falling Asleep	Arousals/ Awakenings	Reinitiating Sleep	Returning to Wakefulness
Routine Presence	-.109	-.123	-.014	-.287	-.145
Consistent Timing	-.644***	-.726***	-.403*	-.459*	-.408*
Consistent Order	-.532**	-.538**	-.345	-.533**	-.164
Consistent Bedtime	-.700***	-.631***	-.390*	-.430*	-.517**
Consistent Bed Place	-.346	-.376*	-.369*	-.315	-.451*

* p≤ .05 **p≤ .01 ***p≤ .001

Conclusions: These results confirm impressions of the importance of bedtime routines. Almost all parents report a routine, but not all routines are related to good sleep. Children that sleep well have routines that are consistent with regard to bed place, timing, and order of activities. Type of routine activity does not seem to be related to sleep quality.

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1441.G

Automated State Identification Strategies for the Full Term Neonate

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Introduction: Evaluation of rudimentary state transitions in preterm infants lack clear operational definitions. More accurate physiologic descriptions may improve the clinician's ability to assess functional brain organization for a given postconceptional age, follow functional brain maturation and detect neurologic dysfunction.[1,2] We developed a system to study the relationship between behavioral states, brain activity and cardiorespiratory output in ELBW infants. Recent advances in the field of digital signal processing has expanded the role of the computer as a tool to assist the clinician in the interpretation of neonatal electroencephalographic/polysomnographic studies and to provide a means for diagnostic support for the evaluation and treatment management of these patients.

Methods: We present a computer method for automated sleep staging in neonates. This study compares various time-frequency domain transforms to extract features used in the determination of state. The methods we use are Wigner-Ville, Gabor Transforms and the Continuous Wavelet Transform (CWT). We also employ Marchov chains to improve classification of states by using long-term trend contextual information.

Results: Four sleep states of the full-term infant were identified: Mixed frequency active sleep, high voltage slow quiet sleep, trace alternant

quiet sleep and low voltage irregular active sleep. Each stage contains signatures that are easily discerned in the time-frequency domain plots.

Conclusions: We argue in favor of the CWT over other time-frequency domain transforms because it maximizes the available information within the limits of the uncertainty principle.

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1128.G

More Mature Neonatal Sleep State Patterning are Associated with Higher Maternal Levels of Docosahexaenoic Acid

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Introduction: Docosahexaenoic acid (DHA) is crucial to neonatal development and is laid down in high concentrations in both the central nervous system (CNS) and retinal tissue of the eye during gestation, especially in the third trimester (Crawford et al 1989). However, functional outcome for the infant with respect to DHA's effect on fetal CNS development remains unexplored. Measurement of neonatal sleep/wake states is uniquely appropriate for assessing neurobehavioral status. We compared the state characteristics of neonates whose mothers were categorized as having high or low levels of plasma phospholipid (PL) DHA.

Methods: Seventeen women were recruited into the study after they were admitted for delivery at a local hospital. Recording of the infants' state was begun upon admission to the nursery. State was recorded non-intrusively using the Motility Monitoring System (Thoman et al 1987): a pressure-sensitive pad placed under the infants' bedding in the crib that produces a continuous, single-channel recording of analog signals from the infant's body movements and respiration. This signal is digitized and stored in a 24-hour data logger until computer scoring and visually editing for the sleep states, transitions, and wakefulness. Maternal venous blood was collected after delivery and plasma PL fatty acids were analyzed by gas chromatography.

Results: Plasma PL DHA ranged from 1.91 to 5.51 weight percent (wt%). Based on previously published data (Wijendran et al 1999), the women were divided info two groups: high (H) (>3.0 wt%), and low (L) (£ 3.0 wt%). The following were significant differences between the groups: during the first postnatal day, infants of women in the H group had a lower Active/Quiet Sleep Ratio (AS/QS) (H=2.7±.35; L=4.9±.92, F=6.5, p<.05), less Active Sleep (AS) (H=44.7±2.31; L=52.4±2.36, F=5.0 p<.05), and more Quiet Sleep (H=18.2±1.78; L=12.5±1.92, F=4.62, p<.05). On the second postnatal day (N=16), these infants had lower AS/QS ratio (H=2.9±.33; L=5.4±.66, F=14.61, p<.01), less AS (H=34.9±4.31; L=54.2±2.46, F=10.58, p=.01), less Sleep/Wake Transition (H=3.62±.47; L=5.93±.88, F=6.51, P<.05), and more Wake (H=48.2±5.55; L=28.33±2.61, F=6.95, p<.05). Regression analyses of maternal DHA values with the sleep/wake states were consistent with these results.

Conclusions: In the months following birth, the developmental trend is towards a decreased ratio of Active Sleep to Quiet Sleep. The lower AS/QS ratio of the infants whose mothers had high DHA suggests a developmental advantage for this group. This is the first report documenting that maternal DHA status during pregnancy, which is significantly influenced by dietary DHA, is associated with CNS integrity of the infant at birth.

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1459.G

Sleep Disturbances in Children with Headaches

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Introduction: Although research with adult headache patients demonstrates prevalent sleep difficulties, little research on sleep has been conducted concerning headaches in pediatric populations. The purpose of this pilot study is to provide data on the relationship between severity and type of children's headache symptoms and their sleep difficulties.

Methods: The Sleep Habits Questionnaire (SHQ) has been completed by the parents of 31 children, ages 5 to 18 years (M=11.8) who were seen for headache evaluations in pediatric neurology. Children had diagnoses of migraine (81%) and tension (19%) headache. The SHQ provides information on sleep behaviors in 8 domains (e.g., bedtime resistance, parasomnias, sleep anxiety) with higher scores indicating greater sleep disturbance. Neurology charts were reviewed for headache diagnosis and symptom features (onset, frequency, duration).

Results: Results demonstrated a significant relationship between headache duration and sleep anxiety; longer average headache duration was associated with higher sleep anxiety (r= .46, p< .02). Trends were found for a relationship between more recent onset of headaches and higher bedtime resistance (r= -.31, p< .10). Group differences emerged between children with migraine vs. tension headaches on two sleep disturbance subscales, sleep disordered breathing (t(24)=2.63, p< .02) and sleep anxiety (t(25)= 2.11, p< .05), with children with tension headaches demonstrating more difficulties compared to children with migraines.

Conclusions: Contrary to predictions, no relationship emerged between headache frequency and sleep disturbances. Our pilot data suggest that

the relationship between children's headaches and sleep is complex. We plan to increase our sample size and present data on repeated measurements of headache and sleep complaints for a subgroup of children in order to clarify the interaction between headaches and sleep disturbance that is needed for adequate diagnosis and treatment for these children.

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1783.G

Predicting and Classifying Sleep Disorders in Toddlers

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Introduction: Previous research has found that during the 2nd half of the first year of life, some infants are able to self-soothe following night awakenings while others signal or cry when they awaken (Anders, et al., 1992). When they persist, these signaled night awakenings are the most frequent complaints of parents to their pediatricians during the second year of life (Ferber, 1999). In the current study, we report on infant predictors of toddler sleep problems. We also report on a tentative classification system to aid in studying problem sleep in early childhood. A pilot study conducted in our lab demonstrated that signaling at one year predicted the development of a night waking sleep disturbance or disorder in preschoolers (Gaylor, et al., submitted). We have now further tested the validity of signaled night awakenings at six months, compared to signaled night awakenings at one year, in predicting later sleep problems. It was hypothesized that signaling at one year would better predict the development of sleep problems in toddlerhood than signaling at six months of age.

Methods: The sample consisted of two groups of children who were followed prospectively during the first year of life. Objective video recordings of each subject's nighttime sleep were gathered at either 6 months (n=63; 54% male) or 12 months (n=71; 55% male) of age depending on the subject's protocol. Signaling at 6 and 12 months was calculated using percentage of total awakenings on video recording in which infants signaled or cried and required parental assistance in returning to sleep. Parents then participated in a follow-up phone call that inquired about the child's current sleep patterns (mean age = 31 months) for both the 6 and 12 month groups.

Results: Approximately 22% of the total sample at follow-up assessment met the criteria for night waking disorder and 36% met the criteria for sleep onset disorder. Only 10% of parents reported that their child had a current sleep problem. For the 6 month group, 77% were identified as signalers; while the 12 month group consisted of 65% signalers. One-third of the 12 month signalers (31%) met criteria for night waking disorder; whereas only 17% of the self-soothers met criteria at follow-up. Equal proportions of signalers and self-soothers in the 6 month group developed a night waking disorder at follow-up assessment (25% vs. 23%, respectively).

Conclusions: These findings are in the hypothesized direction and suggest that signaling at one year is a better predictor of later sleep problems than night waking or signaling at six months. Results are discussed in terms of the utility of signaling at 12 months as a predictor of later sleep problems.

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1137.G

Central Respiratory Pauses of Normal Infants and Children - Developmental Relationships with Sigh and Gross movement

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Introduction: Both sighs (SIs) and gross body movements (GMs) often precede central respiratory pauses (CPs) during sleep. Interestingly, CP during sleep is also terminated by SIs and GMs. Among CPs, biological significance between CP preceded by SIs (SI-CP) or GMs (GM-CP) and CP followed by them (CP-SI or CP-GM) is considered to be different. However, few studies examined the state-dependency or age-dependency of the frequency of SI-CP, GM-CP, CP-SI or CP-GM. The present study aimed to demonstrate the chronological change of the frequency of these 4 types of CPs.

Methods: The frequency of the 4 types of CPs were examined in 7 infants and 13 children who had no abnormal neurological findings. Their respiration during sleep was measured through plethysmography on all single night polysomnography. These 20 subjects had no episodes of airway obstruction which lead to fall of transcutaneous oxygen saturation (SpO2) level less than 90 %. SI was defined as a respiration that had at least a doubling respiratory signal as compared to the previous and following stable respiration. GMs were defined as movements, including trunk muscle activity, lasting 2 seconds or more. The frequency of 4 types of CPs (SI-CP, GM-CP, CP-SI and CP-GM) as well as isolated SIs was determined separately during REM sleep (REMS) and non-REM sleep (NREMS).

Results: SIs decreased gradually with age. The frequency of SIs during REMS was higher than that during NREMS both in infancy and children. However, a statistical significance was only obtained for infancy ($p<0.05$). The frequency of SI-CPs during NREMS was significantly higher than that during REMS (infancy, $p<0.05$; childhood, $p<0.01$). In childhood, the average incidence of GM-CPs during NREMS was significantly higher than that during REMS ($p<0.005$). This difference was not obvious in infancy. The frequency of CP-SIs during REMS exhibited a higher value than that during NREMS in childhood ($p<0.05$), however, this difference was obscure in infancy. The sum of the frequency of CP-SIs and CP-GMs during REMS was significantly higher than that during NREMS both in infancy ($p<0.05$) and childhood ($p<0.005$).

Conclusions: CP-GM and CP-SI are considered to be caused by arousal responses. Probably through automatic regulation, GM and SI are considered to trigger CP. However, these CP inductions could lead to life-threatening respiratory pauses especially in cases with an impaired respiratory control. The appropriate maturational changes of appearances of CPs in relation with SIs or GMs during each sleep state may protect sudden death during sleep in infancy and childhood.

POSTER PRESENTATIONS

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1795.G

OSAS in Children is Associated with a Higher Incidence of ADHD and Hyperactivity

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Introduction: In children with OSAS hyperactivity is a common finding. It is unknown whether OSAS may be a cause of hyperactivity in this patient population. Hyperactivity and the diagnosis of ADHD may result in treatment with stimulant medication. It is important to clarify the possible association of hyperactivity, ADHD and childhood OSAS since OSAS is a treatable condition and its treatment may preclude the need for stimulant medication in some OSAS patients.

Methods: The parents of every child who presented between January 1997 and September 1999 (n=62) for an evaluation for OSAS were asked as part of the initial evaluation whether the child had been diagnosed with ADHD and/or whether the child was hyperactive. The children then underwent polysomnographic testing to evaluate for OSAS. OSAS was diagnosed if the child had a RAI =or > 1 per hour. Eight children had conditions which may have contributed to disturbed behavior including: Down's syndrome (n=3); hydrocephalos (n=1); Crouzon's syndrome (n=1); cerebral palsy (n=1); Noon's syndrome (n=1) and mental retardation (n=1). Analysis for hyperactivity and ADHD was done including (n=62) and excluding (n=54) this patient population. Ages ranged from 2-18 years old. The median age was 8.6 years old. There were 34 boys and 28 girls.

Results: Of the 62 children diagnosed with OSAS, 23% were reported by their parents as hyperactive (14/62). Eight percent (5/62) were diagnosed with ADHD. Of the 14 children that were reported as hyperactive but did not have a diagnosis of ADHD, 7 were less than 6 years old which may have precluded a formal diagnosis of ADHD due to their young age. Of the five children diagnosed with ADHD, two had been treated with stimulant medication. When the 8 children with congenital problems were excluded from the analysis, the findings were as follows: 26% (14/54) were reported as hyperactive; and 9% (5/54) were diagnosed with ADHD. Of all the children diagnosed with OSAS, 29% (18/62) (p=.0001) had developmental delays, and 21% (13/62) (p=.0001) had speech delays. When the 8 children with congenital problems were excluded 20% of the children (11/54) (p=.0000) had developmental delays and 19% (10/54) (p=.0000) had speech delay.

Conclusions: Our study shows that there is a 2.6 fold increase in the presence of ADHD in our OSAS children compared to the general child population (8% vs. 3%, p =.0200).[1] After excluding the 8 cases of children with congenital problems, the percent of OSAS children diagnosed with ADHD was 9% (p=.0104). The reason for the association of ADHD and hyperactivity in this patient population is unclear. To further explore the correlation between hyperactivity/ADHD and childhood OSAS, we will reevaluate these children for hyperactivity symptoms after their OSAS has been treated.

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1798.G

Sleep Patterns of Children with Pervasive Developmental Disorders

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Introduction: Children with Pervasive Developmental Disorders have often been reported to be susceptible to sleep problems. In the past, this issue has been studied mainly by interviewing parents, without the benefit of daily documentation of sleep behavior data over an extended period (e.g., Clement et al., 1986). This study examined parent reports of daily sleep behavior in children diagnosed with a Pervasive Developmental Disorder over a three-month period. Children with more severe impairments were hypothesized to be more problematic sleepers in three categories: time to sleep onset, total sleep, and the number of awakenings during a week. Also, the sample as a whole was expected to sleep less then normally developing children.

Methods: 139 children of varying age and level of functioning were recruited by mail and email. Data was obtained from a contact parent through the mail and by telephone. The protocol consisted of filling out a series of daily sleep logs. Information requested by the log included time the child was put into bed, time the child fell asleep, the number of awakenings during the night, morning rise time, and any nap times during the day. Parents were asked to keep the log for one month initially, then asked to complete a two-week log near the end of the three-month participation period. Information regarding the child's diagnosis and level of functioning were also requested. Preliminary analyses were conducted on four weeks of data from 30 participants. Children were placed into one of three age groups: 3-4 (n=6), 5-6 (n=15), and 7-10 (n=9). They were also classified by level of functioning: severe-delay (n=8), moderate-delay (n=16), and high functioning (n=6) by examination of diagnosis and assessment records provided by the parents.

Results: T-tests revealed no significant differences between weeks. All means for each week were averaged to derive a single value for each of the following variables: average time of sleep latency (M=0:29:28, SD=0:16:07) average total sleep (M=9:28:44, SD=0:40:55) and average number of awakenings per week (M=1.69, SD=1.49). There were no differences by group based on level of functioning for any of the variables. Age group was related to amount of total sleep (F (2,27)=3.6, p=.05), with 3-4 year olds showing the most sleep (M=10:05:57, SD=0:29:06). Overall, the sample as a whole did exhibit less total sleep when compared to published data from a group of normally developing children of a similar age range (Klackenberg, 1982).

Conclusions: The preliminary sample of 30 children did not show any significant differences across level of functioning. Also, latency to sleep onset and weekly night awakenings were not significantly different from normal children. This is interesting since many of the parents in the sample reported that their child had difficulties with sleep. The results between age and total sleep duration were similar to that observed in normal children, with younger children sleeping more than older children. This study is currently still in progress, with a number of participants still completing the protocol.

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1496.G

Psychometric Characteristics of the Bruni-Sleep Disorders Scale for Children (SDSC)

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Introduction: The SDSC (Bruni et al,1996) is screening instrument for sleep complaints in school children that can be used in both clinical and non-clinical populations. As sleep complaints are also frequently observed in Belgian school-aged children (Spruyt at el, 1999), we decided to do a validation study on a Flemish version of the SDSC.

Methods: Of the 5220 questionnaires that were distributed over 31 schools, 1424 valid were returned and analysed. All questionnaires were completed by the parents. A factorial analysis (PCA) with varimax rotation (Statistica. CSS) resulted in the following factors:

Results: The factor analysis (55.12% variance explained) resulted in six factors which represent the most common sleep disorders in childhood and replicate the findings of Bruni. Items in italics are those that did not fit with the original SDSC factors in the Italian study.

Table 1

Factor 1: Sleep Breathing Disorders	**Factor loadings**
11. breathing problems	0.75
12. sleep apnoea	0.79
13. snoring	0.39
24. daytime somnolence	*0.61*
Factor 2 : Disorders of Excessive somnolence	
20. difficulty waking up	0.80
21. tired when waking up	0.84
22. sleep paralysis	0.78
23. daytime somnolence	0.40
1. going to bed reluctantly	*0.49*
Factor 3: Sleep hyperhydrosis	
7. falling asleep sweating	0.81
14. night sweating	0.85
Factor 4: Disorders arousal /nightmares	
15. sleepwalking	0.50
18. sleepterror	0.62
19. nightmares	0.64
16. sleeptalking	*0.76*
6. hypnagogic hallucinations	*0.47*
17. bruxism	*0.23*
Factor 5: Disorders in initiating and maintaining sleep	
2. difficulty in falling asleep	0.74
3. falling asleep anxiety	0.58
8. night awakenings	0.50
9. difficulty in falling asleep after awakenings	0.66
Factor 6 : Sleep-Wake transition disorders	
4. hypnic jerks	0.73
5. rhythmic movement disorders	0.61
10. nocturnal hyperkenisia	0.51

Conclusions: It is concluded that the SDSC is a usuful screening instrument for detecting sleep complaints and its consequences in school children.

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1828.G

Children Aged 1-18 Years Seen in the Sleep Laboratory with Periodic Limb Movement Disorder

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Introduction: The prevalence of periodic limb movements and restless leg syndrome in the general population varies between 2.5%-15%.[1] In the pediatric population however, idiopathic periodic limb movements and restless leg syndrome is less common and limb movements are usually related to an underlying disease eg. Neuropathy, ureamia, leukaemia,, attention deficit hyperactivity disorder,[2] medications etc.

Methods: All children aged 1-18 years admitted to the sleep laboratory for an overnight polysomnogram during the period Jan 1999 – Nov 1999 were included in the study. Results of the overnight polysomnogram and sleep questionaire were retrieved and evaluated retrospectively.

Results: 50 patients meeting entry criteria were included in the study. 65% of patient were male and 32% female. Indication for referral of these patients were for evaluation of sleep related breathing disorders, hypersomnolence , behavioural disorders or others. Thirteen(27.1%) of these patients had an increased myoclonic index (MI) of greater than 5 jerks per hour (5-17 per hour) and 3 patients (4.3 %) with an increased myoconic arousal index (MAI) of greater than 5 per hour (0-9 per hour) . Five of thirteen (38.5%) patients had primary snoring, 2 of 13 patients (15.4%) had epilepsy, 5 of thirteen (38.5%) had obstructive sleep apnea, There was no significant correlation of the presence of increased myoclonic index or myoclonic arousal index with the age, gender, Epworth sleepiness scale score, disease category or apnea hypopnea index. Indices of sleep architecture ie. sleep latency, sleep efficiency were not significantly correlated with MI or MAI. Patients with increased myoclonic index were also not significantly more likely than those with a normal index to complain of increased symptoms of. increased leg jerks, thrashing around in sleep, leg discomfort at night or nocturnal awakenings. None of the patients gave a positive family history of periodic limb movements and or restless leg syndrome.

Conclusions: Excessive limb movements of mild to moderate severity are relatively common amongst patients evaluated in the paediatric sleep laboratory (27%) but do not constitute the chief complaint for referral. Of these 77% occur in association with sleep related breathing disorders. In the majority of cases, periodic leg movements did not disrupt sleep. Idiopathic periodic limb movement disorder / restless leg syndrome and a positive family history is absent in this study group. The periodic limb movements appear to be a non specific manifestation of the underlying disease state.

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1185.G

Insomnia Symptoms in Two General Pediatric Practices

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Introduction: Insomnia affects about one-third of adults and is considerably more common among women than men, but little is known about the general prevalence or gender-specific frequency of insomnia among children. One recent survey focused on 452 children of adults enrolled in an epidemiological study of obstructive airway disease: an excess frequency of insomnia was found in female children as young as 11 to 14 years-old.[1] We studied the frequency of insomnia and associations with age and gender in children whose parents were surveyed as they waited for appointments in 2 university-owned but community-based general pediatric clinics.

Methods: Subjects were 830 children aged between 2.0 and 13.9 years (mean ± s.d. = 6.7 ± 3.2); 458 were boys and 372 were girls. Ages were categorized into groups A, 2.0-4.9 years (N=315); B, 5.0-7.9 (N=231); C, 8.0-10.9 (N=172); and D, 11.0-13.9 (N=112). The Pediatric Sleep Questionnaire (PSQ) completed by parents contains 4 items that ask about common components of insomnia: difficulty falling asleep at night, more than 2 awakenings per night on average, difficulty falling back asleep after waking during the night, and early morning awakenings with difficulty falling back asleep. Responses were "yes", "no", or "don't know".

Results: In the overall sample, the frequency of one or more insomnia symptoms was 41.3% (95% C.I. [37.9, 44.6]). Difficulty falling asleep at night was reported in 25.2% of the subjects, more than 2 awakenings in 9.8%, difficulty falling back asleep after waking in 12.8%, and early morning awakenings in 20.7%. The frequencies of zero, one or more, 2 or more, 3 or more, and 4 symptoms are shown in the Table for each gender and age group. In logistic regression models in which the outcome was the presence of a specified insomnia symptom, no gender, age group, or gender x age interaction term showed a statistically significant association with any of the 4 symptoms ($p > .05$ for each), except that waking more than twice per night was more common in age group A then in groups B, C, or D (16.2% vs. 4.8, 7.6, and 5.4%, respectively, $p < .01$). In additional models of the presence of any 3 or more insomnia symptoms, the explanatory variables — gender, age, and their interaction terms — failed to show significant associations (all $p > .05$).

Table 1

Percent of subjects who had specified numbers of insomnia symptoms.

Number of Symptoms Present	All subjects (N=830)	Boys (N=458)	Girls (N=372)	2–4.9 years (N=315)	5–7.9 years (N=231)	8–10.9 years (N=172)	11-13.9 years (N=112)
0	58.7	59.4	57.8	58.7	58.9	55.8	62.5
≥ 1	22.8	22.7	22.8	20.6	28.6	20.9	19.6
≥ 2	11.3	10.5	12.4	12.7	6.1	18.0	8.0
≥ 3	5.9	5.9	5.9	7.0	5.2	3.5	8.0
4	1.3	1.5	1.1	1.0	1.3	1.7	1.8

Conclusions: These results suggest that insomnia occurs frequently in children 2.0 to 13.9 years-old who are seen at general pediatric practices. We failed to demonstrate any increased frequency of these symptoms among girls in comparison to boys. Our findings suggest that the excess frequency of insomnia among women in comparison to men begins after adolescence.

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1537.G

Snoring and Passive Parental Smoking in Children

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Introduction: In a previous study Corbo et al. investigated the relation between snoring, respiratory symptoms and passive parental smoking.[1] However, the authors only considered respiratory symptoms and snoring prevalence from an administered questionnaire. Snoring resulted significantly associated with passive parental smoking. In a previous epidemiological survey in children aged 3 to 6 years we found a prevalence of reported habitual snoring (snoring often and/or always) in 36% of subjects. However, when we measured the objective snoring by an ambulatory device, snoring was observed only in 10% of children.[2] Aim of the present study was to evaluate the possible associate risk between habitual snoring objectively recorded and passive parental smoking in a group of consecutive children referred to the Pediatric Department for reported habitual snoring (hospital group, n=244) compared to a sample of general population children (n=447).

Methods: Children of the first group (n=244) and the second group (n=447) were not different in terms of age and sex distribution (mean age=4.6 yrs vs 4.2; male % 55.2 vs 58.7). All children underwent 1 night of ambulatory monitors by the Mesam 4 (the device records snoring, heart rate, body position and oxygen saturation). Children were classified as snorer when a percentage of snoring time > 15% was found.Information on parental passive smoking and other variables as anthropometric data, familiarity for snoring, presence of other medical diseases, presence of daytime symptoms were collected by parents interviewed by an expert physician.Households in which both parents had never smoked were classified as non-smoking; those with either one parent or both parents who were current smokers (currently smoking at least 5 cigarette each day) were classified as smoking.

Results: Percentage of children from smoking (SMh) and non-smoking households (non-SMh) were not significantly different in the general population and in the hospital group (SMh: 49.9 % and 57.4%, respectively). The table below shows the relative risk of "objective snoring" in relation to passive smoking.The common relative risk (Mantel-Haenszel test) calculated in the two groups was 0.89 (95%CI 0.60-1.33, p=0.61).

Table 1

	Snorer children/ SMh (%)	Snorer children/ non-SMh (%)	OR (95%CI)
General population (n=447)	10.8	10.7	1.00 (0.55-1.82)
Hospital group (n=244)	34.6	39.3	0.81 (0.48-1.38)

Conclusions: Our study does not confirm previous published data and

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underline no significant association between objective snoring and passive parental smoking in children. This seems not to be a risk factor for developing a pathological respiratory problem in young children. Future step would be to differentiate the mild-moderate and heavy smoking and to consider the onset of snoring as well as the severity of sleep disordered breathing.

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1554.G

Periodic Breathing and Cyclical Mixed Apneas in a Child with Alexander Disease

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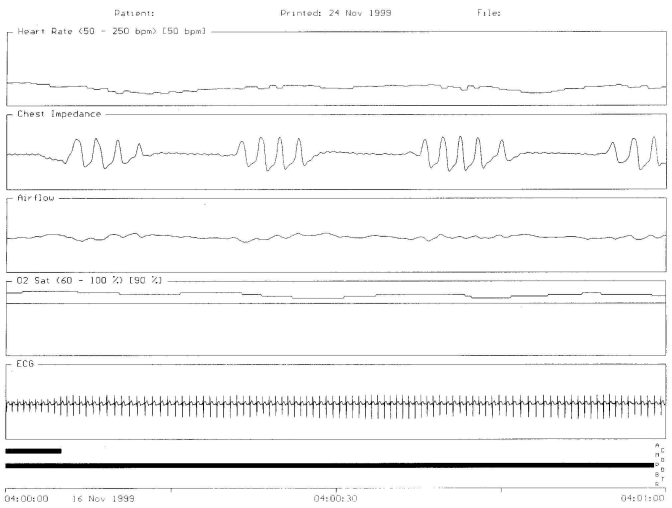
Introduction: Alexander Disease is a rare degenerative disorder of unknown cause which is characterized by macrocephaly, changes of the cerebral white matter (leukodystrophy), and progressive neurologic deterioration. Abnormalities of sleep have not previously been reported in this condition. This patient, a 13-year-old boy with Alexander disease and resultant spastic quadriparesis, was incidentally noted to have recurrent desaturation during nocturnal oximetry while hospitalized for gastroparesis and feeding tube conversion. The parents reported no symptoms of sleep-disordered breathing.

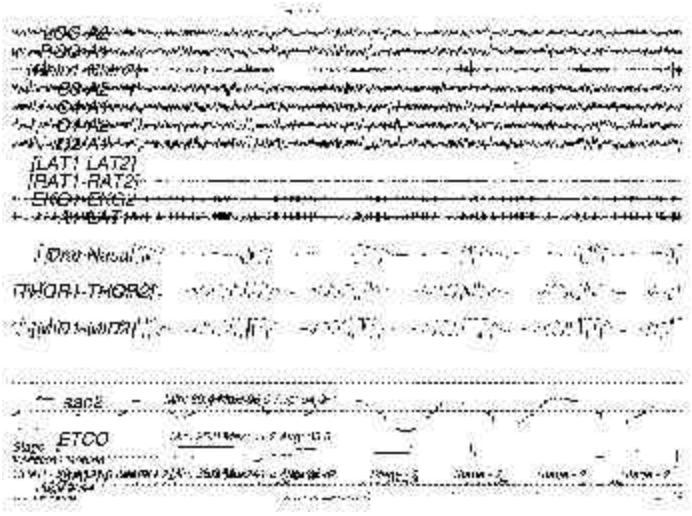
Figure 1. Periodic Breathing



Methods: A multichannel study monitoring heart rate, chest impedance, airflow, oxygen saturation, and ECG) was performed for a single night. Technician-attended split-night polysomnography was performed several nights later. Central and occipital EEG, EOG, submentalis EMG, airflow, ECG, anterior tibialis EMG, pulse oximetry, and end-tidal CO2 were monitored for the polysomnogram. The tracing was scored manually in 30-second epochs.

Results: The multichannel sleep study recorded 57 apneas lasting at least 10 seconds (45 central, 1 obstructive, 11 mixed) during the 699 minute recording, yielding a respiratory disturbance index of 4.89 events per hour. Apneas were frequently associated with arterial oxygen desaturations below 90% and 6% of total study time spent below this threshold. Periodic breathing (defined as 3 or more pauses exceeding 3 seconds with less than 20 seconds between pauses) comprised 15.7% of the study [Figure 1]. The split-night polysomnogram recorded 309 minutes of sleep during a 484-minute study, yielding a reduced sleep efficiency of 63.8%. Numerous apneic events (119 obstructive, 96 mixed, 27 central, 30 hypopnea, 5 awake) were observed, corresponding to a respiratory disturbance index of 53.8 for the entire study and 111.1 events per hour for the 107.5 minutes of sleep recorded prior to CPAP titration. While central apneas most often occurred during cycles of periodic respiration, identical periodicity was frequently apparent for the child's mixed apneas [Figure 2] and occasionally for obstructive apneas as well. Apneic events persisted during CPAP at pressures of 5 cm and 7 cm. Bi-level CPAP reduced both the frequency of events and depth of oxygen desaturation. Optimal improvement was evident at pressures of 11/8 cm (5 apneic events in 44.6 min) and at 13/8 cm (no events in 23.1 min).

Figure 2. Cyclical Mixed Apneas



Conclusions: This represents the first report of specific sleep disturbances associated with Alexander Disease, which joins the spectrum of conditions for which periodic breathing has been reported. In addition, the case demonstrates the potential for period respiration to include obstructive pathology, particularly mixed apnea, in addition to central respiratory pauses. All events were successfully controlled using bi-level CPAP.

1221.G

Apnea and Bradycardia as Localizing Signs for Partial Seizures in Infants and Children

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Introduction: Epileptic seizures may present as apparent life-threating events (ALTE`s) in infants and children.Localization of ictal and interictal abnormalities in epileptic apnea and bradycardia would be helpful in treatment and counseling of patients.Our aim is determine electrographic correlates of ictal apnea and bradycardia in infants and children.

Methods: We performed a retrospective review of our video-telemetry database from 1983 to 1999.We identified 33 children between 6 weeks and 2.5 years of age, who had documented eletrographic seizures.Video-EEG records of patients whose seizures were associated with apnea and/or bradycardia were reviewed to determine seizure onset and interictal epileptiform discharges.

Results: Six children had apnea and/or bradycardia as the initial and primary manifestations of seizures.Ictal apnea was seen in five patients with seizure onset in the right temporal region, and was associated with bradycardia in two of these patients.Isolated ictal bradycardia was seen in one patient with left temporal seizure onset.

Conclusions: In infants and young children, ictal apnea and bradycardia occur as isolated manifestations of partial seizures of temporal lobe origin.Ictal apnea is more likely to be associated with right temporal partial seizures; bradycardia occurs with seizure onset in either temporal region.

1231.H

Effects of Progesterone Replacement in Older Women

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Introduction: As an ancillary study to the Women's Health Initiative, we characterized sleep and the types and severity of depression in a group of postmenopausal women in the Observational Study subsample. Hormone replacement status data were also collected.

Methods: Of those who were already participating in the Women's Health Initiative (WHI) Observational study, 459 women ages 50-81 (mean age = 67.71) volunteered for the present study. They were 4% Asian, 10% Black, 14% Hispanic and 72% White, not precisely representative of the population of San Diego. Actillume activity recordings, illumination patterns and current medication history were obtained for up to 7 days. In-bed and out-of-bed sleep were inferred from wrist activity. Use of estrogen and/or progesterone any night of the 7-day study was tabulated. Following these recordings, volunteers were scheduled for a SCID interview, performed by an experienced psychiatrist (DFK). DSM-IV diagnoses of current major depression, minor depression or dysthymia were obtained from that interview. Multiple linear regressions were computed with sleep or mood as the dependent variable to test age, ethnicity, estrogen use and progesterone use as independent variables.

Results: Of the women studied, 264 (58%) reported current use of an estrogen, and 64 (14%) reported use of progesterone replacement during the study. Estrogen use had marginal partial correlations with out-of-bed sleep and with in-bed WASO ($p<0.10$)which were not considered significant (given the multiple comparisons), nor was total sleep time related. Progesterone use was likewise not related to sleep variables. Estrogen use and age were not significant correlates of mood, and non-Hispanic White ethnicity was marginal ($p<0.16$). There was a significant negative correlation (r(partial)=-0.11, p=0.16) between progesterone use and presence of a diagnosis of major depression, minor depression or dysthymia, indicating an assocation between progesterone and better mood. A similar, slightly less significant negative correlation (r(partial)=-0.09, p=.051) was found between current progesterone replacement and a validated 5-item condensation of the CESD depression scale without sleep items.

Conclusions: Studies have shown that postmenopausal women taking progesterone exhibited more negative mood, and that progesterone may precipitate depressive symptoms.[1] Despite evidence to the contrary in other studies, it appears that in our population of Women's Health Initiative Observational Study volunteers, an admittedly cheerful and cooperative group of extraordinary women, taking progesterone not only does not dampen mood, it may slightly protect good cheer. Remarkably, estrogen use had no detectable effect.

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1245.H

Aging-Related Changes in Sleep Initiation, Continuity, and Length: A Meta-Analysis

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Introduction: Many questions have arisen about the magnitude of observed changes in sleep with age, possible gender differences, possible measurement artifacts, and whether changes are due to age versus correlates of age. The purpose of this meta-analysis was four-fold: (1) to determine the average magnitude of aging-related change in four sleep variables (sleep latency, waking frequency and duration, and sleep length); (2) to explore the influence of health inclusion/exclusion criteria on the magnitude for correlations between sleep variables and age; (3) to explore the extent to which polysomnographic versus self-report measures yield different magnitudes for correlations between sleep and age; and (4) to explore gender differences in sleep change over the adult lifespan

Methods: Major databases were searched through 1998 using multiple keywords related to sleep and age. Also, research reports cited in major narrative reviews of sleep and aging were retrieved as were reports identified through ancestry searching. Kappa coefficients and intraclass correlations were used to assess agreement for categorical and continuous variables, respectively (Floyd et al 1997). Reliability coefficients in the "excellent" range (i.e., kappas and intraclass correlations above .75, Cooper & Hedges 1994) were achieved. Standard methods for averaging and analyzing correlation coefficients were followed including use of r to Z transformations during analysis, weighting effect sizes by the inverse of the variance estimate, homogeneity testing, and use of contrasts to examine moderator variables (Hedges & Olkin 1985).

Table 1

Sleep variable	N for Samples	N for Subjects	Mean weighted *r* (95% CIs)
Sleep latency	22	1266	.19 (.14; .24)
Waking frequency	19	1688	.38 (.34; .42)
Waking duration	23	957	.74 (.71; .77)
Nighttime sleep	35	1515	-.33 (-.37; -.28)

Results: Forty-one studies were found that reported correlations between age and one or more sleep variables of interest. The total number of subjects studied was 3,293. The weighted mean correlation between age and each sleep variable is shown on Table 1. Age-related sleep changes were greater in magnitude for all variables except sleep latency when measured by PSG versus self-report. When researchers did not screen subjects for sleep apnea, age-related changes in waking duration were larger. Significantly smaller magnitudes of age-related change were found for waking frequency, waking duration, and nighttime sleep when researchers had ruled out the possibility that subjects were depressed. Lack of information about screening of subjects for various psychoactive substance use precluded exploration of these potential moderators. Also, too few studies of women's sleep were available to identify gender differences with confidence.

Conclusions: Some variation in investigators' reported results about age-related sleep change can be accounted for by differences in the screening and measurement approaches used, but the existing set of studies is too limited to determine how much age-related change in sleep initiation, continuity, and length is due to factors other than age itself. Subjects in future studies of sleep and normal aging need to be assessed more carefully for health problems and psychoactive substance use. Also, women need greater inclusion.

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(3) Hedges LV, Olkin I: Statistical methods for meta-analysis. Boston, Academic Press, 1985, 223-46.

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1609.H

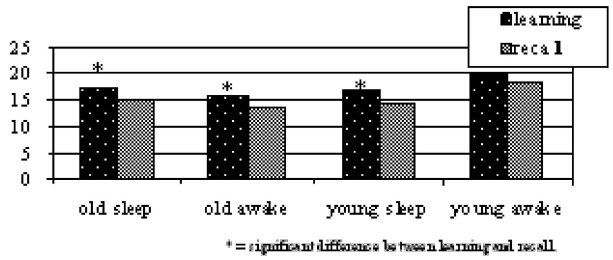
Slow Wave Sleep Influence on Declarative and Procedural Learning in Elderly

LeBlanc M, Lorrain D

Introduction: Numerous studies have suggested that one sleep function is the strengthening of memories.[1] Furthermore, it seems that a few hours of SWS after learning is beneficial for declarative memory and that REM sleep is associated to procedural learning.[2] However, these studies were mainly concerned with young adults. Considering sleep and memory's changes and deficits associated with ageing, it most be interesting to extend those investigations to elderly. The present study was designed to measure the SWS effects on the elderly's declarative and procedural memories, in comparison with young adults.

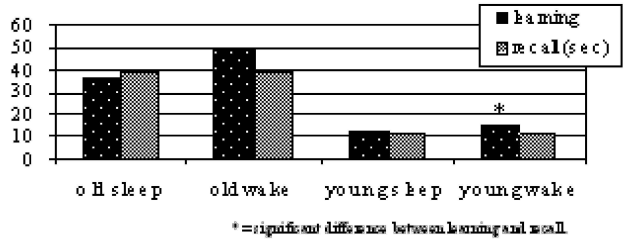
Methods: Sixteen healthy young adults (M age: 23.7, SD= 3.3) and 18 healthy and good sleepers seniors (M age: 65.7, SD= 4.3). The experiment took place between 10 PM. and 3 AM. First, all subjects practice a declarative task (a paired-associate list) as well as a procedural task (the mirror-tracing star). Participants learned the list until they got a minimum of 60% good answers and they practice the mirror-tracing (star) until asymptotic performance was reached. After the learning, half the subjects slept four hours in the laboratory, whereas the other half remained awaked. Sleep was recorded and scored according to R & K standard criteria. After the latent period, all subjects recalled both tasks.

Figure 1



Results: After the 4 h latent period, elderly, whether they slept or remained awaked, forgot 2.3 words ($p < 0.05$) of the paired-associate list, whereas young adults forgot approximately 1 word ($p < 0.05$). For the mirror-tracing task, the performance of every participants having slept remained stable, whereas young adults who stayed awaked significantly improved ($p < 0.05$). Total sleep time was 190 min. for young adults and 160 min. for elderly, which is significantly different ($p < 0.05$). However, the percentage of time spent in the different stages of sleep was not different between young and elderly participants excepted for wake which represented respectively 12 % and 24% of the night. Stage 1 was 11 % for both groups; stage 2 was 69% for the young (Y) and 77% for the elderly (E); stage 3-4 was 10% (Y) and 2% (E) and REM was 8% (Y) and 10% (E).

Figure 2



Conclusions: For the consolidation of the declarative task, sleep was not more beneficial than wakefulness. On the other hand, wakefulness increased the retention of the procedural task. Those results could be associated with the low level of SWS, as well as a high number of awakenings showed by our subjects. Furthermore, it could be that the 4 h latent period was too short for the memory consolidation. Finally, the fact that awakening was more beneficial for the procedural task than sleep, could suggests that procedural learning need a high cortical activity. High activity is prominent in awakening and REM sleep but not in SWS. Further studies should investigate REM sleep effects on procedural learning in elderly.

References:
(1) Cipolli, C: Sleep, dreams and memory: an overview. Journal of sleep research, 1995,4,2-9.
(2) Plihal W, Born J: Effects of Early and Late Noctural Sleep on Declarative and Procedural Memory. Journal of cognitive neuroscience,1995,9,534-547.

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1260.H

The Effect of Donepezil on Sleep in Elderly Healthy Subjects: An Open Pilot Study

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Introduction: Previous research has shown that acetylcholinesterase inhibitors such as galanthaminehydrobromide or rivastigmine may affect REM sleep, especially in elder persons. These findings support the reciprocal-interaction cholinergic-aminergic interaction model of REM sleep regulation (e. g. Hobson et al 1998). Donepezil is effectively used in the treatment of Alzheimer's disease. It was hypothesized that donepezil enhances REM sleep and also cognitive performance since a relationship between the amount of REM sleep and learning was shown in several studies (e. g. Smith 1995).

Methods: Ten healthy subjects (4 women, 6 men) aged 58 to 78 years were studied in the sleep laboratory for five nights. The first night served as an adaptation and also to rule out sleep apnea and periodic leg movements by applying standard measurement procedures. After the baseline night (night 2), the subjects received 5 mg donepezil one hour before

bedtime over six days. Sleep was recorded in the adaptation and baseline night as well as in the first night after drug admission and the two last nights under medication. In the evenings of the baseline night and the last verum night as well as in the following mornings a learning task (list of 20 words, 8 trials) was administered. Sleep records were scored along the criteria of Rechtschaffen and Kales (1968).

Results: The effect of donepezil on REM sleep parameters was as expected, i. e. a reduction in REM latency, increase of REM density (see Table 1). But there was only a small increase in the percentage of REM sleep. The difference between test (evening) and retest (morning) correlated significantly with the amount of REM sleep in that night (r = .67, p = .05).

Table 1

REM sleep parameters after admission of 5 mg donepezil in elderly subjects

Variable	Baseline	First verum night	Last verum night
REM sleep (% SPT)	16.50 ± 4.51	19.00 ± 3.27 (*)	19.55 ± 3.44 *
REM latency (min.)	107.35 ± 50.28	68.25 ± 34.39 **	81.50 ± 35.90
Duration 1. REMP (min.)	21.60 ± 18.53	31.10 ± 13.40 (*)	23.40 ± 20.19
REM density (%)	15.29 ± 7.94	21.05 ± 6.04 **	18.48 ± 6.30 *

(*) p = .10, * p = .05, ** p = .01; paired t-test (verum vs. baseline)

Conclusions: The findings confirm that donepezil, an acetylcholinesterase inhibitor, affects REM sleep (shortened REM latency, increased REM density), although the increase of REM sleep was small and may be explained by adaptation effects. Interestingly, there was a strong positive relationship between cognitive performance and REM sleep under medication which was not found for the baseline night. Overall, the results of this pilot study suggest a REM sleep augmenting effect of donepezil which might be beneficial for memory performance. Future studies should investigate the effects of donepezil on REM sleep and cognitive performance in a double-blind design.

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1262.H

Modafinil Improves Cognitive Function in Aged Rats Measured by a Delayed Alternation Task

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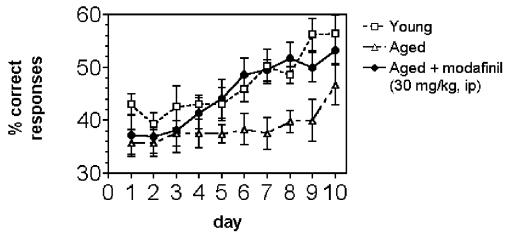
Introduction: Modafinil (MOD) is a novel wake-promoting agent that induces wakefulness through a non-dopaminergic mechanism. Recent data suggest that modafinil may enhance cortical activity and promote wakefulness by activation of hypothalamo-cortical neurons in the tuberomammillary nucleus of the posterior hypothalamus (Estabrooke et al., 1999). This study assessed whether enhanced cortical function by MOD administration could be associated with improved learning and cognition in disorders of cortical hypofunctionality, such as age-related cognitive dysfunction.

Methods: The effect of MOD on aged-related decrements in cognitive function was evaluated in 23 month old male Wistar rats using an operant delayed alternation task (DAT). After 3 weeks of training (single lever), each animal was subjected to a daily DAT acquisition session (two levers) in a Skinner Box over 2 consecutive weeks (10 sessions total). Each session consisted of 35 trials. Each trial involved presentation of a single lever followed 5 seconds later by the presentation of two levers. Animals had to respond on the lever not previously presented (delayed alternation) to receive a food reward. The primary endpoint was percent correct responses (response accuracy). Simple and choice reaction times and the number of failures to respond to one or two levers (omissions) were also measured. Potential effects on short-term memory were assessed by lengthening the interval between presentation of the single and two levers in the choice paradigm (5, 10 or 20 seconds) in aged animals pre-trained to >80% correct responding in the DAT protocol. MOD (7.5-300 mg/kg, i.p.) was administered 30 minutes prior to initiation of each session.

Results: Aged rats showed clear deficits in the acquisition and performance of the DAT when compared with young rats. Aged rats displayed poor response accuracy (impaired learning), slower reaction times and more response omissions (impaired attention). MOD (30 mg/kg, ip) significantly increased the number of correct responses (see figure). There were virtually no differences between aged animals treated with 30mg/kg, ip of MOD and the young controls during the later part of the experiment. At this dose, MOD also tended to decrease simple and choice reaction times. At 60 mg/kg, ip MOD also significantly increased the number of correct responses and tended to improve choice reaction times. However, the effects observed were less regular than those observed at 30mg/kg, ip. MOD (15-60 mg/kg, ip) did not improve the number of correct responses when delay for choice testing was extended to 20 seconds in aged animals pre-trained to >80% correct responding in the DAT protocol. Therefore, the improved cognitive function in aged rats following administration of MOD was not the result of beneficial actions of MOD on short term memory.

Figure 1



Conclusions: Modafinil administration can improve cognitive function in a model of age-related cognitive dysfunction by enhancing efficiency of information processing, not by enhancing short-term memory. Modafinil may have benefit in maintaining normal daily function in aged individuals.

References:

(1) Estabrooke I, Chou T, Miller M, Saper C, Scammell: Modafinil activates arousal and autonomic regions. Soc. for Neuroscience Abstracts 1999;25:1134.

1619.H

Humor as an Alternative Therapy for Elderly Insomniacs

Giroux I, Lorrain D, Belisle D

Introduction: Pharmacological treatment and behavioral therapies are often used in elderly patients suffering from chronic psychophysiological insomnia. However, medication has unwanted side-effects, such as disruption of the sleep-wake cycle and the possibility of developing an addiction, and behavioral therapies, such as relaxation, stimulus control

and sleep restriction, are very demanding and often do not suit the specific limitations of the elderly population. This study is an attempt at identifying an alternative mode of therapy that would harness the power of humor to induce a state of relaxation and overall feeling of well being, in order to improve the sleep of elderly insomniacs.

Methods: Seven (7) subjects (6 women, 1 men) with a mean age of 62,1 (SD 5,4) participated to the study. The inclusion criteria was to suffer form insomnia for at least 6 months, with a sleep latency of more than 30 minutes, or suffering from night awakenings lasting for a total of more than 60 minutes, at least three times a week. The study lasted for 10 weeks, including 2 weeks of pretest, 6 weeks of therapy and 2 weeks of post-test. The Pittsburgh Sleep Quality Index (PSQI) and the Profile Of Mood States (POMS) were used in pre and post-tests. Moreover, the subjects had to maintain a sleep diary for the whole 10-week period. The "humor therapy" sessions were conducted twice a week for six weeks and consisted of 90 minutes of activities designed to induce laughter in a relaxed atmosphere.

Results: As shown in Table 1, analysis of the sleep diary revealed for the 10 week period an increase in sleep quality (p = 0,04), and a decrease of the number of awakenings during the night (p = 0,02). The mean difference of the total score on the PSQI (pre-test = 10,8, post-test = 8,4) was close to significant level (p=0,06). Only the "quality of sleep" scale showed a significant improvement (P = 0,04). No significant changes on the POMS were recorded.

Table 1

Sleep Diary

	Pretest	Post-test	P value
Sleep latency (mins)	37.6 (20.1)	20.3 (6.4)	0.06
No of awakenings	1.9 (0.4)	1.0 (0.3)	0.02*
Mins. of awakenings	46.8 (41.3)	23.2 (29.7)	0.17
Quality of sleep	5.9 (0.5)	7.7 (0.3)	0.04*
Quality of day	6.6 (1.4)	7.6 (0.6)	0.09

* significant difference between pretest and post-test

Conclusions: This pre-experimental study could indicate that exposure to situations conducive to laughter and good humor may improve sleep quality in elderly insomniacs. Further research based on a stronger experimental design should focus on specific effects of humor situations and evaluate the extent to which the observed sleep improvements last over time.

1640.H

Polysomnographic Alterations in Depressed Elderly with Heart Failure.

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Introduction: Depressive symptoms are common in elderly people, mainly in those with other clinical diseases. Heart failure (HF) occurs in 10% of the geriatric population. There is a greater incidence of depressive symptoms in this group of patients, which worsens together with the severity of HF. Cardiac functional prognosis is worse in depressed patients.

Methods: Nine patients from the Heart Institute with clinical and ecographic diagnosis of HF, functional class II and III according to the New York Heart Association (NYHA), aged 68 to 86 years old (M=76.11) were submitted to psychiatric interview for the diagnosis of depression and a Prime MD Test was applied. Five of them fulfilled the criteria for major depression diagnosis.All the patients were submitted to an all night polysomnography. Sleep architecture, REM sleep parameters and respiratory and cardiac monitoring were observed.

Results: The depressed patients showed shorter REM sleep latency (Mean of depressed patients (Md)=122.32min; Mean of non-depressed patients (Mnd)=159.30min), increased REM sleep stage (Md=39.9min; Mnd=16.37min), reduced slow-wave sleep(Md=26.52min; Mnd =39.65min), increased total sleep time (Md=251min; Mnd=223.18min; Standard Deviation (SD)SDd= 64.67, SDnd=102.51). Seven in nine patients (75%) studied showed a Cheyne-Stokes respiratory pattern.

Conclusions: In this study we could observe relevant polysomnographic alterations in the depressed patients with HF compared to the non-depressed. We also observed a higher prevalence of Cheyne-Stokes pattern in both groups.

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1643.H

Driving Simulation Performance in the Elderly with Mild Cognitive Impairment

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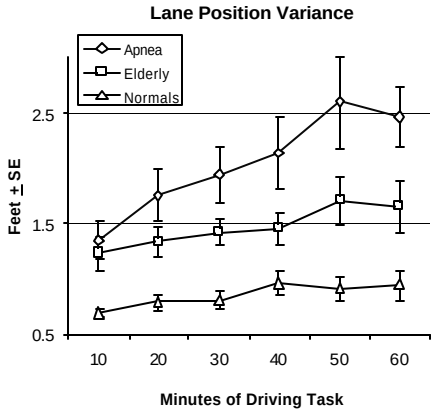
Introduction: Objectively measuring the driving performance of the elderly may help to isolate factors contributing to driving problems. Potential problems include changes in vigilance, motor skills, visual and auditory acuity and cognition. Earlier studies using driving simulation have identified marked impairments in the sleep apnea patients (Risser et al., 1999).

Methods: Six men and four women (75 to 86 years old; mean = 80.6 + 5.4) with valid drivers' licenses were tested after providing informed consent and completing a normal clock draw test. Mini mental status examination (MMSE) scores ranged from 22 to 30 (Mean = 27.1 + 2.42). Exclusion criteria were 1) dementia; 2) symptoms of a significant sleep disorder; 3) a significant medical disorder; 4) alcohol abuse; 5) consumption of more than five caffeine beverages/day; 6) smoking more than ½ pack of cigarettes per day; and 7) use of sedative or stimulant substances (including caffeine or cigarettes) within 3 hours of the task. A PC based driving simulator (Systems Technology Incorporated) was equipped with steering wheel, gas and brake pedals, 21" display, and sound. After subjects removed pagers and watches, they completed a 10-minute practice drive through a city scenario that included intersections, stoplights, traffic, and pedestrians. This allowed adaptation to the vehicle dynamics. Subjects then completed a 60-minute task designed to replicate a highway-driving scenario with long wide curves and an oncoming vehicle introduced every ten minutes. Performance was continuously sampled and grouped in six 10-minute time blocks for analysis. Subjects were instructed to maintain a speed of 55 mph during the 60-minute task.

Results: One subject could not complete the practice trial, because she could not understand the task. She was excluded from the analysis. A

repeated measures ANOVA indicated that performance, as measured by lane position variability, deteriorated during the drive ($p = 0.007$). The lower the MMSE score (i.e., the greater the cognitive impairment), the greater the lane position variability ($r = -0.798$, $p = 0.01$). Compared to normal subjects and apnea patients from an earlier study (Risser et al., 1999), the performance of the elderly appears better than the performance of apnea patients and worse than the performance of normal subjects (figure).

Figure 1



Conclusions: For these subjects, cognitive ability as measured by the MMSE predicted driving simulator performance on a vigilance task. Even though this task showed differences, a divided attention driving task would likely be more sensitive to those with cognitive impairment. Of importance, is that these elderly patients with mild cognitive impairment outperformed the sleep apnea patients studied earlier (Risser, et al, 1999). This not only emphasizes the severity of apnea patients' impairment, but also suggests that multiple factors affect driving simulator performance in the elderly. Further research is needed to examine the interaction between cognitive impairment, sleepiness, and simulated driving performance and to correlate simulator performance to on-road performance.

References:

(1) Risser MR, Ware JC, Freeman FG, Wooten VD, Billmann SJ. Driving Simulation Performance and EEG Evaluation Associated with Obstructive Sleep Apnea. Sleep 1999; 22 (sup.): S119.

1658.H

Interleukin-1 (IL-1)-Beta Predicts Sleep and Cortisol Responses to Mild Stress

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Introduction: Stress responsivity (cortisol increases and sleep decreases following a stressor) is enhanced in old age. Increased cortisol levels at the circadian nadir also accompanies aging. The pro-inflammatory cytokine, IL-1β, is known to initiate a cascade of events (in immune, HPA and ANS systems) in response to psychological or physiologic stressors: IL-1β initially stimulates release of cortisol and noradrenaline.[1] Here we examined circulating levels of IL-1β in healthy senior women who had a range of sleep and cortisol changes in response to a mild 24-hour stressor.

Methods: The study compared baseline and 'stress' conditions using a repeated measures design. Subjects were studied in a General Clinical Research Center under baseline conditions and a mildly stressful procedure (24 hours of an indwelling iv catheter). Twenty-six healthy, non-obese postmenopausal women (mean age 70.6 [6.2] yrs) were selected from a large study of successful aging. 24-hour urine was collected for cortisol assay (RIA) under baseline and 'iv stress' conditions. Blood was sampled at three diurnal time points (afternoon, mid-sleep, pre-awakening) in the 'iv stress' condition for IL-1β assay (ELISA). Sleep architecture and sleep EEG were analyzed (after an adaptation and screening night) on baseline and 'stress' nights via human scored polysomnography and EEG power spectral analysis.

Results: IL-1β was below assay detection threshold for some, but usually not all, samples for a given subject. We therefore formed a mean of all 3 assay values for each subject. Increased mean IL-1β was associated with higher cortisol response to 'stress' (Fig.1.)and with lowered mean EEG delta power (2-4 Hz) during stages 2, 3 & 4 sleep in response to the 'stress'(Fig.2.); IL-1β explained 23% and 35% of the variance in these stress responses, respectively. Mean IL-1β was unrelated to human ratings of sleep architecture and fragmentation.

Figure 1. Scatterplot of 24-hour free urinary cortisol and the ranking of mean IL-1b values

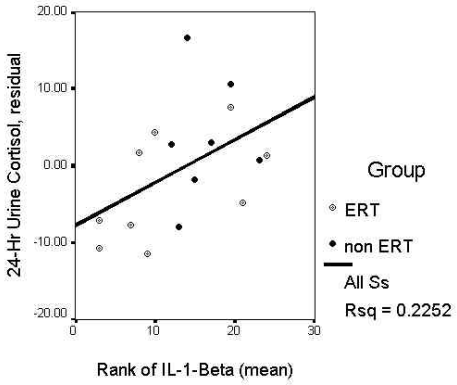
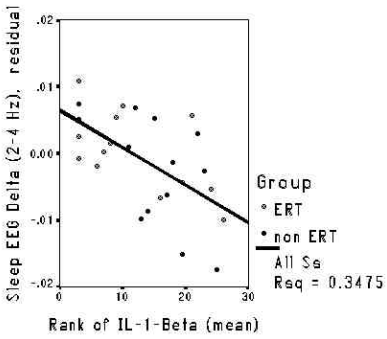


Figure 2. Scatter of residual values of sleep EEG delta (2-4 Hz) values and ranking of mean IL-1b values



Conclusions: These results indicate that seniors with higher IL-1β undergo greater responses to a mild iv 24-hour stress. The results raise questions about a possible role of IL-1β in the hypercortisolemia of aging, and suggest that IL-1β blockers (eg, IL-1 receptor antagonist or designer anti-cytokine drugs) may ameliorate sleep impairments in stress-reactive, healthy senior adults.

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POSTER PRESENTATIONS

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1333.H

Correlates of Excessive Daytime Sleepiness in Older Men and Women

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Introduction: Excessive daytime sleepiness (EDS) is a significant contributor to decreased quality of life and is a known risk factor for accidents as well as all-cause mortality. EDS is secondary to a variety of conditions including excessive consumption of alcohol, depression, and several disease states. There have been surprisingly few studies of correlates associated with EDS in the elderly. One recent study of an adult sample 65 years and older identified a number of health and health-behavior correlates of EDS (Whitney et al., 1998). The purpose of the present analysis was to confirm previously reported results and to examine other potential correlates of EDS.

Methods: Three hundred eighty five individuals from the Western Collaborative Group Study, a long-term health and aging study, were included in this analysis. Men (n = 256) were of mean age 80.0 ± 3.7 (SD) years and women (n = 129) were of mean age 75.6 ± 5.4 years at the time of examination. As part of the 36-year follow-up of this cohort, all participants completed the Epworth Sleepiness Scale (ESS; Johns, 1991), provided an updated medical history, and wore an Edentrace II sleep monitor for the duration of an in-home sleep period. Participants were monitored for airflow, respiratory effort, body position, heart rate, oxygen desaturation, and snoring. After completion of scoring of the sleep data, apneas (chest or airflow pause of 10 seconds or longer) and hypopneas (decreased airflow of 50% or more for an interval of 10 seconds or longer and a 4% or larger drop in O2) per hour were summed to create an apnea/hypopnea index (AHI). A desaturation index (DI) was also created by determining the number of desaturations less than 90% per hour. EDS was defined by ESS scores ≥ 11. In addition to the measures of sleepiness and SDB, participants were also assessed for current level of sleep disruption, diagnosed sleep apnea, the presence or absence of snoring, snoring loudly, and breath holding, body mass index (BMI), resting systolic and diastolic blood pressure, pulse pressure, the use of antihypertensive and psychotropic medication, diagnosed hypertension, ankle/brachial blood pressure index (I .90), APOE genotype, diagnosed coronary heart disease, diabetes, stroke, bronchitis, emphysema, or asthma, number of years smoked, current smoking, current alcohol consumption (weekly ounces consumed), physical activity (Physical Activity Scale in the Elderly), activities of daily living, cognitive performance (speeded performance and verbal memory), depression (Geriatric Depression Scale score of > 5), perceived health, life satisfaction total score, and recent negative life events total score.

Results: In a forward logistic stepwise regression procedure with EDS (present or absent) as the dependent variable, gender, age, and depression were forced into the model. Remaining variables were entered into the model and allowed to remain in the model if a $p < .05$ significance level was maintained. Of the variables forced into the model, men and those with depression were more likely to report EDS (OR = 3.48, 95% CI = 1.57, 7.69; OR = 3.79, 95% CI = .78, 18.40, respectively). Remaining significant contributors to the presence of EDS included the non-use of antihypertensive medications (OR = .2.00, 95% CI = 1.12, 3.60), a history of diagnosed asthma (OR = 4.34, 95% CI = 1.16, 16.20), per unit increase of AHI (OR = 1.10, 95% CI = 1.03, 1.16), pre unit decrease of typical hours of sleep (OR = 1.46, 95% CI = 1.12, 1.92), and the presence of frequent napping (OR = 3.38, 95% CI = 1.90, 6.01). Variables not associated with EDS were: age, BMI, use of psychotropic medication, self reported sleep disruption and snoring, and most measures of physical health, health behaviors, cognitive function, and life satisfaction.

Conclusions: The present analysis found a number of factors to be associated with self-reported EDS. As in the Whitney et al. (1998) analysis, we found male gender and depression to be significantly associated with EDS. Other findings similar to Whitney et al. include the lack of independent association of alcohol use, use of psychotropic medications, coronary heart disease, and cognitive function with EDS. Unlike Whitney et al. we did find an increase in the frequency of EDS in individuals with asthma, higher AHI, fewer typical hours of sleep, and more frequent napping. Increased frequency of EDS was independently associated with less frequent use of antihypertensive medications.

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1679.H

Differences in Health Factors Between Snorers and Non-snorers in a Cohort of Community Dwelling Elderly

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Introduction: Snoring, known to be a significant symptom in sleep disordered breathing (SDB), is associated with adverse health factors. Studies have shown that excess weight, smoking, and alcohol consumption tend to exacerbate SDB in younger populations (Kauffmann et. al, 1989) as well as in clinical patients (Stradling et. al, 1991). We asked whether the same would be true in community dwelling elderly where the prevalence of SDB is known to be high. This study examined differences in health factors in older persons reporting snoring vs. those reporting no snoring.

Methods: Data were collected as part of the Rancho Bernardo Heart and Chronic Disease Survey, which began in 1972 as a population based heart disease risk factor screening survey. A multitude of variables which may be associated with an increased risk of developing SDB were collected during six additional visits and spanning approximately 20 years. Preliminary analyses were conducted with data from 1081 subjects (between 40 and 80 years) who completed two visits and a mailer exploring sleep, snoring, and health issues. Analyses examined differences between subjective reports of snoring (independent variable) and total sleep time (TST), naptime, systolic (SBP) and diastolic blood pressure (DBP), body mass index (BMI), waist-hip ratio (W:H), Beck Depression Inventory (BDI), weekly alcohol intake (grams; ETOH), and number of years smoking (dependent variables). Because raw data were highly skewed, t-tests were done for each dependent variable using a

normal score transformation.

Results: 39.2% of the older respondents reported snoring, 39.2% reported no snoring and 21.6% reported that they didn't know. Only data for snorers vs. non-snorers were examined. Significant differences were found in naptime, BMI, DBP, W:H , alcohol consumption, and years smoking. No differences were found in total sleep time, depression, or SBP. (see Table 1).

Table 1. Group means (SD)in snorers vs. non-snorers

VARIABLE	SNORERS (N=424)	NON-SNORERS (N=423)	p-value
TST (hrs)	7.25 (1.18)	7.18 (1.16)	.406
NAP (hrs)	0.19 (.43)	0.14 (.32)	.029
BDI	5.15 (3.97)	5.00 (4.02)	.596
SBP	133.35 (18.31)	131.78 (20.66)	.118
DBP	76.84 (9.12)	75.63 (9.18)	.048
BMI	25.78 (3.69)	24.13 (3.36)	.001
W:H (in)	0.86 (.08)	0.81 (.08)	.001
ETOH (gms/wk)	107.82 (127.75)	82.16 (95.26)	.009
Smoke (yrs)	16.30 (17.67)	12.84 (17.06)	.001

Conclusions: Data in younger and in clinical patients have suggested that SDB is associated with increased weight, alcohol use and smoking. Our data suggest that the same may be true in the community dwelling elderly who report snoring. Although the study was not able to assess SDB directly, snorers also reported more daytime sleepiness, suggesting that snoring may be a symptom of SDB. Future analyses will focus on the progression of symptoms suggestive of SDB and other diseases, such as coronary heart disease, pulmonary diseases, dementia, etc.

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1682.H

Factors in Sleep Disturbance in Post-Menopausal Women

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Introduction: Studies have shown that postmenopausal status is associated with increases in sleep disturbance (Owens & Matthews, 1998), although findings concerning the role of estrogen replacement therapy (ERT) in improving sleep quality have been mixed (Purdie, et al, 1995; Polo-Kantola, et al, 1998). The purpose of this study was to investigate whether selected health factors, including the use of ERT, would be predictors of sleep quality five years later in a group of community-dwelling postmenopausal women.

Methods: Two-hundred eighty-three women (mean age at baseline=71.0 ± 5.1 years) from the Western Collaborative Group Study (WCGS), a health and aging study now in its 39th year of follow-up, completed a questionnaire in 1992 concerning symptoms associated with their menopause, and whether or not they ever took ERT. At the same time, they also completed the 20-item CES-D depressive symptoms questionnaire and answered questions about their health behaviors. Five years later, at follow-up, they were questioned about sleep disturbances, using a 4-item scale which included report of trouble falling asleep, waking at night, waking too early, and feeling tired upon waking in the morning. The sum of these items ranged from 0 to 20 (mean = 5.8 ± 4.5). The independent variables in the multiple regression model included age, ERT use/non-use, CES-D to the score, and other health-related activities such as exercise level (using the 10-item Physical Activity Scale for The Elderly [PASE]), smoking, and alcohol consumption. Menopausal symptoms such as headaches, trouble sleeping, "blue mood," and discomfort from hot flashes were also included. The total sleep disturbance score represented the dependent variable.

Results: The overall prediction model was significant, $F(12, 268) = 3.38$, $p < .0001$. Multiple regression analysis revealed that the strongest predictors of sleep disturbance at the 5-year follow-up were baseline CES-D depressive symptoms ($r = .13$, $p = .04$), menopause-related trouble sleeping ($r = .25$, $p = .0001$), and the PASE exercise activity level ($r = -.15$, $p = .009$). Higher PASE scores were associated significantly with less sleep disturbance. The women who reported menopause-related trouble sleeping at baseline also had sleep disturbance at the five-year follow-up. The use or non-use of ERT in this sample appeared to have little utility in the prediction of sleep disruption. This may be explained in part by the fact that most, 77% (n = 216), of these women had ever taken ERT.

Conclusions: This study supports conclusions of previous studies that have shown the benefits of regular exercise on quality of sleep. For the women in this sample, PASE scores predicted fewer problems in sleep five years later. CES-D depressive symptoms at baseline were predictive of sleep disruption five years later. Self-report of trouble sleeping due to menopause predicted sleep disturbance at the 5-year follow-up independently of a history of ERT use.

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1697.H

Restoration of Slow-wave Sleep and Nocturnal Growth Hormone Secretion in Older Adults by Gamma Hydroxybutyrate Administration

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Introduction: Aging is associated with pronounced alterations in sleep architecture and hormonal profiles. In particular, older adults have markedly decreased amounts of slow-wave (SW) sleep and circulating growth hormone (GH) concentrations. There is a consistent temporal association between GH secretion and sleep. Pharmacological enhancement of SW sleep in young adults results in a simultaneous and proportional increase in GH secretion during early sleep. Whether SW sleep can be restored in older adults and whether restoration of SW sleep would result in restoration of sleep-related GH secretion is not known. The present study was designed to test the hypothesis that daily oral administration of gamma hydroxybutyrate (GHB) restores SW sleep and simultaneously increases GH release in older adults.

Methods: Eighteen healthy non-obese volunteers (12 men, 6 women, 50-80 years old) were studied in the Clinical Research Center on three separate occasions: at baseline, after 7 days of treatment, and after 28 days of treatment. Recruitment of additional women subjects is still ongoing. Subjects took 3.0 g of GHB (n=10) or placebo (n=8) at bedtime each night. The subjects were blind to the treatment. Sleep was polygraphically recorded and blood samples were collected during a 24-h period for the measurement of hormonal levels.

Results: Currently, a complete analysis of sleep data is available for 16 of the 18 subjects. Treatment with GHB was associated with a marked enhancement of SW activity during the first 4 hours of sleep. After 7 days of treatment, the amounts of stage III and IV was 51 ± 15 min under GHB versus 10 ± 6 min under placebo ($p<0.02$). After 28 days of treatment, the amounts of SW sleep were 41 ± 12 min under GHB versus 15 ± 9 min under placebo ($p<0.05$). SW activity during the first 2 hours of sleep, as estimated by EEG power density in the 0.5-2.9 Hz, was two- to three-fold higher under GHB than under placebo. The enhancement of SW sleep and SW activity in early sleep was associated with a significant ($p<0.0002$) increase in amount of GH secreted in GHB-treated subjects (baseline: 80 ± 21 µg; 7-day: 184 ± 41 µg; 28-day: 238 ± 38 µg). GH secretion during early sleep remained low in placebo-treated subjects (baseline: 85 ± 24 µg; 7-day: 72 ± 21 µg; 28-day: 101 ± 28 µg). Consistent with the short half-life of GHB, the GHB-treated subjects consistently woke up after 2-4 hours of sleep, resulting in a significant increase in total amount of wake as compared to placebo-treated subjects (7 days of treatment: 132 ± 17 min under GHB versus 64 ± 13 min under placebo, $p=0.0001$; 28 days of treatment: 160 ± 26 under GHB versus 74 ± 14 under placebo, $p=0.0001$).

Conclusions: These results demonstrate unequivocally that SW sleep may be restored in older adults and that the restoration of SW sleep is associated with increased sleep-related GH secretion.

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1374.H

Cerebral Oxygenation During Sleep in Older Adults: A Pilot Study

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Introduction: Sleep represents a period of increased risk for hypoxia that may have a negative impact on cognitive systems. Arousal is an important protective response to decreased cerebral oxygenation during sleep. Older adults with blunted arousal may experience more hypoxia during sleep and be at greater risk for cognitive decline. This study examined a noninvasive method to measure cerebral oxygenation during sleep and explored how cerebral oxygenation differ during arousal in older and younger adults.

Methods: We monitored 10 older adults (65-84 yrs, 5 males, 8 right-handed) and 10 younger adults (21-39 yrs, 4 males, 10 right-handed) under controlled conditions at a General Clinical Research Center. All were admitted under a standard protocol consisting of a 6-hour period of sedentary activity followed by a 2-hour sleep-nap conducted from 10pm-12am. Right- and left-sided cerebral oxygen saturation (RCSO2) were measured with the INVOS 4100 (Somanetics Inc, Akron OH). Standard methods were used to record sleep and arousals (central and posterior EEG, 2-channel electrooculogram, submental EMG), respiratory movements (Respitrace, Ambulatory Monitoring, Ardlsey NY), and arterial oxygen saturation (N200 Nellcor Inc, San Diego, CA). We used the ASDA criteria to identify arousals. Signals were stored to computer using the Windaq Waveform Acquisition Software at a sampling rate of 250 s/s. Data were collected on weekdays-from June 1-July 31, 1999.

Results: Older adults spent more time awake, but once asleep, they spent more time in SWS than the younger adults. There were no differences in the amount of time spent in REM sleep and the number of arousals. All subjects had normal arterial oxygen saturation values (95-97%). RCSO2 values ranged from 56-77% in older and 72-97% in younger adults. The older adults had lower RCSO2 values than the younger adults at the start of each nap. Once asleep, the RCSO2 values of the older adults decreased or remained unchanged over the 2-hour nap with a 3-5% difference between right- and left-sided measures. The RCSO2 values in the younger adults tended to increase during the 2-hour nap with little difference (1-2%) between right- and left-sided measures. In most subjects, RCSO2 increased during arousals. Two older subjects with low baseline RCSO2 values (55-60%) and three younger adults with fairly high RCSO2 values (70-80%) had little or no change in RCSO2 during arousals. Further analyses will examine the relationship between RCSO2 and other parameters of arousal during sleep (periodicity of breathing, heart rate variability and pulse transit time).

Conclusions: Our preliminary analysis shows that older adults have lower waking RCSO2 values and very little change in RCSO2 during sleep. Older subjects also had less increase in RCSO2 during arousal. These results suggest that older adults with lower oxygen reserves may have a diminished response to hypoxic challenge during sleep and may be at greater risk for cognitive decline. Future studies will examine the relationship between RCSO2 patterns and decline in cognitive and physical function in a larger sample of community dwelling older adults.

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1383.H

Nocturia and Early Morning Dehyration: Consequences of Sleep-Disordered Breathing

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Introduction: Nocturia and sleep-disturbed breathing are often characterized as problems of the obese, the middle-aged and the elderly. The consequences of these problems are costly. Some accidental falls in the elderly have been identified as nocturia-related. Sleep fragmentation commonly leads to fatigue and decreased quality of life. Historically, the only connection made between these two seemingly distinct problems has been that nocturia may interfere with sleep. It is known that the increase in intra-thoracic pressure caused by sleep-disordered breathing can cause excess urine production at night (polyuria) by stimulating the cardiac atrium to produce natriuretic (Na) and diuretic peptides (ANP). In some instances, the volume of urine produced through this mechanism is significant. It may seem obvious that losing high volumes of fluid for any reason, including polyuria, has far-reaching implications. However, no work has examined the difference in hydration status of the persons who experience sleep-related polyuria and those who do not. The purpose of this analysis is to examine nocturnal urine production and early morning hydration measures in a sample of community-dwelling older adults with nocturia and in comparison with young, healthy adults.

Methods: A sample of community-dwelling elders (n=29) was recruited based on self-reported sleep apnea symptoms and nocturia (≥ 2/night) as part of an on-going, multi-phase study. This sample was balanced for gender (52% female, n=15; 48% male, n=14) and included minority subjects (African-American, n=18; Caucasian, n=11). The mean age was 65.5 (SD 8.38; range 51-91). These subjects participated in a clinical research study that included a 24-hour stay on a metabolic unit including polysomnography (11:00 pm to 6:00 am). In a parallel study, young, healthy adults (n=18, mean age 30.1, SD 8.64, range 21-49) were monitored for nocturnal urine output and bioimpedance indicators of hydration in early morning under controlled conditions. This group was balanced for gender (50%/50% male/female) and for ethnicity (African-American, n=8; Caucasian, n=8; other, n=2). In the elder sample, subjects were not restricted from fluids (ad lib) while the younger sample had scheduled hydration at 2300 hours (250ccs) the night before and 0700 hours (300cc) the morning of testing. Both groups were restricted from ambulating overnight.

Table 1

Comparison between older and younger samples

	Older Adults N=29 *Mean(SD)*	Younger Adults N=18 *Mean(SD)*	ANOVA *p value*
Night Urine ml/min*	1.5(0.9)	1.2(0.5)	.0010
BMI	32.3(6.6)	24.3(6.4)	.0002
%Fat	34.9(11.6)	25.7(11.6)	.01
%TBW	49.4(6.4)	54.2(6.4)	.0161
%ICW	54.2(4.7)	60.3(6.2)	.0003
%ECW	45.8(4.6)	39.1(3.4)	.0000

Results: As a group, older adults made significantly more urine at night (Table 1). Although a higher percent of body fat reduces body water content, more older adults (20%, n=6) were dehydrated, using bioimpedance standards, compared to young adults (11%, n=2). Older subjects had significantly lower percentages of total body water (TBW), intracellular water (ICW) and higher extracellular water (ECW). In addition, 66% (n =19) of the older adults were found to have OSA (AHI≥5/hr) by polysomnography.

Conclusions: These results suggest that the polyuria caused by sleep-disordered breathing may cause early morning dehydration in older adults. Chronic early morning dehydration in the elderly has implications for acute orthostatic hypotension upon arising, medication toxicity by water-soluble drugs (digoxin) and hazards of taking potassium depleting diuretics when dehydrated/hyponatremic. Further research will be required to fully examine this problem and effect of sleep disordered breathing to alterations in hydration and water balance.

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1386.H

OSA and Nocturia in Older Adults

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Introduction: Nocturia in older adults is commonly overlooked as a symptom of OSA because bladder problems are also prevalent in later years due to prostatism and weakened pelvic floor anatomy. In addition, poorly controlled diabetics are thought to have nocturia due to glycosuria, which causes osmotic diuresis. Regardless of cause, nocturia interferes with sleep maintenance and negatively affects sleep quality. The purpose of this study is to examine the interaction between nocturia and sleep disturbance symptoms among older community-dwelling adults.

Methods: A sample of 2000 older adults were surveyed by mailed questionnaire to recruit volunteers for intensive clinical interviews and ultimately a 24-hour stay on a metabolic unit. Sixty older adults participated in clinical interviews including the following battery of sleep questionnaires, a 3-day nocturia bladder diary, and HbA1c to detect poorly controlled diabetes. From that sample, 27 subjects (Mean age 65.3, SD=8.3) have completed the 24-hour observation period, which included overnight polysomnography and measures of intake, and urine output.

Results: Many subjects (70%, n=19) had AHI>5/hour, which is diagnostic of OSA and only two of seven diabetic subjects had mild glucosuria overnight. Nocturnal urine production, obesity and sleep problems were pronounced in many subjects (Tables 1 & 2). As previously reported, the findings vary by gender and ethnicity, reflecting group differences in BMI and glucose control. For example, among black women BMI is negatively associated with sleep efficiency ($r = -.82$, $p<.05$), and total sleep time ($r = -.83$, $p<.01$), but positively associated with overnight urine output ($r = .78$, $p<.05$). Additionally, nocturia by bladder diary was negatively associated ($r = -.80$, $p<.05$) with output between 1000-1400 hours in this group. Among white men, total sleep time was negatively associated with ($r = -.87$, $p<.05$) poor glucose control (higher HbA1c levels) but positively associated with nocturia by diary ($r = .85$, $p<.05$). Black men showed negative associations between nocturia by diary and the following: AHI ($r = -.76$, $p<.05$); total sleep time ($r = -.72$, $p<.05$); and sleep efficiency ($r = -.78$, $p<.05$). They had a strong association ($r = .86$, $p<.01$) between poor glucose control and early morning (0600-1000 hours) output. Among white women, BMI was positively associated with early morning (0600-1000 hours) output ($r = .92$, $p<.05$) and evening (1800-2200 hours) urine output ($r = .90$, $p<.05$). AHI was associated with late afternoon (1400-1800 hours) output ($r = .97$, $p<.005$). Poor glucose control was negatively associated with mid-day (1000-1400 hours) output ($r = -.91$, $p<.05$), but positively associated with sleep

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efficiency (r = .95, p<.05).

Table 1

Characteristics of sample: OSA by polysomnography, BMI, overnight urine production

	N	OSA n	BMI Mean(SD)	Mean Night Urine
Black				
Men	8	7	34.6(8.9)	977ml (389)
Women	8	4	33.2(7.4)	918ml (375)
White				
Men	6	4	30.4(3.1)	853 ml (222)
Women	5	4	30.9(5.2)	608 ml (326)
Total Group	27	19	32.6(6.7)	864 ml (349)

Table 2

Symptoms of sample (N=27)

	Min	Max	Mean	SD
Night Urine Volume	240mls	1750mls	864mls	349mls
Total Sleep Time	46 min	459 min	254 min	73 min
Sleep Efficiency	13%	91%	66%	16%

Conclusions: These findings do not support the common causal assumptions for nocturia (prostatism and glucosuria). Many of the findings are suggestive of circadian alterations in body water management, which may be caused directly or indirectly by OSA. Upon completion, this phase of the study will ultimately include 30 subjects and will explore potential biochemical factors that can cause alterations in nocturnal urine production such as vasopressin, and natriuretic peptides.

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1076.H

Circadian Activity Rhythms, Sleep/Wake and Light Exposure in Nursing Home Patients

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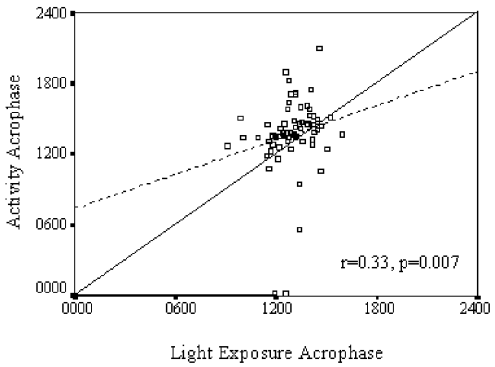
Introduction: Patients living in nursing homes have extremely fragmented sleep, and are exposed to little bright light.[1,2] Some have hypothesized that the low light may contribute to the poor sleep.[3] The current study examined the relationship between light and sleep in nursing home patients.

Methods: 77 patients (58 women, 19 men, mean age=86 years, sd=7) had their wrist activity and illumination exposure recorded with the Actillume (Ambulatory Monitoring, Inc., Ardsley, New York) for 3 days. 66 technically sound recordings were analyzed. Sleep/wake scoring and cosinor analyses (to determine acrophases) were done using Action3 software (Ambulatory Monitoring, Inc., Ardsley, New York). Data were examined separately for "day" (0700-1859) and "night" (2200-0559). Mean data were aggregated across the 3 days; median data were computed for each day separately. Spearman correlations were computed for light, sleep and circadian rhythm measures. For significant correlations, multiple regression analyses were conducted to examine the simultaneous effects of dementia level and light exposure on sleep and circadian rhythms. Statistically significant relationships are reported (p<.05).

Results: Mean daytime light exposure was 485 lux (sd=761, range=43-3565, median=54). Patients spent a median of 10.5 minutes (mean=34, sd=63, range=0-314) in light >1000 lux. 17% of patients were never exposed to light >1000 lux. Higher levels of daytime light exposure was associated with fewer nighttime awakenings (r=-.035, p=.004) even when level of dementia was included in the model (overall F(2,63)=3.36, p=.041; t(63)=-2.50, p=.015). No other light variables were predictors of daytime or nighttime sleep when dementia level was included. Later light exposure acrophase was associated with a later activity acrophase (r=.33, p=.0070). In most patients, the light acrophase preceded the activity acrophase (see figure). Later activity acrophase was associated with more light >1000 lux with dementia level in the model (overall F(2,63)=4.68, p=.013, t(63)=2.8, p=.007).

Figure 1



Conclusions: These data suggest that light exposure may be causally related to the extreme sleep fragmentation seen in nursing home elderly. The association between light exposure and nighttime awakenings does not appear to be due to more severe dementia. The fact that the peak of the light rhythm precedes the peak of the activity rhythm suggests that the alternative explanation that more active patients seek out more light exposure is less likely to be true. These data suggest that bright light therapy may effectively increase daytime activity levels as well as consolidate nighttime sleep.

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1419.H

Long-term Changes in Circadian Rest-Activity Cycle Organisation in Two Patients with Alzheimer's Disease

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Introduction: In a naturalistic study we have begun to document the time course of circadian rest-activity cycles in patients with dementia of the Alzheimer's type (AD) without any experimental interventions (Werth et al. 1999). Here we present analyses of two long-term actograms.

Methods: Patients' motor activity was measured in 1 min intervals with an activity monitor (Actiwatch, Cambridge Technology, UK). Medication was given according to clinical needs. The study was approved by the local ethics committee.

Results: Patient #1 (F, 55y, early-onset AD) was studied for 555 days. After changing neuroleptic medication to haloperidol, the rest-activity cycle became completely arrhythmic for two months, concomitant with a marked worsening of cognitive state. Circadian integrity returned (as did clinical improvement) after treatment was switched to the atypical neuroleptic clozapine. Higher doses induced early morning awakening. Whether due to early bedtime in the nursing home or clozapine itself, dim light melatonin evening onset (18:30h) was markedly phase advanced. Patient #2 (M, 83y) with terminal AD was studied for 589 days. In this case it was physical illness that induced disturbances of the rest-activity cycle. Before death the rhythm appeared to free run before becoming arrhythmic. Circadian and sleep analysis documented gradual insertion of wakefulness into sleep and naps into the waking period.

Conclusions: There is evidence that the gradual decline of circadian organisation observed in AD mirrors degeneration of the biological clock (Van Someren et al 1993). In real life, however, there are multiple positive and negative "masking" effects that require careful observation of the patient in order to dissect out endogenous components from extrinsic factors. The rest-activity cycle of patient #1 was profoundly disturbed by the very treatment given to improve nocturnal agitation, but improved after changing to clozapine. We have previously documented similar effects in schizophrenic patients (Wirz-Justice et al 1997), indicating that this phenomenon is drug- and not illness-related. If replicated, the finding has widespread implications for strategies in treating agitation and sleep-wake disturbances in AD. Patient #2 initially showed a gradual decline in circadian rest-activity organisation that was later masked by stereotypic agitation ("pacer") throughout the day and could only be seen again during the terminal phase of his illness.

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1454.H

Salivary Melatonin Measurement: Feasibility and Validation in Elderly Subjects

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Introduction: Most studies of melatonin have relied upon labor-intensive serum melatonin measurement. Recent discoveries of a circadian rhythmicity of melatonin in saliva specimens have led to a growing interest in the use of saliva melatonin levels.[1] However, saliva flow rates are decreased in the elderly relative to younger patients.[2] In the elderly, is saliva melatonin a valid surrogate marker for serum melatonin levels in studying melatonin onset, peak and offset?

Methods: 20 elderly subjects (age>65) were recruited as part of an ongoing study of melatonin secretion in the elderly. Subjects were placed in dim light conditions (<50 lux) and had an indwelling intravenous line inserted. Serum melatonin and saliva melatonin specimens were collected concurrently every 30 minutes from 18:00 to 24:00, then every hour from 24:00 to 04:00, and again every 30 minutes from 04:00 to 08:00 for a total of 25 serum and 25 saliva specimens per subject. Saliva was collected using the Sali-saver (Alpco, Inc). It has a maximum saliva collection volume of 1.5 ml, and involves placing a cotton roll between the cheek and gum for 2-3 minutes. The saliva specimens were assayed using the Direct Saliva Melatonin RIA (Buhlman Laboratories AG, Switzerland),[3] and the serum specimens using the Melatonin Direct I-125 RIA (IBL Laboratories, Germany).

Results: Of the saliva specimens, 20.8% had a volume <200 microliters and could not be assayed (mean 5.2 ± 5.0 per subject), whereas only 2.4% of the serum specimens were unusable (mean 0.6 ± 1.7). When both specimens were obtained, saliva melatonin levels were 19.7% of serum levels, and the correlation was r=0.84, p<0.001. The saliva/serum correlation decreased as the study night progressed, with the correlation in the later specimens (from 04:30-07:00) being lower than that noted in the earlier specimens (from 21:00-23:30) with a p<0.02 (Fisher's z-test).

Table 1. Percent of inadequate saliva specimens (<200 microliters) per subject and correlation with serum melatonin levels at various time intervals.

Time Interval	% of inadequate saliva samples	Correlation (Pearson)
Melatonin secretion onset (21:00-23:30)	11.0%	r=.85, p<0.001
Peak melatonin levels (00:00 - 03:00)	38.8%	r=.73, p<0.001
Melatonin secretion offset (04:30-07:00)	47.5%	r=.72, p<0.021

Conclusions: When samples can be obtained, saliva melatonin levels have a very good correlation with serum melatonin levels. However, elderly subjects tended to have greater difficulty producing adequate saliva quantities as the study night progressed, with a resultant higher percentage of inadequate specimens. The serum/saliva correlation decreased slightly as well. Thus, our findings suggest that while saliva melatonin remains a useful surrogate marker of serum melatonin levels in the elderly, it may be a more accurate indicator of melatonin secretion onset and peak level rather than of melatonin secretion offset.

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1533.H

The Effects of CPAP Treatment on Cognitive Function in Dementia: A Pilot Study

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Introduction: The prevalence of sleep disordered breathing (SDB) in elderly patients with dementia is very high, with 80% having a respiratory disturbance index (RDI)>10, and 47.7% having an RDI>20.[1] Both dementia and SDB cause cognitive impairment. Nasal CPAP treatment has proved effective in improving cognitive functioning.[2] The goals of this pilot study were: 1. To determine whether dementia patients with SDB could tolerate CPAP treatment. 2. To determine whether a 2-week treatment period with CPAP would improve cognitive functioning.

Methods: Three male dementia patients (mean age: 76.0 yrs, range: 71-82; mean education: 14.7 yrs, range: 13-18; mean Mini-Mental State Exam (MMSE) score: 21.3, range: 16-26) completed the study. All were living at home with spouses. Dementia level was assessed by the MMSE. Sleep, RDI and oximetry were assessed by a one night sleep recording using the Respitrace/Medilog and the VX4 portable recorders. Patients received CPAP treatment for two weeks with a Sullivan V Elite (ResMed Corp). CPAP pressure was computed based on the predictive equation by Nahmias et al..[3] A battery of neuropsychological tests as well as mood and quality of life (QOL) questionnaires were administered both pre- and post-treatment. Test scores are reported only for MMSE and the memory test - the CVLT (California Verbal Learning Test), as other tests showed minimal changes.

Table 1

Patient	Age	Education (years)	RDI	Compliance	MMSE (Pre)	MMSE (Post)	CVLT (Pre)	CVLT (Post)
001	71	13	32	<1 hour	16	10	2	0
002	82	13	32.5	>6 hours	22	24	77	60
003	75	18	14	>6 hours	26	29	71	80

Results: The table shows patients' age, education level, RDI, compliance based on mean duration of CPAP use per night, and pre and post treatment MMSE and CVLT overall scores. One patient with severe dementia was not compliant with the CPAP treatment, and no improvements were found in his cognitive functioning. Two patients were compliant with CPAP treatment. One showed slight improvement on the MMSE, but a decline in memory, and a slight decline in mood and QOL. The last patient showed moderate improvement, both in the MMSE and the CVLT.

Conclusions: Our preliminary findings suggest that CPAP can be successfully tolerated by mildly demented patients with sleep apnea. CPAP treatment may also improve some aspects of cognitive and mental functioning. Level of education may be predictive of successful outcome. Controlled trials of CPAP treatment are needed to determine if in fact, cognitive functioning can be improved.

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Supported by the Stein Institute for Research on Aging, ResMed, AG08415, AG02711, Research Service of the VASDHS.

1557.H

Age-Associated Changes in the Serotonergic System in Rat Superior Colliculus and Pretectum

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Introduction: Previous work from this laboratory has suggested that the pretectum (PT) and superior colliculus (SC) are involved in the modulation of the sleep-wakefulness cycle by acute lighting changes (Miller et al., 1998). Additionally, albino, but not pigmented rats, show increases in rapid eye-movement (REM) sleep following acute light-to-dark shifts. Other research has shown that behavioral sensitivity to the light-dark cycle decreases with aging. The neuromodulator serotonin (5HT) is known to play a role in both sleep-waking behaviors and light-dependent behaviors. The serotonergic system has also been shown to undergo specific regional changes with age. It is therefore possible that differences in the robust serotonergic input to the SC and PT may underlie the differences in REM sleep modulation by light and/or age-associated changes in sleep-waking responses to light.

Methods: We investigated possible differences in the serotonergic system in young and old congenic F344 c/c (albino) and c/+ (pigmented) rats. Young rats were less than six months of age (six albino and six pigmented) and old rats were greater than eighteen months of age (five albino and five pigmented rats). Light microscopic immunocytochemistry was used to study the distribution and relative density of 5-HT, the serotonin transporter, and 5-HT2A receptor immunoreactivity in the SC and PT in these animals.

Results: An inverse relationship was seen between levels of 5-HT and 5-HT2A receptor immunoreactivity in the SC and PT of young and old rats. Specifically, 5-HT staining was greater in the SC and PT of old rats compared to young rats. Conversely, 5-HT2A receptor staining was greater in the SC and PT of young rats compared to older rats. This inverse relationship was most striking in the SC, but was also present in all of the pretectal nuclei. No differences were seen in serotonin transporter immunoreactivity with age. Differences were found in 5-HT immunoreactivity in the SC between albino and pigmented rats. Whereas there was variability across animals, there was a trend towards greater levels of serotonin immunoreactivity in albino compared to pigmented rats in the superficial layers of the SC. No changes were seen in

serotonin transporter or 5-HT2A immunoreactivity between albino and pigmented rats.

Conclusions: Serotonergic input to the SC and PT appears to differ in albino and pigmented rats, and undergoes specific changes with aging. We propose that the decrease in 5-HT2A receptor expression in the SC and PT in older rats is compensatory to increased levels of 5-HT. Age-related changes in the serotonergic system in the SC and PT may account for some of the changes seen in light-mediated behaviors with aging. Visual abilities selectively decline with age, suggesting that aging may affect the visual system in a regionally specific manner. While some of these changes can be attributed to optical changes, others are likely due to changes in the central visual pathways. These data may have implications for the modulation of sleep-wakefulness by light.

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1578.I

Implicit Verbal Recall Correlates Positively with EEG Sleep Spindle Activity

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Introduction: We have shown that sleep spindles correlate positively with selective attention and negatively with spatial orientation.[1,2] The present study tested this relationship on three modules of memory, namely explicit recall (ER), implicit recall (IR), and word span (WS).

Methods: The sleep of eight healthy participants (6 males, 2 females; age = 21.4 ± 4.9; education = 13.5 ± 1.7 years) was recorded for two consecutive nights. Sleep data were extracted from the second night. Stage 2 sleep spindles were visually identified on the C3 lead. Participants were tested for ER, IR and WS on the morning following the second night of recording. For the ER task, participants first learned pairs of words. ER was tested immediately and after a delay of 20 minutes by calling to participants an item of each pair. Following a neutral diverting task and without telling the participants, IR was then tested by asking participants to give the first word that would come to their mind by priming them with the first 2-3 letters of words taken from the previously learned list. Finally, WS was tested by having the participants learn a list of words with increasing number of elements, until three consecutive errors were made. The number of words in the last completed set would determine WS. Correlation coefficients (Spearman's Rho) were calculated between sleep variables and results on memory tasks.

Table 1. Spearman's Rho Correlation Coefficients between Sleep Spindles and Performance on Memory Tasks

	Explicit Recall	Implicit Recall	Word Span
Number of Sleep Spindles (Stage 2)	.02	**.77***	.30

*p< .05

Results: A significant correlation was found between IR and the number of sleep spindles (rho = .77, p = .04). We also found a strong, although non significant, positive correlation coefficient (rho = .66, p = .076) between REM sleep latency and the IR task. Results proved to be non significant regarding correlation coefficients between the two other aspects of memory and sleep variables.

Conclusions: Based on sleep deprivation studies and post-training sleep rebound measures, it has been suggested that implicit memory is particularly associated with REM sleep.[3] In the present study, another paradigm was used: performance was measured after a normal night of sleep and correlation analyses between sleep parameters and cognitive performance were then performed. We found a significant correlation between IR and sleep spindle activity but not with REM sleep. Rather we found a positive correlation between IR and REM sleep latency. Both sets of results are compatible since the longer the REM sleep latency, the longest time there is in non-REM sleep, increasing the possibility for spindle occurrence. The present study indicates once more that non-REM sleep EEG phasic events may be related to daytime cognitive performance.

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1879.I

Sleep Knowledge, Behavior, and Attitudes: A Comparison Between United States and Japanese Samples

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Introduction: Sleep attitudes are evaluative feelings or intended behaviors associated with sleep. Sleep knowledge is what an individual knows about sleep. Little information is available in the current literature with regard to whether cultural differences of sleep knowledge, behaviors, and attitudes exist. Although these issues have not been given much consideration, cultural variations are known to exist in napping and co-sleeping.[1,2] These differences may impact the preparation for sleep, the processes of sleep, and patterns of sleep. The purpose of this research was to investigate the possibility of differences between Japanese and American cultures with regard to sleep knowledge, behaviors, and attitudes.

Methods: Subjects consisted of two samples matched for age. The first sample included 11 males and 13 females (mean age = 44.5 years, SD = 14.14 years) residing in Japan. Sample two was comprised of 15 females and 9 males (mean age= 43.5 years, SD = 15.51 years) recruited from the United States. Participants were given a questionnaire containing four measures: the Epworth Sleepiness Scale (ESS), a measure of daytime sleepiness; the Sleep IQ (SIQ), a measure of sleep knowledge; the Attitudes About Sleep Questionnaire (ASQ), which includes eighteen statements on which respondents indicate their level of agreement; and a portion of the National Sleep Foundation's (NSF) 1998 Omnibus Sleep in America Poll (OSAP), a survey of demographic information and sleep related behaviors.

Results: The majority of both the Japanese sample (96%) and the

American sample (96%) failed to meet a passing score on the SIQ, consistent with data from the NSF's OSAP. The mean ESS scores of the two samples did not differ (t(22)=1.25; p>.05): U.S.=8.48 (SD= 3.65) and Japan=7.13 (SD= 2.9). The two samples did differ with regard to sleep aids, with the Japanese sample reporting a greater use of alcohol and the American sample reporting greater use of over the counter (OTC) medication (see figure 1). Significant differences were found for attitudes regarding sleep and driving, impact of exercise on sleep, importance of sleep scheduling, and the impact of sleep loss (see figure 2).

Figure 1: Use of Sleep Aids

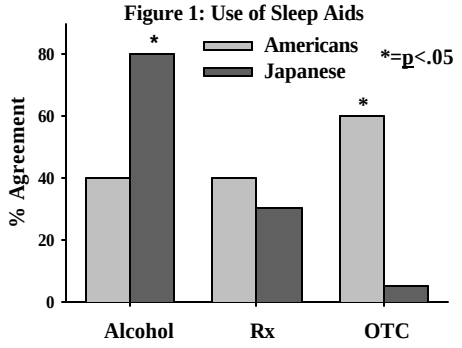
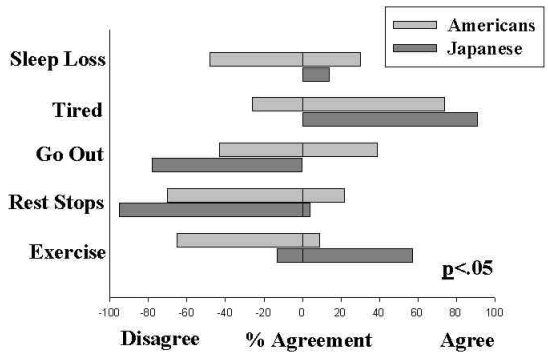


Figure 2: Sleep Attitudes



Conclusions: A large percentage of both samples failed a measure of sleep knowledge, suggesting that many people in both cultures do not have sufficient knowledge of sleep. Both samples had similar scores on a measure of daytime sleepiness. Although sleep knowledge and daytime sleepiness in these two samples was similar, a number of attitudinal differences were found. These differences suggest the possibility that Japanese and American cultures may engage in different sleep behaviors. These cultural differences may be important in assessment of sleep disorders and in sleep hygiene education of these two populations.

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1240.I

Comparisons of Sleep Patterns Between Mothers in the Postpartum From Nine to Twelve Weeks and Non-Pregnant Women

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Introduction: In our previous study, wakefulness of mothers at night in the early postpartum (from one to six weeks after delivery) increased to about 20%.[1] In addition, there was a high synchronization between their wakefulness and their infants' movements. The study suggested that mothers' sleep patterns were strongly influenced by their infants' development. In the postpartum from nine to twelve weeks, when most infants have obtained their circadian sleep-wake rhythm, we observed that two sleep patterns for postpartum mothers were mixed: interrupted sleep when mothers took care of infants, and non-interrupted sleep.[2] In order to evaluate the two patterns of sleep, we compared them with the sleep patterns of non-pregnant women.

Methods: Subjects were ten primiparae (mean 33.1, range 26-40 yrs), and twelve non-pregnant women (mean 32.5, range 28-39 yrs). Eight mothers were breast-feeding, one was formula-feeding, and the other was mixed feeding. Polysomnographic recordings (EEG, EMG, EOG) of the mothers were made using a Medilog 9200 recorder at home during one night in the ninth and twelfth postpartum weeks. Polysomnographic recordings for the non-pregnant women were made by the same methods on two consecutive nights during their follicular phase. Sleep stages were scored according to Rechtschaffen and Kales criteria. We classified the mothers' sleep into two patterns, interrupted and non-interrupted. We used data from the second night recordings for the non-pregnant women. Using t-tests, we evaluated the same two patterns of sleep for the non-pregnant women. We were unsuccessful in recording one mother's polysomnogram in the twelfth postpartum week for reasons related to the recorder.

Table 1

	Non-pregnant	Interrupted	Non-interrupted
	Mean(SD)	Mean(SD)	Mean(SD)
TIB(min)	418.8(63.5)	431.2(41.5)	363.9(35.0)
SPT(min)	399.7(59.3)	404.0(47.9)	341.1(41.1)
TST(min)	390.3(55.6)	324.4(24.4)*	336.8(40.1)
SE(%)(TST/TIB)	93.4(2.4)	75.6(5.1)**	92.4(5.2)
Sleep latency	16.0(10.7)	24.1(11.1)	19.2(20.4)
Waking time	10.1(6.7)	84.8(35.7)**	5.8(4.1)
%Wake(/SPT)	2.5(1.6)	20.5(6.5)**	1.8(1.3)
%Stage 1(/SPT)	5.4(2.5)	5.1(1.6)	4.2(4.3)
%Stage 2	47.3(7.4)	34.8(5.6)**	47.0(5.0)
%Stage 3	12.0(2.4)	10.8(3.7)	10.2(2.4)
%Stage 4	7.6(6.4)	9.8(3.3)	15.3(3.5)*
%Stage 3+4	20.1(6.6)	20.5(6.1)	25.5(5.8)
%REM	23.1(5.1)	18.3(4.0)	21.0(7.2)

*p<0.05, **p<0.01

Results: The table shows mean and standard deviation values for sleep parameters during interrupted and non-interrupted sleep, and the same for non-pregnant women. We obtained ten observations of interrupted sleep for six mothers and nine observations of non-interrupted sleep for five mothers. In interrupted sleep, we found significantly low sleep efficiency, decreased total sleep time, increased waking time from sleep

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onset to final awakenings, and a decreased percent of stage 2 for sleep period time compared with the parameters of the non-pregnant women (df=16). These results were similar to sleep patterns in the early postpartum (1-6 weeks).[1] In non-interrupted sleep, there were no significant differences in sleep parameters, except for the percent of stage 4 (df=15). These findings of non-interrupted sleep patterns were similar to recovery sleep after sleep deprivation arising from interruption. A high correlation between slow wave sleep and prolactin has been reported.[3] Increased prolactin from breast-feeding might have been a factor contributing to an increased percent of stage 4.

Conclusions: In the postpartum from nine to twelve weeks, when infants have obtained their circadian sleep-wake rhythm, mothers' sleep fluctuated between interrupted sleep similar to the early postpartum sleep and non-interrupted sleep similar to recovery sleep after sleep deprivation.

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1607.I

Sleep EEG Spindle Activity Correlates Negatively With Spatial Orientation Performance In A Human-Size Maze

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Introduction: Several reports have shown a relation between sleep and cognitive processes[1] but few have focussed on spatial memory. We studied the correlation between spatio-cognitive performance in a human-size maze and nocturnal sleep organization in healthy young participants.

Methods: 20 subjects (10M, 10F; age = 23.7±4.4) spent two consecutive nights in a sleep laboratory. Sleep was scored according to Rechtschaffen and Kales (1968) using 20-seconds epochs. Stage 2 sleep spindles were identified visually on the C3 lead according to the following criteria: bursts of EEG activity at 12-15 Hz and lasting 0.5 to 2.0 seconds; no amplitude criteria were applied. In the morning following the second night, subjects were tested on human maze (8mx12m ; 2,5m-high walls, 1m-wide corridors). Subjects had to learn three different routes of increasing difficulty (4, 6 and 8 intersections).The route with 8 intersections is shown in Figure 1. For each route, subjects were first guided once by an experimenter. They were then asked to follow the same route they were just shown, on five successive trials; immediate feedback was provided upon an error (wrong choice at intersections). Time taken and number of errors were noted, results on the fifth trial serving as the learning index. At the end of the fifth trial of each route, subjects were asked to point toward the start position; degree errors were noted. Then the subjects were taken out of the maze asked to identify the route just walked, out of five different sketches. Performance on the maze was correlated with sleep data from the second night using Pearson product moment.

Results: There was a positive correlation between sleep spindle density (i.e., no./h stage 2) in the last third of the night and: a) number of errors; b) time taken to carry out the routes (Figure 2). There was no significant correlation between the rest of the sleep variables, whether by total night or by thirds, and the two other tasks (pointing and drawing identification).

Figure 1. Example of a 8-intersection route in the human-size maze. Route starts at "S" and ends at "F". Subjects are taken back to the start position via the doted line.

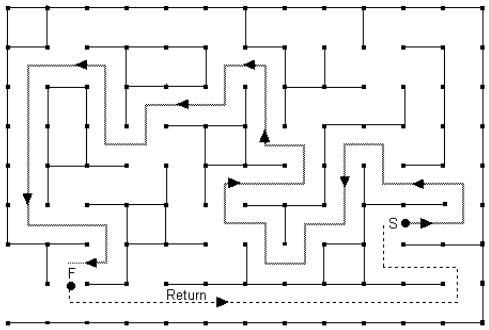
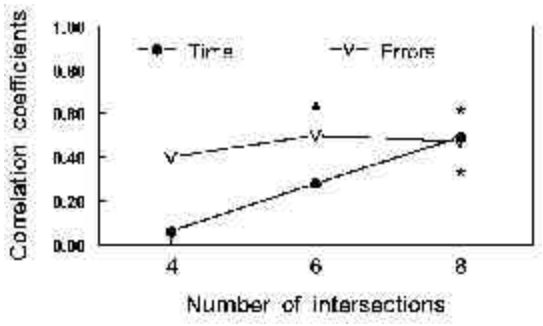


Figure 2. Correlation coefficients between the density of stage 2 sleep spindles in the last third of the night and performance in the human-size maze.



Conclusions: These results show that subjects with higher numbers of spindles late in the night took more time and made more errors while learning the routes. It suggests a negative impact of nonREM sleep mechanisms on explicitly learned, non-cued spatial information. Together with other evidence[2,3] it suggests once more that non-REM sleep EEG phasic events can be correlated with daytime cognitive performance.

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Supported by the "Fonds de la recherche en santé du Québec".

1253.I

Driving Simulator Performance in Obstructive Sleep Apnea-Hypopnea-Syndrome (OSAHS) and Narcolepsy

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Introduction: OSAHS and narcolepsy are major reasons for daytime sleepiness. The present study compares driving simulator performance in these two groups of patients.

Methods: Driving simulator performance (60 min., highway driving, different weather and daytime, obstacles, mean spead 100 km/h) was investigated in 5 patients with narcolepsy (4 men, 1 woman, age: 43.4± 8.8 years) and 23 patients with OSAHS (22 men, 1 women, age: 55.9±10.2 years; AHI 26.9±22.2/h).

Results:

	Narcolepsy	OSAHS
Accident rate:	2.8 ± 1.3	2.6 ± 1.9n.s.
Concentration faults:	10.6 ± 5.2	12.9 ± 5.7n.s.

Most accidents both in OSAHS and in narcolepsy occurred under good weather conditions. In both groups no correlation was found between accident rate and daytime sleepiness (Epworth Sleepiness Scale). Concentration faults (before CPAP: 12.9±5.7, 42 days CPAP 5.3±1.9) and accident frequency (before CPAP: 2.6±1.9, 42 days CPAP 0.7±0.9) improved significantly ($p<0.05$) in patients with OSAHS.

Conclusions: Conclusion: Patients with OSAHS or narcolepsy report difficulties remaining alert and attentive. OSAHS and narcolepsy compromise daytime performance and may account for a substantial portion of sleep-related motor vehicle accidents. Computerized test batteries have been able to show neuropsychological deficits. It is still unclear whether these deficits correlate with increased accident rates. Driving simulator investigations are an additional diagnostic tool with closer relationship to real traffic situations.

1616.I

Gender Differences in Waking EEG Delta Activity Before and After a Night of Sleep

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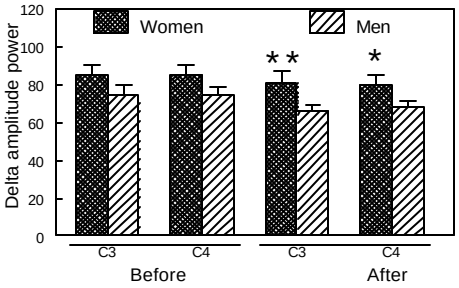
Introduction: Some studies have reported that women tend to have more EEG delta power in non-REM sleep than men, while others have not.[1-3] Authors have proposed several hypotheses to explain these gender differences, including possible differences in sleep regulatory mechanisms.[3] In the present study, we analyzed waking EEG delta activity in young men and women prior to and following a night of sleep. This study had two objectives: first to determine whether gender differences exist in waking EEG delta activity and, second, to determine whether sleep itself has a gender-related differential impact on morning waking delta EEG.

Methods: Seven healthy women (age: 21.7 ± 0.6 years) and eight healthy men (age: 22.9 ± 0.6 years) spent two consecutive nights in a sleep laboratory. Night 1 served as an adaptation night and screening of sleep disorders. On night 2, waking EEG recordings with eyes closed were performed for five minutes in the evening, before going to bed (between 22h00 and 23h00) and on the following morning (between 07h00 and 08h00) using monopolar C3 and C4 recordings referred to linked ears. EEG amplitude power (µV/Hz, 0.75Hz to 19.75Hz) was determined with spectral analysis performed on 10 to 15 four-second artefact-free epochs. Four frequency bands were created: Delta (0.75-3.75 Hz), Theta (4.0-7.75 Hz), Alpha (8.0-12.75 Hz), and Beta1 (13.00-19.75 Hz). Only Delta results will be reported here. Comparisons between men and women were performed before and after the night, using t-tests for independent samples.

Results: Men and women were not statistically different before the night. On the following morning women showed more Delta than men on C3 ($t = 2.26$; $p<.05$) and C4 ($t = 2.08$; $p = .057$) (see Figure 1).

Figure 1. Waking EEG Delta power amplitude for C3 and C4, before and after a night of sleep in young men and women.



Conclusions: The absence of differences on evening recordings is consistent with the litterature.[3] The morning results suggest that gender differences previously shown for delta activity during NREM sleep[1-3] are still present in the morning. This is consistent with early propositions according to which women have a greater sleep debt than men when they wake up in the morning. Dijk et al.[1] also found that women have higher power densities during NREM sleep over a wide frequency range (0.25 to 11 Hz). It will be interesting to investigate whether our results can be replicated with other frequency bands and other electrode sites.

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1618.I

Steering Rate Variance as a Measure of Driver Sleepiness

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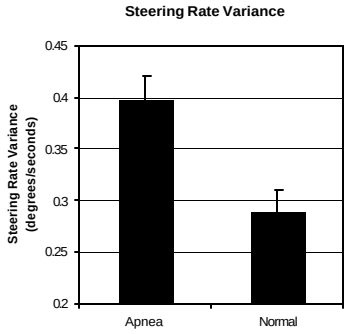
Introduction: According to the National Highway Transportation Safety Administration, 16,608 fatal crashes were related to failure to maintain proper lane positioning or running off the road. In addition, 1,848 of drivers in fatal crashes were drowsy, asleep, or fatigued. More than 1,732 drivers involved in fatal crashes had overcorrected/oversteered

(NHTSA, 1999). Although many studies have demonstrated driving performance deficits associated with excessive daytime sleepiness, no study has specifically examined steering control. To address the question of driver input, steering rate variance was analyzed from data collected in a previous simulation study (Risser et al., 1999).

Methods: Fifteen obstructive sleep apnea patients (mean age = 42 + 6 years) and 15 control subjects (mean age = 38 + 6 years) were tested in a driving simulator. The PC based driving simulator was equipped with steering wheel, gas and brake pedals, 21" display, and sound. After a 10-minute practice drive through a city scenario, participants completed a 60-minute vigilance task designed to replicate a highway-driving scenario. Steering rate variance data (degrees/seconds) was continuously sampled for the duration of the task and grouped in six 10-minute time blocks for analysis.

Results: Steering rate variance was analyzed by repeated measures analysis of variance (ANOVA). Normal and apnea patient groups were the between-subjects factor, while time block was the within-subjects factor. Analysis of covariance was used to calculate correlations between performance measures. Steering rate variance of the apnea group (0.399 + 0.189) was greater than normal controls (0.289 + 0.206) over all time blocks ($p < .05$) (see Figure). There was no effect for time block and no group by time block interaction. Despite less steering rate variance for the normal control group, their variance correlated significantly with lane position variance ($r = .41$, $p < .001$). For the apnea group, there was no significant correlation for lane position variance ($r = -.03$) and crashes ($r = -.23$).

Figure 1



Conclusions: The measure of steering rate variance results from a driver's response to changes in lane position. Control subjects recognized deviations from optimal lane position earlier than apnea patients and made subtle steering corrections. Apnea patients, presumably due to attention lapses, had a delayed response to lane position changes and therefore made greater steering adjustments once lane deviations were recognized. Measures of driving performance such as lane variability or crashes, which demonstrate measures of output, are in many cases beyond intervention. Monitoring the behavior of driver input on the steering wheel provides earlier information about driver performance and fatigue. Potentially, real-time monitoring of steering rate variance can be used as an intervention to prevent crashes.

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1277.I

Components of Daytime Sleepiness and Self-reported General Health Status in a General Population

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Introduction: Daytime sleepiness is a common problem in society and negatively impacts public health and safety. Commonly used instruments such as the Multiple Sleep Latency Test, Stanford Sleepiness Scale, and Epworth Sleepiness Scale, each derived to be sensitive in measuring a certain aspect of sleepiness, have been used in previous studies to quantify daytime sleepiness. It is poorly understood how different measures of daytime sleepiness relate to other aspects of health. In an ongoing population-based study of the natural history of sleep-disordered breathing, we identify the components of variation in daytime sleepiness using a spectrum of measures including self-reported and behavioral manifestations of daytime sleepiness and assess the relationship between the components of daytime sleepiness and self-reported general health status (MOS SF-36).

Methods: Data from the Wisconsin Sleep Cohort Study was used for this analysis of daytime sleepiness and general health status. Using a 2-stage sampling procedure, all men and women, ages 30-60 yr, who were employed at one of five state agencies were identified and surveyed on sleep characteristics. Survey respondents were recruited by mail and telephone for participation in an overnight sleep and daytime study at a sleep laboratory. The data on daytime sleepiness from the sleep survey, and nighttime and daytime studies were used for principal component analysis. The sleepiness variables included self-reported problems: (1) feeling of excessive daytime sleepiness (EDS), (2) not feeling rested during the day, no matter how many hours of sleep you had (RES), (3) difficulty getting up in the morning (MOR), (4) need for coffee, or other stimulants to stay awake during the day (COF), (5) falling asleep or dozing momentarily-watching TV, reading, etc. (TV), (6) falling sleep or dozing momentarily- at meetings, church, etc. (MT), (7) having fatigue that interferes with everyday life (FAT), (8) having uncontrollable sleepiness that interferes with life (SLP); self-reported sleeping patterns: (9) hours of daytime naps during a typical week (NAP); and standard measures of daytime sleepiness: (10) Multiple Sleep Latency Test (MSL), (11) Stanford Sleepiness Scale (SSS), and (12)Epworth Sleepiness Scale (ESS). The data on the SF-36 was obtained from all current cohort participants by a separate survey.

Table 1. Rotated Factor Loadings for the Sleepiness Variables*

	PC 1	PC 2
EDS	**0.73**	0.31
COF	**0.62**	0.09
RES	**0.74**	0.09
MOR	**0.64**	-0.09
FAT	**0.68**	0.03
SLP	**0.56**	0.22
TV	0.12	**0.75**
MT	0.31	**0.70**
NAP	0.04	**0.52**
MSL	-0.13	**0.48**
ESS	0.27	**0.77**

*Stanford Sleepiness Scale was deleted from the PCA due to low loadings on both components.

Results: A principal component analysis (PCA) with varimax rotation revealed 3 components with eigenvalues greater than 1, but a sharp elbow in the scree plot at the third eigenvalue, suggesting that 2 principal components (PC) may be sufficient to explain a large portion of the

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variance (47%). Based on the clustering of high factor loadings, PC 1 was interpreted as "perceived sleepiness" and PC 2 as "sleepy behavior" (Table 1). A multiple regression analysis showed statistically significant relationships between both component scores and all the SF-36 subscales, except for the relationship between PC 2 and mental health and physical functioning (Table 2).

Table 2. SF-36 subscales fitted by component scores, age, gender, and LogAHI†(n=456)

	PC 1	PC 2
	β (SE)	β (SE)
Vitality	-8.5(0.9)*	-3.9(1.0)*
GHP	-5.7(0.9)*	-2.6(1.0)*
Mental	-6.7(0.7)*	-1.4(0.8)
Pain	-5.1(1.0)*	-4.1(1.0)*
Physical	-2.7(0.8)*	-1.4(0.9)
Role, Em	-7.7(1.6)*	-3.6(1.7)*
Role, Phy	-7.6(1.5)*	-3.4(1.6)*
Social	-7.8(1.0)*	-2.8(1.1)*

† ln (Apnea-Hypopnea Index);*p-value<0.05;
β is the coefficient of the sleepiness component score variable;
SE is the standard error of β

Conclusions: The findings from our study suggest that, in a spectrum of daytime sleepiness measures, there are two components of variation in daytime sleepiness in the general population. The data demonstrate that "perceived sleepiness" component, compared to "sleepy behavior", has greater association with general health, well-being and functional status.

1285.I

Gender Differences in Napping Behavior in Urban Greece

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Introduction: Naps are disappearing from many industrialized cultures (Valencia-Flores, et al., 1998; Soldatos, et al., 1982). How these changes affect men and women has not been addressed (Webb & Dinges,1989). The purpose of this study was to describe gender differences in sleep patterns in adults living in an urban setting where naps are culturally accepted.

Methods: A convenience sample included 9 Greek couples living in Athens who expressed interest in the study and intentionally napped on a regular basis. An intentional nap was defined as reclining for an intended length of time. Couples were excluded if either spouse worked nights, had a sleep disorder, or had a chronic health problem. Qualitative and quantitative data were collected, after both spouses were given an Information Form and Experimental Subject's Bill of Rights. Wrist actigraphs (Ambulatory Monitoring, Inc. Ardsley, NY) were worn for 48 hours. Data were collected during May, 1999. Equipment failure resulted in a final sample of 7 couples.

Results: There was no difference in acrophase between the men (15:42+54 mins) and women (16:00 hrs+60 mins), but women had significantly (t=2.2, p=.048) stronger 24-hr rhythms (autocorrelation=.41+.12) than men (autocorrelation=25+.17). There was no gender difference in time spent in naps or night sleep: men (54 mins, 350 mins, respectively) and women (69 mins, 378 mins, respectively). Total sleep, including naps, for women (7.4+1.1 hrs) compared to men (6.8+.97 hrs) was not statistically significant in this small sample. Sleep was less efficient for men due to awakenings (t=2.4, p=.038). Women averaged 5.6+4.3 awakenings/ night and 96+6% SEI, while men experienced 11.3+6.8 awakenings and 89+9% SEI. Qualitative data indicated that Greeks do not nap as they did in the past because of women's roles in the work force and child responsibilities. Initially, couples reported they no longer "napped" because napping was considered something the entire family did in the home at the same time. Greek adults, today, still nap but often stagger naps to accommodate work schedules.

Conclusions: The definition of naps is changing in Greek culture, but naps are prevalent. The extent to which naps supplement night sleep is unknown in the U.S. Greek women in this sample slept longer and had more efficient sleep than their spouses, but couples still averaged only 6.5-7.5 hrs, including naps. Regardless of the opportunity for culturally sanctioned naps, urban dwelling adults fail to obtain the recommended 7-8 hrs sleep per night and may use naps to supplement inadequate sleep at night.

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1324.I

Sleep Perception on MSLT and Motor Vehicle Accidents

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Introduction: Drowsy driving has been estimated to account for 3-15 percent of motor vehicle accidents. Individuals involved in sleep related accidents are more likley to have acute sleep deprivation upon a baseline of chronic sleep deprivation. Previous studies have shown that normal individuals, tested in a driving simulator, are able to recognize the physiological symptoms of drowsiness prior to having a deterioration in their driving skills. Recently, we found that 42 percent of drivers involved in sleep related driving accidents had little or no warning of drowsiness prior to their accident.

Methods: To investigate the relationship of the lack of perception of sleep as a risk for motor vehicle accidents, we asked twenty consecutive patients undergoing multiple sleep latency tests (MSLT) to estimate the length of time it took them to fall asleep. Patients estimated the sleep latency at the end ofeach nap. Additionally, the Epworth Sleepiness Scale was adiministered prior to the MSLT and Standford Sleepiness Scale was administered prior to each nap. Patients were also questioned about motor vehicle accidents and near accidents in the last two years. Results were tabulated and correlation coefficients were calculated for significance (p<0.05).

Results: The twenty subjects in this study ranged in age from 28 to 88 years and there were 12 males. Patients had a variety of diagnoses including 7 had OSA, 2 had hypoventilation and 2 had REM behavior disorder syndrome. The average Epworth Sleepiness Scale for the group was 12, and 11 patients had an Epworth score greater than 10. The aver-

age Standford Sleepiness Scale for each nap was 5.7 for nap 1, 5.0 for nap 2, 3.4 for nap 3 and 3.8 for nap 4. The overall average mean sleep latency was 6.1 and for each nap was 5.4 minutes for nap 1, 5.0 for nap 2, 7.2 for nap 3 and 6.6 for nap 4. Of the twenty subjects, 6 incorrectly estimated no sleep in one nap, 2 in two naps and 6 in three or more naps. Six of the eight subjects that incorrectly estimated no sleep in at least two naps had motor vehicle accidents or near accidents. Whereas, none of the six subjects who correctly estimated sleep in all of the naps had a history of motor vehicle accidents or near accidents. The number of naps incorrectly estimated by patient as no sleep does correlate with the history of motor vehicle accidents or near motor vehicle accidents (correlation coefficient r=0.59,which is significant). Correlation coefficients of motor vehicle accidents or near accidents to Epworth Sleepiness Scale was -0.04, average Standford Sleepiness Scale was 0.08 and mean sleep latency was -.13. None of these latter coefficients were significant.

Conclusions: We have found a significant relationship between the lack of perception of sleep on MSLT and motor vehicle accidents. This study highlights the need for awareness to the lack of recognition of the physiological symptoms of drowsiness by some individuals and the potential for sleep related motor vehicle accidents. Driver education must be directed not only at the need for preventive and counter measures to reduce drowsy driving but also focus on the lack of perception of drowsiness.

1671.I

Meteorological Factors and Subjective Sleep Continuity

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Introduction: While much is known about the effects of light exposure on sleep (e.g., 1), little is known about whether other meteorological factors influence sleep continuity. We evaluated the association between several meteorological factors (e.g., light, temperature, barometric pressure, etc.) and self-reported sleep continuity measures in a sample of undergraduates.

Methods: Sleep data were collected via sleep diaries from 43 undergraduates enrolled in a "Sleep Research and Sleep Medicine" class from January 13th to May 2nd (105 days). Subjects, as a course requirement, completed a daily diary. Diaries were collected once a week. Each diary contained two major sections. The first was completed at bedtime and composed of 7 questions to assess daytime behavior, mood, and time spent exercising and outside. The second section was completed upon awakening and composed of 10 questions to assess standard parameters such as subjective perception of sleep latency (SL), number of awakenings (IWT), wake after sleep onset (WASO), total sleep time (TST), bedtime (TTB) and wake time (TOB), total sleep opportunity (TSO) and sleep efficiency (SE). Meteorological data were obtained from the National Climatic Data Center website, which provided daily meteorological profiles for the Rochester area. The variables obtained from this database included barometric pressure, precipitation, average temperature, dew point, snow depth, average wind speed, minutes of sunshine per day, average visibility, and lunar phase. The sleep diary data were averaged to yield mean sleep continuity profiles for each of the 105 days. These data, in turn, were correlated with the meteorological variables for the 105 days. The resulting correlational analyses yielded an 8 x 11 correlation matrix.

Results: Of 88 potential correlations, 22 were significant and 7 tended to be significant ($p < .10$). Correlational magnitudes ranged from 0.007 to -0.42. The sleep continuity measures that showed the greatest association with meteorological phenomena were WASO, TST, TSO and SE. Meteorologic variables that showed the greatest association with subjective sleep continuity measures were temperature, dew point, snow depth, precipitation and barometric pressure. The largest single correlation was between precipitation and SE ($r = -0.42$, $p < .0005$). Precipitation was also significantly correlated with WASO, TSO and TST. Barometric pressure was most significantly correlated with TST ($r = 0.36$, $p < .0005$). It was also significantly correlated with TSO, SE and WASO. Lunar phase was not correlated with any sleep measure. Minutes of sunshine per day was significantly correlated only with WASO ($r = -0.20$, $p < .05$).

Conclusions: These data suggest that meteorological factors other than light are associated with sleep continuity. Indeed, our data suggest that precipitation and barometric pressure are more related to sleep continuity then light and may be particularly associated with sleep maintenance. The possibility that barometric pressure influences sleep continuity measures is consistent with documented sleep disturbance at high altitude. In these cases, however, sleep maintenance problems are thought to be related to respiratory disturbance due to low O2 tension (O2 saturation in ambient air x barometric pressure). The present data suggest that barometric pressure may also directly influence sleep.

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1685.I

Effects of Experimental Pain Models on Pilocarpine-Induced Yawning

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Introduction: Yawning is a common phenomenon that is an expression of certain physiological, psychological and pathological states. It can be elicited by several pharmacological agents, including dopamine agonists, cholinomimetics and polypeptides, suggesting that different systems are involved in the modulation of this behavior. Other factors, such as aging, sleep deprivation (TUFIK et al., 1987) and stress (DE KLOET, 1991) can also interfere with yawning behavior. SATOH & OMOTE (1996) suggest that pathological pain state can activates or increases the activity of system as serotonin, noradrenaline, dopamine, glycine, GABA. Considering that yawning is influenced by various neurotransmitter systems and different factors, we analysed if neuropathic pain and arthritis induced by adjuvant (AIA) models would cause alterations in yawning induced by pilocarpine.

Methods: Male WIstar rats were used. Under deep anesthesia, chronic constriction injury (CCI) procedure was induced by 4 chromed catgut ties on the sciatic nerve. Arthitis was induced by s.c. administration of 0,1 ml of Freund adjuvant (denatured Mycobacterium butyricum) in the right paw. The control group (CTRL) group was not submitted to any manipulation. The animals were divided in threee groups (CCI, AIA, and CTRL) of 10 rats each and were injected, i.p.; of 2mg/kg of pilocarpine on the second day, one week and two weeks of pain and the number of yawns recorded for 30 minutes.

Results: The data analysed by ANOVA showed a significant difference between the groups ($p=0.005$). Tukey test indicate that there is a significant difference between CCI and CTRL ($p=0.004$). There is also significant difference between the times ($p=0.041$). Bonferroni corrected t-test indicate that there is a significant difference between Day 2 and one

week of pain (p=0.014).

Conclusions: The results of the present study shows that yawning can be altered by experimental pain models, such as neuropathic pain. Stressful procedures, such as immobilization and paradoxical sleep deprivation also decrease the number of yawns. Thus, our results indicated that neuropathic pain seem to play a role in yawning-induced by pilocarpine, maybe by modulating the cholinergic system, however more studies are necessary to clarify the mechanisms involved.

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1686.I

The Effects of Exercise on Subjective Measures of Sleep Continuity

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Introduction: A variety of studies have evaluated the effects of exercise and physical activity on sleep. Some studies are experimental and assess the effects of short-term manipulations on polysomnographic sleep (e.g., 1) in healthy subjects. Other studies are epidemiologic and evaluate the relationship of exercise to subjective sleep quality in a broad cross-section of subjects (e.g., 2). Most studies, regardless of design, yield mixed results. It has been suggested that the mixed findings may be related to ceiling effects, sample considerations, methods of assessment, and/or to the use of mean data.[3] The purpose of our study was to assess prospectively both sleep continuity and exercise and to determine the degree of association on an individual subject basis.

Methods: Data were collected via sleep diary from 43 undergraduates enrolled in a "Sleep Research and Sleep Medicine" class January 13-May 5, 1999, at the University of Rochester. All subjects completed daily sleep diaries for a period of up to 15 weeks (105 days). The sleep diary included the following measures: time to sleep onset, number of awakenings, wake after sleep onset time, bed time and wake time, sleep efficiency, and number of minutes spent exercising. Within subject correlations were calculated for time spent exercising and each of the sleep continuity measures.

Results: On average, subjects took 16.1 minutes to fall asleep, woke up 1.5 times, spent 12.3 minutes awake, slept for 437.3 minutes. Sleep efficiency was 93.6% and an average 465.2 minutes was spent in bed. The overall group correlations between exercise and sleep continuity were not significant. No correlation had a value of greater than r = 0.10. At the level of the individual, 32.5% (14/43) of subjects exhibited significant within-subject correlations for one or more of the sleep continuity variables ($p < .05$). The largest within-subject correlation was r = 0.41 (exercise and total sleep time; exercise and total sleep opportunity). The most frequent correlation, negative or positive, was with total sleep opportunity (n=8), followed by total sleep time (n=6), number of awakenings (n=5), sleep latency and wake after sleep onset (n=3), and sleep efficiency (n=1). The direction of association, however, was not consistent. Some subjects exhibited poorer sleep while others exhibited improved sleep with increased daily exercise.

Conclusions: Our results are strengthened by the long-term prospective design in a natural context. We found that exercise had no direct effect on sleep continuity for most subjects (67%), a positive effect on sleep for some (19%) and a negative effect for others (14%). We did not have subjects record the time of day of exercise and this parameter may have been critical in the variability. The pattern of our results shed light on why so many of the results in this area have been mixed. As suggested recently by Youngstedt et al.,[3] future research within this domain might benefit by fine tuning identification of groups most likely to show sleep continuity changes given long-term exercise interventions. One such group might be individuals with insomnia.

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1690.I

Three Year-Follow Up in Medical Residents with Excessive Daytime Sleepiness

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Introduction: The evaluation of the excessive daytime sleepiness (EDS) by Epworth scale[1] has been sufficiently spread out and some studies demonstrated having oscillations of sleepiness degree between different populations, being important the related factors as age, gender, environment and country, impairing the concentration capability due to sleep deprivation [2] . Medical residents are exposed to a great work load, also on call duties each 72 hours at the first training year with a gradual reduction of shifts over the years. We have applied the Epworth scale in order to evaluate this same population of residents during the three years of training.

Methods: The Epworth scale[1] was applied to identify individuals with EDS (Score Sum > = than 10 points). The questionnaires were applied in the same population of residents (R1 in 1997, R2 in 1998 and R3 in 1999). The data had been stored and compared.

Table 1

Year	Population follow-up					
1997 (R1)	***Total pop.***	*Male*	53 (62,35%)	**EDS pop.**	*Male*	29 (64,44%)
		Female	32 (37,65%)		*Female*	13 (35,56%)
		Total	85		***Total***	42
1998 (R2)	***Total pop.***	*Male*	28 (42,42%)	**EDS pop.**	*Male*	12 (40,00%)
		Female	38 (57,58%)		*Female*	18 (60,00%)
		Total	66		***Total***	30
1999 (R3)	***Total pop.***	*Male*	25 (60,97%)	**EDS pop.**	*Male*	12 (66,67%)
		Female	16 (39,03%)		*Female*	06 (33,33%)
		Total	41		***Total***	18

Results: 1997: 49,41% of the studied group presented EDS (it props up >=10), with general average of 9.55 points and DP=4,21; (population in

the first year of residence) 1998: 45,45% of the same group presented EDS (average generality of 9.68 points and DP=2,12); (population in the second year of residence) 1999: 43,90% of these individuals presented EDS (average generality of 9.46 points and DP = 4.39). (population in the third year of residence). In this population, the specialties that had gotten scores characterizing EDS (greater or equal 10 points) were: Gynecology-Obstetrics, Anesthesiology, Orthopedics, General Surgery, Hematology, Gastroenterology, Pediatrics and Otolaryngology.

Conclusions: Medical residents have a decreasing tendency to somnolence over the years of training. These results are due at least in part because of decreasing night shifts number with time. The high score in third year residents deserve mention because they have few night shifts and high somnolence. We are tempted to explain this discrepancy by the pressure of external medical activity beyond the training schedules.

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1036.I

Sleepiness Measured by Epworth Scale and Everyday Life Risk of Accidents

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Introduction: The Epworth Sleepiness scale (ESS) provides a measure of daytime sleepiness based on the self-rating of the average sleep tendency in eight real life situations.[1] The original character of the scale makes conceivable that it may be a particularly suitable tool in predicting the impact of somnolence on daily routine activities. Some literature data suggest a positive relationship between car crashes liability and ESS score.[2] Our study aims to evaluate whether an ESS score over 10 is predictive of an increased risk of problems and/or accidents at work and driving in a series of young Italian workers.

Methods: 13 consecutive subjects working in the industrial or tertiary sector of Pavia and its district. Only 4% of the subjects were shift-workers. 365 were men, 248 women. Their ages ranged from 18 to 25 years and their education from 8 to 17 years. 488 subjects were car drivers.PROCEDURE: each subject completed an Italian version of the ESS and a multiple choice questionnaire aimed at exploring the physical health status,life style,sleep habits and disorders,the occurrence of problems or accidents at work and driving in the past six months. We evaluated the relationships between an ESS score over 10 and the occurrence of 1) drops in efficiency at work 2) work accidents 3) problems at the wheel 4) daytime car crashes, all due to somnolence in the subject's opinion. The chi square test was used for the analysis when applicable.

Results: Problems at work or work accidents due to somnolence were reported by 5.2% and 1.4% of the subjects respectively. Problems at the wheel or car crashes due to somnolence were reported by 4.8% and 1% of the car drivers respectively.The mean ESS score for the entire case series was 4.3, range 0-19. Thirty-six out of the 613 subjects (6%) had an ESS score over 10 (mean value 12.8, s.d. 2.1, range 11-19).The rate of drops in efficiency at work and work accidents was higher in subjects with ESS >10 than in the others (30.5% versus 18.5%, $p<0.05$; 2.8% versus 1.4%).As far as the subgroup of car drivers was concerned the rate of problems at the wheel and car crashes was higher in the subjects with ESS >10 than in the others (50% versus 20%, $p<0,001$); 3.3% versus 0.9%).

Conclusions: The data show that subjects with an ESS score > 10 are more at risk of somnolence-related problems or accidents at work and driving than those with ESS score <10. If replicated in bigger samples of subjects this data would reinforce the present suggestion that an ESS score > 10 indicates a degree of daytime somnolence which adversely affect daylife activities and is potencially harmful for people's safety.

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1380.I

Sleep Patterns During the Pre-Menopausal Years

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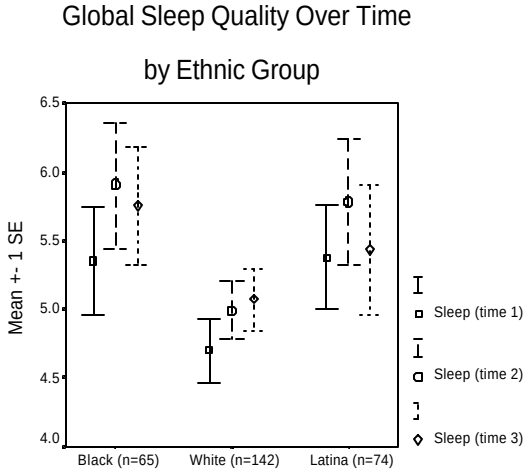
Introduction: Women's sleep patterns during the menopausal years can be disrupted by many factors, including hormonal fluctuations, family dynamics, stressful lifestyles, and chronic health problems. The results presented here are part of a larger, ongoing longitudinal study to examine changes in sleep as healthy women transition from pre-menopause to post-menopause. The purpose of this particular analysis was to describe the stable sleep patterns of women in the decade prior to cessation of menstruation, and investigate lifestyle factors that may influence their sleep patterns prior to the onset of menopause.

Methods: This study prospectively describes sleep over a five year period before and during menopause. A community-based sample of 346 healthy, regularly menstruating women 40-48 yrs old began the study in 1996. The sample consists of European American, Mexican American, and African American women living in the U.S. for at least 20 yrs. Among the many health indicators in the study, the Pittsburgh Sleep Quality Index (PSQI) assesses subjective sleep at 6-month intervals. Results for pre-menopausal women during their first year (3 time points) are reported here and excludes any subject with irregular menstrual cycles or elevated FSH levels that would indicate cessation of ovarian function.

Figure 1



Results: The mean age for the 268 pre-menopausal women was 43.5 + 2.4 yrs at the initial occasion. Global sleep quality as rated on the PSQI, is depicted by time and ethnic group in Figure 1. The mean was 5.0+3.04

at time 1( ), 5.4+3.3 at time 2 (O), and 5.3+3.35 at time 3 ( ). There is a relationship between PSQI scores at time 1 and time 2 (r=.54) and time 1 and time 3 (r= .57). Although the European Americans appear to sleep better than the other two groups, there was no significant ethnic difference. There were, however, ethnic differences in physical activity and dietary measures that may explain PSQI scores. There was a significant relationship between PSQI scores and body mass index (BMI) at time 1 ($r=.21$, $p < .001$), but not other dietary indicators such as hemoglobin or intake of vitamins, minerals, calories, proteins, or carbohydrates. There was no relationship between PSQI scores and paid employment, child care responsibility, nocturia, or hot flashes. There was an inverse correlation between PSQI scores and feeling supported in personal relationships ($r = - .26$, $p < .001$) and a strong correlation between PSQI scores and depression scores on the CES-D ($r = .63$, $p < .001$). Those who currently smoked cigarettes (n=96, 22%), also scored significantly ($t=2.6$, $p =.01$) higher on the PSQI (5.7+3.1) that those who were not currently smoking (4.75+2.6).

Conclusions: While it may appear that sleep is worse for women of color compared to Caucasians, lifestyle factors, such as smoking, inactivity, and obesity play a larger role in complaints of disturbed sleep than children or employment. As women enter midlife, these lifestyle factors, as well as depression and lack of supportive relationships, influence their sleep quality more so than age, physical symptoms, nutritional intake, or menopausal status.

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1059.I

Potential Sleep Disorders in a Welfare-to-Work Population

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Introduction: Sleep disorders can have devastating effects on an individual's ability to function, and the cumulative loss to society is large. This retrospective, cross-sectional analysis estimates sleep disorder prevalence among a small group of welfare recipients.

Methods: Welfare recipients self-administered a sleep questionnaire (TQAS, "Twenty Questions About Your Sleep") and the Epworth Sleepiness Scale (ESS) as part of a routine intake evaluation of a "welfare-to-work" program in Tucumcari, NM. Results were obtained from 22 consecutive participants; 14 females and 8 males. Subjects averaged 31 years of age (range of 19-56 years of age). The TQAS contains simple "yes/no" questions skewed to screen for sleep disorders of a severe nature. Every "yes" response endorses a high frequency (e.g. breathing difficulties "most nights") or severity (e.g. "very" sleepy) of symptoms. Results were used to predict the presence of six sleep disorders. Excessive daytime sleepiness (EDS) was presumed present if daytime function was "frequently" affected by fatigue or sleepiness, or scored 10 or higher on the ESS. Sleep-onset insomnia was present if they took "longer than 30 minutes to fall asleep" on "most nights." Sleep-maintenance insomnia was present if both frequent awakenings and difficulty returning to sleep occurred. Sleep-related breathing disorder (SRBD) was present if they snored loudly and either avoided sleeping on their back or had frequent nocturnal breathing difficulties. Periodic limb movements of sleep (PLMS) was present in subjects often awakened by "LEG JERKS or TWITCHES". Restless legs syndrome (RLS) was combined with PLMS information. Nightmare disorder was present if they indicated weekly presence of "BAD DREAMS or NIGHTMARES".

Results: On average, each welfare recipient had 1.5 sleep disorders (32 disorders/22 recipients). A sleep disorder was considered present in most (13/22) of the subjects. The breakdown for each of the sleep disorders considered is outlined in Table 1. ESS score average was 6.4. Of the seven welfare recipients with EDS, five had ESS scores of 10 or higher and four qualified based on their questionnaire responses. These seven subjects also had most (13/25) of the remaining sleep disorders. Another three subjects were "very SLEEPY or very TIRED" during the day but did not qualify for EDS. Additionally, more than half of all recipients (12/22) had some risk for SRBD. All three subjects with RLS also had PLMS. Among the nine subjects with no apparent sleep disorder were the three recipients with the highest reported caffeine intake.

Table 1. Number (%) of Patients with Disorders

Sleep Disorder	Number (Percentage) of Patients effected
Excessive Daytime Sleepiness	7 (32)
Sleep-Onset Insomnia	5 (23)
Sleep-Maintenance Insomnia	6 (27)
Sleep-Related Breathing Disorder	5 (23)
Periodic Limb Movements of Sleep	4 (18)
Nightmare Disorder	5 (23)

Conclusions: In this small sample of participants in a welfare-to-work program, severe sleep disturbances were commonly reported. Despite the limitations of the study, we speculate that a sizeable proportion of the welfare population suffers from sleep disorders that may be affecting their ability to work. If this proves accurate, then conceivably, sleep disorders may be one of the prime factors influencing a person's successful transition from welfare to work. Further study is urgently needed to determine the prevalence of sleep disorders in the welfare population, and to assess their response to conventional treatments.

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1060.I

Sleep Behaviors and Symptoms in Acutely Traumatized Individuals

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Introduction: Acutely traumatized individuals may develop Acute Stress Disorder (ASD) followed by posttraumatic stress disorder (PTSD). Symptoms of intrusion, avoidance and arousal are observed in both disorders, but ASD manifests with more dissociative phenomenon, such as numbing and amnesia. Sleep complaints are common in both disorders and "difficulty falling or staying asleep" has been incorporated into each nosology. Recent research in PTSD patients suggests that this "insomnia" may actually be a more complex disorder that involves sleep-disordered breathing (SDB) or other sleep disorders. However, due to heightened avoidance behavior, acute trauma survivors are often reluctant to seek professional help soon after an event; therefore, little is known about their sleep problems. The current study evaluated sleep symptoms and behaviors in acutely traumatized individuals.

Methods: Fifteen females were enrolled in a program to treat acute nightmares. All suffered trauma within the past three months: sexual assault (11); physical assault (1); kidnapping (1); robbery (1); and, gunshot (1). Twelve met diagnostic criteria for ASD and all suffered PTSD (notwithstanding criteria for symptom duration > 3 months). Self-reported information was obtained from Pittsburgh Sleep Quality Index and Wisconsin Cohort Sleep Survey. Snoring was assessed dichotomously. Other percentages of symptom reports reflect frequencies of "often" or "very often." Excessive motor activity in bed ("often" or "very often") was noted by bed partner complaints of kicking or other disruptive

movements, and by patient report of "restless legs and bothersome twitches." Caffeinated drinks included coffee, tea, soda and cocoa.

Results: Mean age was 33, mean BMI was 24, and 60% snored. Moderate to severe insomnia was present in 14 participants (Table 1). Overall, sleep disorders data indicated very poor sleep quality; and, nearly half the sample reported symptoms suggestive of either SDB (AM Headaches) or restless legs and periodic limb movements. Sleepiness was even more common, and among caffeine users (n=13*), average consumption was excessive.

Table 1. Sleep in Acute Trauma Survivors

Insomnia Behaviors & Symptoms		
Mean (SD) sleep latency (minutes)	80.50 (80.90)	
Mean (SD) total sleep time (hours)	5.80 (2.20)	
Sleep onset complaints		80%
Sleep maintenance complaints		80%
Sleep Disorders Behaviors & Symptoms		
Non-restorative sleep		93%
Bed partner kicked		40%
Restless legs & twitches		47%
Morning headache		40%
Sleepiness Behaviors & Symptoms		
Excessive daytime sleepiness		73%
Caffeine & stimulant use		60%
Mean (SD) Caffeinated drinks/day*	6.38 (0.96)	

Conclusions: Sleep disturbance was common in these acutely traumatized individuals. Although both acute and chronic stress disorders routinely describe insomnia as secondary to a stress response, the findings from this research indicate that other sleep disorders may be an overlooked factor that exacerbates the condition. Many of these patients suffer from sufficient symptoms to potentially benefit from a sleep specialist evaluation. However, it is unknown whether these symptoms persist beyond the acute phase. Conversely, it seems unlikely that all these symptoms would develop acutely. For example, caffeine consumption might be chronic, and if so, strongly suggests severe underlying sleepiness. While severe sleep deprivation following acute trauma might account for many of these symptoms, research is needed to monitor these behaviors and symptoms longitudinally and to assess the prevalence of other sleep disorders.

Research supported by Frost Foundation, New Mexico Crime Reparations Commission (Violence Against Women Act), UNM Research Allocation Committee

1081.I

Diagnostic problems of insufficient sleep syndrome in Japan

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Introduction: Chronic sleep deprivation is very common in Japan due to long working hours and commuting time, and excessive daytime sleepiness (EDS) is considered nothing extraordinary or unrecognized. Objective quantification of sleepiness, therefore, is sometimes essential for the diagnostic procedure for EDS, while multiple sleep latency test (MSLT) is routinely available in very few places in Japan. We will present three cases with the diagnosis of probable insufficient sleep syndrome (ISS), analyzing various diagnostic problems that we encountered in the process of evaluating them.

Methods: Three patients (all women, Patient 1, 2, and 3; 22, 25 and 26 yrs) with a complaint of a sudden doze were studied. The Epworth Sleepiness Scale (ESS) was scored 10, 13 and 13, respectively. Though Patient 1 was pointed out frequent sleep attacks by her friends, she denied excessive sleepiness. Patient 2 described her sleepiness as the same extent to her colleagues, but she admitted dozing off during her work, decorating a cake in a confectionery. Patient 3 said she often found herself driving to the wrong side, and wondered why. Patients 1 and 2 consulted several hospitals before coming to us, but no investigation had been made. A review of their sleep history indicated no problem of sleep-wake schedule or drug/alcohol abuse, no witnessed snoring or apnea, or no cataplexy. Physical, neurological, and psychiatric examination reveled no abnormality. All the patients were instructed to keep sleep/wake logs for more than one months, and all-night polysomnography(PSG) and multiple sleep latency test (MSLT) were performed.

Results: Sleep/wake logs showed that the average total sleep time of Patients 1 and 2 was 6-7 hours, and 4-5 hours in Patient 3. Patient 3 tended to sleep much longer on weekends, but Patients 1 and 2 did not do it as Patient 1 had regular training sessions of sailing on weekends from 6 a.m. to 11 p.m. and Patient 2 had to work on most of the weekends. The results of PSG and MSLT are summarized in Tables 1 and 2. No apneas, hypopneas, or periodic leg movements were observed in the PSG recordings of three patients, and no sleep onset REM sleep period occurred during MSLT.

Table 1. Sleep parameters of three patients

	Pt. 1	Pt. 2	Pt. 3
Total sleep time (min)	470.0	464.0	443.0
Sleep efficiency (%)	93.2	92.3	98.4
% Stage 1	11.2	8.0	9.0
% Stage 2	40.2	48.7	66.5
% Stage 3+4	27.4	13.7	1.4
% Stage REM 21.2	28.6	23.1	
Sleep latency (min)	5.0	12.5	2.0
REM latency (min)	75.0	61.0	53.5
No. of REM periods	6	4	5
Arousal index(/h)	6.7	6.0	6.4

Table 2. MSLT results

Patient 1		Patient 2		Patient 3	
nap time	sleep latency (min)	nap time	sleep latency (min)	nap time	sleep latency (min)
11:00	9.3	9:30	20.0	9:00	3.5
13:00	11.7	11:30	6.7	11:00	11.0
15:00	9.0	13:30	5.1	13:00	3.0
17:00	10.0	15:30	4.3	15:00	3.0
mean	7.8	mean	9.0	mean	4.1

Conclusions: We presented three cases with probable ISS, and through its diagnostic process we encountered various problems which are specific to Japan. As sleepiness can be easily unrecognized when it is chronic, it is often difficult to evaluate sleepiness simply based on subjects' reports. It is difficult to assess it objectively because MSLT is only available in a few places in Japan. Comprehensive clinical services in sleep medicine are not widely offered in clinical practice. This lack of service hinders clinicians from offering appropriate care. Due to the social pressure that exists in Japan, and the behavior of subjects that is impacted by these pressures, we could not apply the treatment criterion present in the International Classification of Sleep Disorders, despite the positive findings in all other categories.

References:

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1403.I

Self-Reported Nap Behavior in Mid-Life Women in a Home Sleep Study

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Introduction: Insomnia affects approximately one-third of adults in the US, yet the daytime consequences of this sleep disorder are not fully understood. Individuals with insomnia are considered to be 'hyper-aroused' without daytime sleepiness. A recent survey of sleep problems by the National Sleep Foundation and Gallup Organization reported individuals with chronic insomnia napped more often than those with occasional insomnia and no insomnia (Roth & Ancoli-Israel, 1999). Based on this report, we studied the extent of self-reported nap behavior in a sample of mid-life women who participated in a week-long prospective polysomnographic (PSG) home study of sleep.

Methods: Women (mean age 46 /pm 4) with (n = 104) and without (n = 30) insomnia were enrolled for a week-long home study of sleep. All subjects had no history of major medical or mental illnesses and did not take medications for insomnia or depression. Those enrolled were carefully screened for insomnia and control subjects were good sleepers. Subjects' sleep was recorded with a standard montage using a portable SAC (Oxford) system for six consecutive nights in their homes. Subjects completed a diary on each day of the sleep recordings. Subjects were asked questions related to overall health and symptoms, and to rate their sleep quality (very good to very poor) and number of nighttime awakenings. Subjects were requested not to take naps, but if they did, nap start and end times were recorded in the diary, with a maximum of two naps/day.

Table 1. Number of naps and nap duration by study day and season

Study Day	Summer		Winter	
	n	Nap Duration	n	Nap Duration
Day2	12	47.9 ± 31.8	6	37.5 ± 29.1
Day3	15	40.4 ± 34.8	5	39.0 ± 30.5
Day4	17	63.1 ± 61.6	9	68.9 ± 52.8
Day5	12	73.8 ± 40.7	16	72.1 ± 64.2
Day6	15	72.5 ± 49.3	7	73.0 ± 55.6
Total	71	60.6 ± 40.9	43	59.1± 47.0

Table 2. Frequency of napping per person by sleep efficiency

Sleep efficiency	Nap Frequency = 1	Nap Frequency > 1
[3] 85 %	19	20
<85 %	12	10

Results: Sixty-three or 47% of the women napped and a majority (80%) of them napped once or twice. Among all subjects, nap duration lengthened over the duration of the protocol, with nap duration longer on days 5 & 6 compared to day 3 (See Table I). Most naps (51%) occurred in the afternoon (1201pm to 5pm). More naps were taken in the summer months (March to August) and more women napped in the summer (/chi= 4.1, p=. 04). There were no significant correlations between how rested or alert subjects felt in the morning, or how they rated their sleep quality and whether they napped. The amount of time spent in each sleep stage (averaged over at least 3 nights of the study) was not significantly different between women who napped and didn't nap. Of the subjects with self-reported insomnia, 74% napped at least once during the study. The nap group was divided by sleep efficiency into two sub-groups (< 85% for the insomnia group, n = 22; geq 85% for the no insomnia group, n = 39). More subjects without PSG insomnia napped (see Table II). However, there were no statistically significant differences in the number of naps taken by each subject by PSG insomnia (/chi=. 2, p=. 7).

Conclusions: Despite the request not to nap during this study, a large number of women napped. Women with self-reported insomnia napped most often (corroborates recent survey) but this nap behavior was not related to PSG pattern. Women with insomnia possibly became progressively sleepier as the protocol progressed, perhaps due to the rigors of the protocol.

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Research supported by National Institute for Nursing Research Grants: 5T32NR07039, NR01118, NR04001

1740.I

Epworth Sleepiness Scale Outcome in Three Brazilian Populations

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Introduction: The Epworth sleepines scale (ESS) measures the subjective daytime sleepiness degree. This investigation studies 3 age groups from a sample of healthy Brazilians and determines:1. ESS means and the average reported sleep time (RST). 2. The prevalence of subjects with ESS scores > than 10 points; 3. Correlation of ESS scores and RST.

Methods: ESS was applied to 468 subjects. Three groups were created: Group A (18-39 years); group B (40 to 59 years), and C (60 years old and up). One-way ANOVA was employed for comparisons and Simple Linear Regression for correlation.

Results:

	GROUP A (18-39)	GROUP B (40-59)	GROUP C (60-87)
N	282 (60.3%)	122 (26.1%)	64 (13.7%)
ESS > 10	32.6%	24.6%	20.3%
AVERAGES			
AGE	28.33 ± 5.58	48.01 ± 5.73	67.97 ± 6.33
ESS	8.62 ± 3.69(1,2)	7.01 ± 4.36(1)	7.45 ± 5.04(2)
RST	6.91 ± 1.11	6.80 ± 1.30	6.98 ± 1.32

	MALE	FEMALE	MALE
N	110 (39.0%)	171 (60.6%)	56 (45.9%)
	FEMALE	MALE	FEMALE
	65 (53.3%)	17 (26.6%)	46 (71.9%)
	MALE	FEMALE	MALE
ESS > 10	34.5%	31.6%	37.5%
	FEMALE	MALE	FEMALE
	12.3%	29.4%	17.4%

AVERAGES

	MALE	FEMALE	MALE
AGE	28.96± 5.35	27.87± 5.66	46.27 ± 5.10
	FEMALE	MALE	FEMALE
	49.46 ± 5.90	67.65 ± 6.53	68.24 ± 6.30
	MALE	FEMALE	MALE
ESS	8.50 ± 3.66	8.68 ± 3.73 (3) (5)	8.21 ± 4.39 (4)
	FEMALE	MALE	FEMALE
	5.87 ± 3.97 (3) (4)	7.18 ± 4.04	7.54 ± 5.44 (5)
	MALE	FEMALE	MALE
RST	6.75 ± 0.99 (6)	7.02 ± 1.16 (6)	6.78 ± 1.19
	FEMALE	MALE	FEMALE
	6.86 ± 1.40	6.61 ± 1.32	7.10 ± 1.31

N: Total of subjects; ESS: Epworth Sleepiness Scale; RST: Reported Sleep Time. (1) p<0.0001; (2) p<0.01; (3) p<0.0001; (4) p<0.01; (5) p=0.01; (6) p<0.05 There was no correlation between RST and ESS scores (Pearson's r^2=0.01).

Conclusions: Group A presents significantly elevated ESS scores (with a non-significant RST difference) and a higher ESS>10 prevalence when compared with groups B, C and other populations, thus confirming increased ESS-measured degree of sleepiness in this age group.[1,2] This difference is due to lower ESS average scores in group B and C females. The significantly higher ESS score and ESS>10 prevalence in group B men versus women (despite similar RST averages) might be due to higher prevalence of sleep-related breathing disorders males and insomnia in females.

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1408.I

Simultaneous and Retrospective Judgements of Impairment During Simulated Driving

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Introduction: Arnedt et al. (1999) have recently shown that the magnitude of impairments on measures of vehicle control on a simulated driving task following 24 hours of prolonged wakefulness and at a blood alcohol of 0.08% are, in many respects, similar. In addition to the actual driving impairments, it is important to consider the perceived levels of impairment that may influence a driver's decision to operate a motor vehicle under these conditions. In this study, the relationship between ratings of impairment and actual decrements in simulated driving performance during prolonged wakefulness, both with and without alcohol, is examined.

Methods: Twenty-two healthy males (mean age = 21.7 years; SD = 3.0) drove for thirty minutes on a simulated driving task under conditions determined by the factorial combination of 16 and 20 hours of wakefulness and blood alcohol concentrations (BAC) of 0.00% and 0.08%. For each condition, subjects consumed a beverage containing either only tonic water and ice or tonic water and ice mixed with 100% ethyl alcohol. While driving, subjects made simultaneous self-assessments of their impairment by toggling between a green and a red button, located on the steering wheel of the simulated car, to indicate "alert enough to drive safely" and "too impaired to drive safely", respectively. At the conclusion of each session, subjects also retrospectively rated their overall driving performance on a scale from 0 - 100, with 100 representing optimal driving performance. The percent of time spent driving within a "safe zone" was computed provided subjects were traveling over 60 km/h. This was defined as maintaining a lane position within 0.914 metres (3 feet) of the centre of the right lane and a speed within 20 km/h of the posted speed limit.

Results: During the driving task, the percent of time that subjects rated themselves as "too impaired to drive safely" was higher following both prolonged wakefulness (F[1,20]=28.47, p<0.0005) and alcohol consumption (F[1,20]=14.40, p=0.001), with no significant interaction. Ratings did not differ significantly whether subjects were inside or outside of the "safe zone". Subjects also retrospectively rated their driving performance as impaired following prolonged wakefulness (F[1,20] = 26.39, p<.001) and alcohol consumption (F[1,20] = 35.77, p<.001), with no significant interaction. Table 1 shows the Pearson product moment correlations between these retrospective ratings and the percentage of time subjects spent driving outside of the "safe zone".

Table 1

Condition	% time outside "safe zone"	Retrospective rating	Pearson *r*
16 hours wake/0.00% BAC	20.2	81.6	-0.42*
20 hours wake/0.00% BAC	25.5	61.6	-0.66**
16 hours wake/0.08% BAC	38.4	48.0	-0.54*
20 hours wake/0.08% BAC	43.2	35.0	-0.28

*p<.05; **p=.001

Conclusions: There was a modest association between perceived and actual impairments in driving performance except when prolonged wakefulness and alcohol were combined. These findings, coupled with previous results (Arnedt & MacLean 1999), suggest that not only is driving performance worse when prolonged wakefulness and alcohol are combined but, perhaps of more concern, the ability of subjects to recognize their impairment is severely compromised.

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1760.I

Stimulus Sequence Effects on Reaction Time and the P300 during Drowsiness

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Introduction: Cognitive processing requires the brain to respond both to the immediate features and the context in which a stimulus is presented. During wake, the repetition of stimuli identified as targets (e.g., AA) produces an automatic expectancy that the next stimulus will also be a target (AAA). On the other hand, stimulus alternations (AB) or the presence of non-targets (BB) creates an automatic expectancy that a target is less likely to occur.[1] For this reason, when a target follows several non-

targets (BBA) there is a violation of expectancy that results in slowed behavioral responding and an increase in cortical responses related to surprise (such as a larger P300).[2] This study was designed to measure the neurobehavioral effects of arousal-state on automatic expectancy formation resulting from stimulus sequences.

Methods: Eleven university students (M=19yr) had EEG and reaction times (RTs) recorded as they listened to a continuous stream of equiprobable, randomly alternating high and low tones (4000 and 1000 Hz respectively) presented at 65 dB through earphones. Subjects were recorded during a 1.5 hour afternoon session, when they actively attended to targets, and a 2-4 hour evening session when they lay awake in bed, became drowsy, and then fell asleep. Responses were evaluated according to on sequence length (2-item = BA or AA; 3-item = AAA, BAA, ABA, and BBA) and by comparing sequences that fulfilled the automatic expectancy that a target would occur (AAA) versus sequences in which the target tone was relatively unexpected (BBA). The difference in reaction times between highly expected versus unexpected sequence endings were entered into a sequence-length (short versus medium) x arousal-state (attentive, wake, drowsy) ANOVA. Arousal-state related changes in the P300 were measured by entering the mean EEG voltages from the 150-300 msec post-stimulus time window into a sequence (AAA, BAA, BBA) x electrode site (Fz, Cz, Pz) ANOVA for each arousal state.

Figure 1. Mean RT (in msec with S.E.) difference between high and low expectancy sequences in each arousal state for 3-item (medium) and 2-item (short) sequence

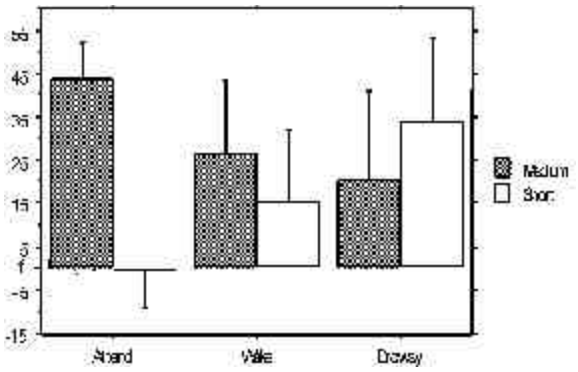
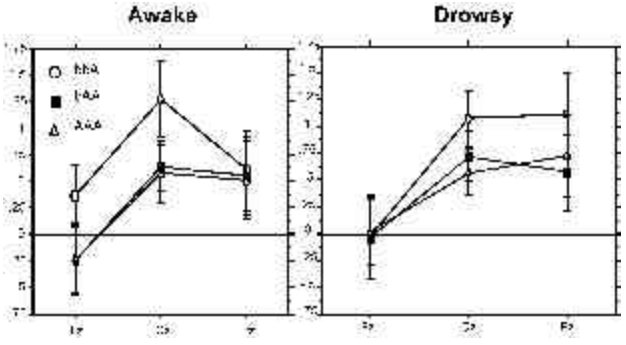


Figure 2. Figure 2. Mean voltage (uV with S.E.) for the three midline electrodes in response to BBA, BAA, and AAA sequences.



Results: Figure 1 illustrates the RT differences between high and low expectancy targets in each arousal state for both medium and short sequences across which a significant arousal-state by sequence-length interaction ($F(2,20)= 4.01$, $p=0.034$) was found. Figure 2 illustrates the mean P300 voltages in each of the midline electrodes in response to sequences BBA, BAA, and AAA during attentive wakefulness and drowsiness. The sequence x electrode site ANOVA during attentive wakefulness showed a main effect of sequence ($F(2, 20)=9.14$, $p=0.0015$) and a significant sequence by electrode site interaction ($F(4, 40)=3.66$, $p=0.012$). Drowsiness resulted in a significant main effect of sequence ($F(2, 20)=3.64$, $p=0.045$) but a non-significant interaction. Post-hoc analysis of the P300 data during drowsiness did find a significant contrast of means for site Pz ($F(1)=4.03$, $p=0.037$) and a trend at site CZ. Topographically, targets presented during attentive wakefulness produced a larger P300 at site FZ in response to expectancy violations, while in drowsiness expectancy violations caused a larger P300 response at site PZ.

Conclusions: These results suggest that drowsiness alters automatic expectancy formation by reducing the brain's ability to maintain the duration over which expectancies can be held. Furthermore, cortical responses to unexpected tones in drowsiness appear to arise from locations that are functionally distinct from the brain areas recruited to respond to sequence alterations during attentive wakefulness.

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1435.I

Paradoxical First Night Effect in the Clinical Sleep Laboratory: A Diagnostic Marker for an Environmental Sleep Disorder

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Introduction: First Night Effect (FNE) is the tendency for patients and research subjects to sleep worse than usual during the first night of laboratory sleep compared to subsequent nights.[1] FNE is manifested in longer sleep latencies, more frequent awakenings and lower sleep efficiency. Occasionally, patients report sleeping better than usual on the first sleep laboratory night. A paradoxical or reverse FNE is a well-known diagnostic sign of pychophysiological insomnia.[2] However, a paradoxical FNE (PFNE)has also been reported in almost 20% of a large group of clinical sleep patients without pychophysiological insomnia.[3] A review of the AM sleep questionnaires of these patients suggested that many attributed their PFNE to the better sleeping environment of the sleep laboratory compared to their home bedrooms. This study examined the question of whether paradoxical FNEs in clinical sleep patients could be a sign of an environmental sleep disorder.

Methods: Based on the results of the initial FNE study,[1] the AM questionnaire was revised to include a list of 10 environmental factors that patients were asked to compare to their usual sleeping environment. Polysomnographic data and the revised AM questionnaires for 1,338 consecutive patients admitted to the sleep laboratory for an initial diagnostic polysomnogram in 1997-1998 were examined retrospectively. None of the patients had undergone a previous study. A review of the AM questionnaire data determined that 182 patients (13.5%) of this group had reported on the morning after their sleep study sleeping "better" or "much better" than usual or had reported awakening feeling "more alert" or "much more alert" than usual. Of these 182, the AM

questionaires of 140 (60 females, 80 males, mean age 45 SD 22)were examined. Each AM questionnaire was then further examined to determine what factors the patient identified as resulting in improved quality of sleep or improved AM alertness in the sleep laboratory

Results: All but 8 of the 140 patients had an RDI >5 and a final primary diagnosis of obstructive sleep apnea. Mean RDI for the group was 35.6 SD 38.8/hr. of sleep. None had signs or symptoms of psychophysiological insomnia. Table 1 shows the results of the AM questionnaire review. 84 of the 140 patients (60%)identified 1-6 environmental factors as prime reasons for their "better sleep" or "increased alertness". Patients cited 15 different environmental factors as contributing to their good sleep in the sleep laboratory and bad sleep at home. Most frequently cited factors were the absence of noise (51%) and presence of darkness (25%)in the sleep laboratory compared to their home bedroom.

Table 1. Environmental Factors Cited By Patients As Contributing to Reports of Better Sleep in the Sleep Laboratory Compared to Home

Environmental Factors	# Pats.	% Reporting
Quiet	43	51.2%
Darkness	21	25.0%
Mattress	17	20.2%
Bed	14	16.7%
Temperature	13	15.7%
Pillow	10	11.9%
No Spouse	10	11.9%
Linen	9	10.7%
No Children	8	9.5%
Technician	8	9.5%
Body Position	7	8.3%
Security	4	4.8%
Sleep Room	4	4.8%
No Pets	3	3.6%
Food	1	1.2%

Conclusions: Many patients without signs or symptoms of psychophysiolgical insomnia report paradoxical or reverse FNE. Patients in this group with a primary diagnosis of obstructive sleep apnea reported that they slept better than usual or awakened feeling more alert than usual during an initial diagnostic sleep study and frequently cited environmental factors. Among the leading factors cited were that the sleep laboratory was quieter, darker and safer than their home bedroom. Reports of better sleep or improved AM alertness following the initial diagnostic sleep study may have diagnostic importance and suggests the possibility of a co-existing or primary environmental sleep disorder.

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(1) Agnew HW, Webb WB, Williams RL. The first night effect: An EEG study of sleep. Psychophyiology 1966 2(3): 263-266

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1129.I

Sleep of Trainee Anaesthetists Across a Two-Week Roster

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Introduction: Laboratory studies show that chronic sleep restriction causes cumulative degradation of alertness and performance (e.g. Dinges, 19981). A recent national survey of New Zealand anaesthetists[2] found that 32% recalled making a fatigue-related error in clinical practice in the preceding 6 months. To investigate these issues further, the present study monitored the sleep and performance of 28 New Zealand anaesthesia residents across a two-week work cycle.

Methods: Sleep was monitored using logbooks and actigraphy. Two different roster cycles were studied. The first included 11 consecutive 12 h shifts (4 day shifts followed by 7 night shifts; N = 12). The second included 4 x 10 h night shifts, 3 days off, and 5 x 9 hr day shifts (N = 16). To estimate individual baseline sleep requirements (BSR), total sleep per 24 hours was averaged for a combination of days off and day shifts. Comparisons between day and night shift sleep durations were made using the Wilcoxon W test.

Results: The average BSR was 7.7 h. Sleep episodes associated with night shifts were shorter than those associated with day shifts (median 7.25 vs 5.07 h, $p < .001$). However, multiple sleep episodes were more commonly associated with night shifts (median 1.4 vs 1.0, $p < .001$). As Figure 1 illustrates, trainees were often able to obtain some sleep during the night shift, depending on workload. Thus, overall, total sleep durations on night shifts fluctuated widely. Nevertheless, 23% of night shifts were associated with an acute sleep loss of 2 or more hours. The highest cumulative sleep debt observed in the study occurred at the end of the 7 consecutive 12 h night shifts.

Figure 1. Percentage of resident anaesthetists asleep across the 24-h day when working day shifts

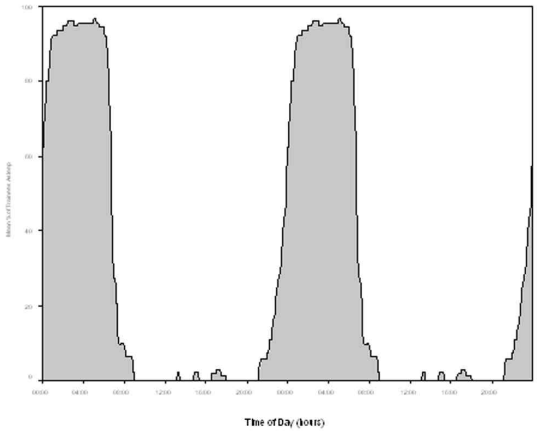
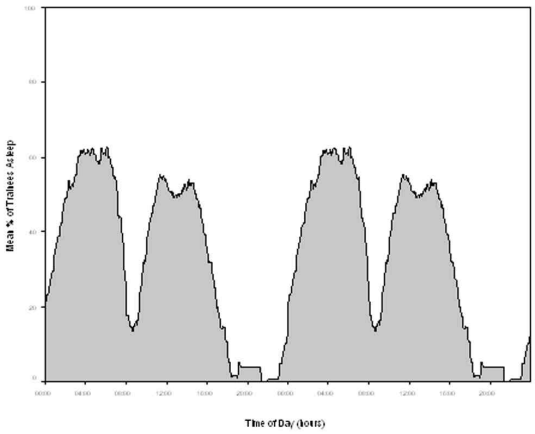


Figure 2. Percentage of resident anaesthetists asleep across the 24-h day when working night shifts.



Conclusions: Acute sleep loss was more likely to be associated with night shifts than day shifts. On a quarter of night shifts, resident anaes-

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thetists were functioning with at least 2 h sleep loss, a level associated with increased sleepiness and performance decrements1. As expected, the shift pattern with the longer night shifts resulted in the largest cumulative sleep debt. The effects of this level of sleep loss on performance capacity are explored in a companion abstract.

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(1) Dinges D, Pack F, Williams K, Gillen K, Powell J, Ott G, et al: Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4-5 hours per night. Sleep 1997; 20(4): 267-277.
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1130.I

Time-on-Duty and Time-of-Day: Effects on Optimal Reaction Times

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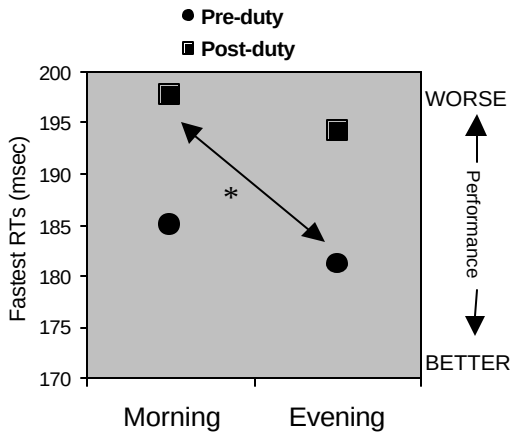
Introduction: Various work characteristics, such as work duration and the number and the type of shifts worked, may influence performance. This abstract focuses on trainee anaesthetists from 2 hospitals where different shift durations and sequences were worked, and compares their optimal response times (fastest 10% of responses) on a 10-minute visual reaction time task (PVT).

Methods: PVT tests were performed by anaesthetists at the beginning and end of shifts during a two week work cycle which incorporated sequences of both night and day shifts. In order to examine the influence of time-of-day on pre- and post-duty performance, data obtained at shift changeover times (0600 – 0900 h and 1700 – 2200 h) were included in unbalanced mixed model ANOVAs, with individuals included as a random factor. In order to examine any additional effects of longer duty periods, data from the 2 hospitals were compared using mixed model ANOVAs with terms variously included for: work location, pre/post-duty, shift type, shift sequence, and their interactions.

Figure 1. Fastest Reaction Times: Least Squares Means for morning and evening, and pre- and post-duty performance comparisons (significant difference indicated).



Results: Examination of simple effects, after multiple comparisons adjustment, found reaction times were significantly faster in tests done at the beginning of night shifts than in tests done at the end of night shifts ($t(39.7) = -2.96$, $p < .01$, Figure 1). Between hospital comparisons indicated that this effect was only significant at the hospital that had longer night shifts (12 h vs 10 h). The significant interaction and simple effects are summarised in Table 1.

Table 1. Significant simple effects from ANOVAs. Times of better performance are underlined.

	F	*p*
Location* Pre/post-duty*Shift type	4.41 (1, 34.2)	.043
Prenight vs Postnight	30.80 (1, 28.4)	.0001
Postday vs Postnight	8.24 (1, 58.9)	.0057
Preday vs Postnight	12.47 (1, 70.7)	.0007

Conclusions: Taken together, these analyses suggest that reaction time may be affected by an interaction between prior work duration and time-of-day. A similar finding was reported by Hildebrandt et al[1] for vigilance lapses among locomotive engineers. The present data were also collected in the workplace, during a roster cycle that was not modified for the purposes of the study. Thus, the effects identified were sufficiently strong to be evident in the face of all the other factors that affect real workplace performance such as the amount of prior sleep and shift sequence effects. These are explored in a companion abstract.

References:
(1) Hildebrandt G, Rohmert W, Rutenfraz J: 12 & 24 h Rhythms in error frequency of locomotive drivers and the influence of tiredness. International Journal of Chronobiology 1974; 2:175-180.

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1144.I

Relationship of Objective Measures of Daytime Somnolence and Alertness with a Continuous Performance Test

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Introduction: Previous reports[1,2] have failed to exhibit a relationship between conventional variables of sleep architecture and objective measures of daytime sleepiness and alertness. The goal of the present study was to evaluate the interrelationships among these objective parameters of daytime sleepiness and alertness versus performance on a test of attention. We evaluated the performance of subjects on the Continuous Performance Test (CPT), a measure of sustained attention, by examining both errors of omission (i.e. failing to respond to target) and commission (responding to target inappropriately) along with the subjects' reaction time. High errors of omission and/or commission suggest poor task orientation while a slow reaction time coupled to such errors would indicate inattentiveness.

Methods: The data of 10 patients (5 male, 5 female, mean age = 43.7 ± 12.2 years) with reported excessive daytime sleepiness (EDS) was compared with that of 10 age- and gender- matched controls (5 male, 5 female, mean age = 42.2 ± 18.5 years). All subjects underwent 2 overnight sleep studies with the polysomnographic (PSG) recording consisting of: C3 - C4 EEG leads, left and right electrooculogram, chin EMG, nasal and oral airflow, thoracic and abdominal respiratory belts, ECG, and leg EMG. Using SPSS software for windows the following

sleep parameters were compared across all subjects: sleep onset latency, sleep efficiency, total sleep time, REM onset latency, the amount of slow wave sleep (SWS), stage 1 sleep, and REM sleep. The Multiple Sleep Latency Test (MSLT) and Maintenance of Wakefulness Test (MWT) were carried out following overnight sleep studies, each performed at 2-hour intervals starting at 9:00 a.m. according to standard procedures. The three performance variables measured on the CPT included omission errors, commission errors, and hit reaction time.

Results: During the first nocturnal PSG study, normal subjects had significantly lower amount of stage 1 sleep as compared to those patients who were referred to the Sleep Clinic with the complaint of EDS (4.4 ± 2.6 minutes vs. 7.4 ± 3.2 minutes, $p<0.05$). On the second night, control subjects demonstrated significantly shorter sleep onset latency (9.5 ± 9.3 vs. 28.4 ± 19.2, $p<0.05$). Only sleep onset latency and MWT scores correlated significantly in normal subjects (rho = -.69, $p<0.05$). The MSLT scores in normal subjects correlated negatively with errors of commission on the CPT (rho = -.78, $p<0.01$) and positively with hit reaction time (rho = .69, $p<0.05$). In patients with EDS complaints, the MWT correlated significantly with errors of commission (rho = -.70, $p<0.05$). There were no correlations for patients with reported EDS among MSLT scores, performance parameters and preceding night' sleep variables.

Conclusions: Despite patients subjective reports of EDS, the MSLT and MWT failed to demonstrate differences in measured daytime sleepiness and alertness in these patients versus gender- and age- matched controls. However, for normal subjects, those who displayed normal MSLT scores were found to have lower errors of commission on the CPT and a higher hit reaction time. Conversely, in patients with EDS complaints, normative MWT scores were predictive of less commission errors on the CPT.

References:
(1) Huterer N, Salahovic D, Shapiro CM. Does night sleep predict subjective or objective daytime sleepiness? Sleep Research, 1996, 497.
(2) Kayumov L, Huterer N, Shapiro C. Relationship between the MSLT and MWT results and different nocturnal sleep parameters. Sleep Research, 1997, 352.

1152.I

Critical Incident Exposure and Sleep Quality in Police Officers

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Introduction: This study compares subjective sleep quality in active duty police officers with control subjects not involved in police or emergency services. The aim is to examine if police- related critical incident exposure or routine work environment stressors have an effect on different domains of sleep quality.

Methods: The study data are derived from a large survey of active duty police officers in San Jose and Oakland, California and New York City. Subjective sleep disturbances were measured by the Pittsburgh Sleep Quality Index (PSQI) in police officers (day/evening shift N= 429; night shift N= 219) and peer-nominated comparison subjects (day/evening shift N=221; night shift N=66). A PSQI global score of greater than 5, in one study, yields optimal sensitivity and specificity for distinguishing good sleepers from clinical insomnia subjects (Buysse et al., 1989). The main predictor variables include critical incident exposure related to police work and work environment stress related to the administrative aspects of police work. The Critical Incidents History Questionnaire was employed to obtain a quantitative estimate of cumulative exposure to critical incidents. It is derived from a checklist of critical incidents potentially experienced in the domain of police work. The total score incorporates both frequency of exposure and a rating of coping difficulty. The Work Environment Inventory was used to assess routine work stress separate from critical incident stressor exposure. The police version includes items related to police specific work stressors such as court decisions, as well as generic work stressors such as racial or gender discrimination.

Results: Police officers reported more disturbances in most domains of subjective sleep quality than comparison subjects. Both groups of police officers had greater global sleep disturbances than either of the two comparison groups. The percentage of respondents with PSQI global scores greater or equal to 5 were 64.6% for day/evening shift police officers, 63.5% for night shift police officers, 46.6% for day/evening shift control subjects, and 51.5% for night shift control subjects. Night shift police officers had significantly greater exposure to critical incidents and significantly lower exposure to routine work environment stressors than their day/evening shift counterparts. The magnitude and direction of the correlation between critical incident exposure, work environment stressors, and sleep quality did not differ between the two police officer groups. Cumulative critical incident exposure was only weakly correlated with poor global sleep quality ($r=.15$, $p = .004$). In contrast, work environment stressors was moderately correlated with poor global sleep quality ($r=. 31$, $p < .001$).

Conclusions: A large percentage of police officers report disturbances in subjective sleep quality. Sleep disturbances are weakly associated with critical incident exposure and moderately associated with routine work environment stressors. The higher exposure to work environment stressors in day/evening shift officers may explain, in part, why their reports of sleep disturbances are similar to their night shift counterparts.

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1153.I

Shiftworkers Display Search Activity Behavioural Attitudes and Increased Chances of Sleeping Disorders

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Introduction: Firms benefit economically from shiftwork because it allows the longer use of expensive capital. The evaluation of behavioural attitudes in indefinite situations can provide information regarding the psychological status of an individual. Such information can be valuable in determining whether or not an individual is adept to working a rotating shift schedule and would thus aid firms in hiring employees. Our study of underground mineworkers, who at the time worked 8-hour rotating shifts at a base metal plant in Northern Ontario was initiated to determine whether or not a particular personality trait was shared by the shiftworkers and how shiftwork can effect sleep quality, snoring, family life, job performance and satisfaction.

Methods: Two questionnaires were mailed to 300 of the mineworkers. A total of 53 respondents returned and properly completed both questionnaires. Of these respondents all were male with a mean age of 39.1 ± 8.3 and had worked shifts a mean duration of 17.0 ± 8.0 years. The first

questionnaire titled "Shiftwork and You" contained questions regarding, sleep quality, sleep patterns, job satisfaction, job performance, alertness levels, the Epworth Sleepiness Scale (ESS), as well as other related parameters. The ESS refers to 8 hypothetical situations in which the respondent must rate on a scale of 0-3 the chance of them dozing. The ESS is the sum of the responses. The second questionnaire was Behavioural Attitudes and Search Evaluation Test (BASE). The BASE is a semiprojective test, which combines the principles of both a projective test and personality questionnaires and is designed for the estimation of certain behavioural characteristics. The preferences of the subject provide an opportunity for quantitative measurement of behavioural attitudes which can be categorised as search activity, stereotypical behaviour, chaotic behaviour, and passive renunciation of search.

Results: Of the 53 respondents it was found that the preference for search activity was the greatest, with a mean of 4.5 ± 2.9. The responses that were most disfavoured were those that indicated a passive renunciation of search personality, with a mean of –2.5 ± 3.3. Further analysis revealed that the respondents that had worked shifts for more than 20 years and those that had worked 20 years or less had mean preferences for search activity of 4.2 ± 2.8 and 4.6 ± 3.0 respectively, p=0.69. The mean ESS among the shiftworkers was 8.8 ± 3.7, where a score above 6 is considered to be abnormal. 36% of respondents indicated that their snoring was so loud such that it disturbed other people. Among these respondents the mean ESS was 10.5 ± 3.7 and among respondents who reported that they did not snore or their snoring did not disturb others was 8.0 ± 3.5 respectively. This difference was statistically significant (p=0.03).

Conclusions: The results indicate that the shiftworkers who responded displayed a behavioural pattern of search activity and that this behavioural tendency does not change with increasing numbers of years working shifts. Firms, which operate with rotating shift schedules, could increase worker efficiency by screening employees based on behavarioual attitudes. The high ESS score is an indication of the effect of shiftwork on an individuals alertness level. The high percentage of loud snoring among these shiftworkers, which was correlated to a higher ESS score, indicates the increased level of sleep deprivations and possible precursors to sleeping disorders among shiftworkers.

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1808.I

Sleep Inertia Before and After the First REM Period

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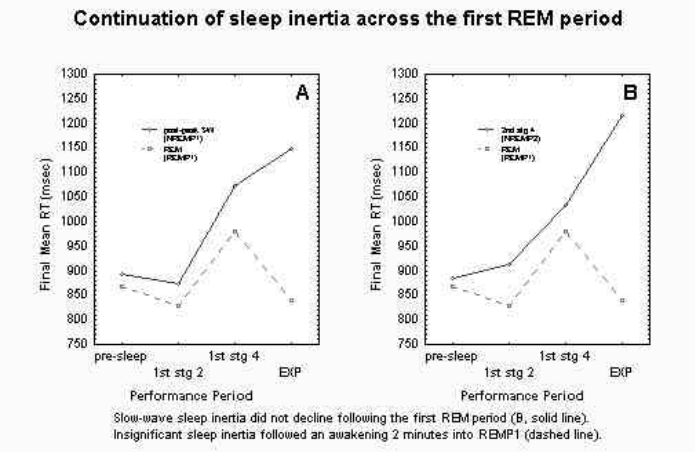
Introduction: Cognitive impairment is an important common consequence of interrupted sleep, which can produce 'sleep inertia' (SI) seen as performance deterioration below pre-sleep levels. Sleep inertia can be dramatic, with impairments more severe than those produced by extended sleep deprivation. Although SI predictably follows forced awakenings (FW) from slow-wave sleep (SWS), its severity has been related to the duration of preceding NREM sleep. By contrast, SI resolves within minutes following awakenings from even brief periods of REM sleep. Dinges' (1990) found SI increased monotonically with the amount of preceding NREM sleep, and related SI to sleep 'depth' rather than particular sleep stages. Prompt dissipation of SI after brief REM periods, and the fact that SI does not buildup across full nights of sleep earlier led Dinges to implicate REM in reversing NREM-induced SI effects.Sleep inertia has been studied during FW from naps, from brief periods of sleep during extended sleep deprivation experiments, and rarely from un-manipulated nocturnal sleep. Thus, it is unclear how SI relates to the buildup of SWS activity following the first REM period (REMP1) and whether REM sleep resets, or interrupts, the build up of SI.

Methods: Two paid groups of healthy college students were forcibly awakened (FW) by their own name presented at 80dB SPL. Each subject was awakened after 2 minutes of stage 2 and after 5 minutes of stage 4 sleep. In a REM-awakening group (n=8) subjects were also awakened after 2 minutes of REMP1. On a second night, a SW-awakening group (n=10) was also awakened after 5 minutes of decline in 0-3Hz delta integrated amplitude. REM awakenings were compared to SW awakenings at the end of the first SWS period and the beginning of the second. During each FW subjects performed a memory-scanning task for 12 minutes. (Irrelevant 20 and 60 dB-HL tones were also presented to stimulate event-related-potentials, reported elsewhere.)

Results: SWS produced robust SI (Figure 1), seen in each FW's target identification RTs during the final 5-minutes. SI differed significantly between REMP1 awakenings and both the post-peak SWS decline (p=.0007) and post-REMP1 SWS buildup (p=.0002). Pre- and post-REMP1 awakenings did not differ.

Figure 1



Conclusions: Sleep inertia was not reduced following the first REM period, supporting Dinges' formulation that SI reflects sleep depth driven by an SWS-relieved 'sleep pressure'. The prompt resumption of post-REMP1 SI could support the view of REM as an 'escape' from a NREM sleep state as suggested by Feinberg and March (1995).

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POSTER PRESENTATIONS

1180.I

Sleep, Sleepiness and Subjective Health

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Introduction: The day-to-day covariation between sleep and subjective health is largely unknown. However, intuitively, it seems reasonable that insufficient or poor sleep could cause minor health complaints. The aim of the present study was to investigate the day-to-day fluctuation and covariation of subjective sleep, sleepiness, stress and minor health complaints.

Methods: Twenty-two healthy subjects (14 women and 8 men, mean age 38 years, 17-61) kept daily records of sleep (sleep times, sleep quality, sufficient sleep etc.) and a number of different health complaints (all scales ranging from 1=severe symptoms - 5=none at all, if nothing else is stated) for 6 weeks. Whilst awake, they rated their sleepiness every second hour. The data were subjected to an Analysis of Variance to evaluate the effects of days of the week. Intra-individual correlations (using pooled data) between ratings of sleep, sleepiness, stress and health was also performed. The sleep ratings always preceded the health ratings the subsequent day.

Results: Bed times were later on Fridays and Saturdays than on Sundays-Thursdays (24:17±:14, 23:22±:10, p<.0001). Those sleep periods were also longer (8:32h±:15, 7:51h±:12, p<.0001) and judged being more sufficient (3.9±.1, 3.5±.1, p<.0001). Sleep periods between Sundays and Mondays had the poorest quality (3.4±.2, 3.7±.1, p<.001). During work days, the participants were more stressed (2.5±.2, 2.1±.1, p<.0001, 1-9=maximum), had more difficulties to concentrate (4.5±.1, 4.7±.1, p<.005) and were more restless/tense (4.4±.1, 4.7±.1, p<.005) compared with week ends. Sleepiness (mean ratings 8am-8pm) was more pronounced during the early weekdays, Mondays–Thursdays, than Fridays-Sundays (4.7±.1, 4.4±.1, p<.005, 1-9=very sleepy). The subjects rated themselves as having a poorer global health during the week, especially Mondays–Thursdays, than during weekends (5.0±.2, 5.4±.1, p<.0001, 1-7=very good). The most common health problem was fatigue (4.0±.1), followed by tense muscles (4.5±.2); ache/pain in shoulders/back (4.5±.1); and cold symptoms (4.7±.1). Even though the mean sleep period was as long as 8-hours, more than a third of the sleep periods were rated as insufficient and 12% were rated having a poor quality. The intra-individual correlations demonstrated that health covaried with sleepiness (-.43, p<.001), sufficient sleep (.24, p<.001), sleep quality (.11, p<.01), sleep length (.11, p<.01) and stress (-.08, p<.05). Sleepiness was associated with ratings of sufficient sleep (-.31, p<,001), sleep length (-.20, p<.001) and sleep quality (-.16, p<.001). Sleep length (-.19, p<.001) and ratings of insufficient sleep (.15, p<.001) also covaried with higher stress, the following day. Interestingly, ratings of health and stress the same day did not predict sleep ratings.

Conclusions: Sleep quality showed a clear variation across the week. The best sleep episodes occurred on weekends, whereas the poorest sleep appeared on the first weekdays. Subjective health was also improved over the weekend. Poorer health was associated with sleepiness and stress, predicted by insufficient sleep, poor sleep quality, shorter sleep length. Short and insufficient sleep periods were associated with stress the following day. The relatively low magnitude of the correlations was probably due to the low variation of sleep quality and more severe health complaints that rarely occurred in the present sample.

1837.I

Fluctuations in Sleep Duration Alter the Salience of Stressful Experience

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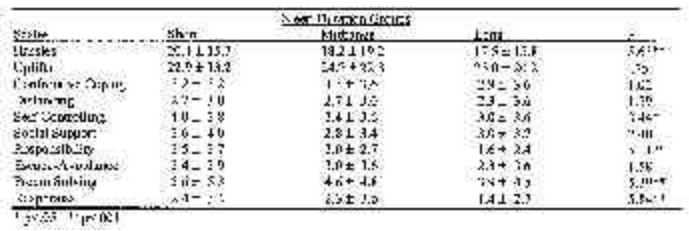
Introduction: The results of a set of earlier studies suggest that fluctuations in sleep duration may influence the salience of subsequent stressful experiences. We tested this assumption by asking a group of university students to complete daily diaries in which they recorded their presleep routines, sleep durations, exposure to stressors, and coping strategies.

Methods: From a larger group, we selected 82 students who were satisfied with their well-established sleep habits and who were willing to keep a daily diary for a 14-day period. Each day, these students responded to a sleep survey, the Hassles and Uplifts Scale and the Research Edition of the Ways of Coping Questionnaire. In the sleep survey, they recorded total sleep time and noted presleep events or the use of any substances that could effect their normal sleep duration. The 863 sleep nights that were not contaminated by presleep behaviors that might have effected sleep were used as the data points for this study. In turn, 137 of these nights were classified as short-sleep nights (≤6 hours sleep), 495 were classified as mid range-sleep nights (6 to 9 hours sleep), and 231 were classified as long-sleep nights (≥9 hours sleep). For each sleep night, the following day's responses to the two subscales of the Hassles and Uplifts Scale and the eight subscales of the Ways of Coping Questionnaire were scored.

Results: The means and standard deviations for each of stress-related scales for the three sleep duration groups are listed in the Table. These data were analyzed by computing separate one-way analyses of variance for each scale. The results of these analyses are also listed in the Table. For the majority of these scales, we observed an inverse relationship between sleep duration and the means of the stress-linked scales. The significant results for the Hassles Scale indicates that exposer to stressful experience increased as a function of decreases in sleep duration. The pattern formed by the four significant coping scales (i.e., Self-controlling, Accepting Responsibility, Planful Problem Solving, and Positive Reappraisal) suggests that following nights of shortened sleep, there is an increasing effort to deal effectively with emotions and feeling that are associated with stressful situations, and to accentuate problem-focused efforts to alter these situations.

Table 1



Research supported, in part, by NIH-MBRS Grant 08192-19.

POSTER PRESENTATIONS

1543.I

Aircraft Noise and Subjectively-Reported Night-time Awakenings in the Home

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Introduction: We[1,2] have previously reported on this field study in relation to findings with actimetry. We now report on subjective responses. There have been few such field studies. Although there have been more laboratory studies[3] these have largely been contrived and failed to consider noise habituation.

Methods: The effects of night-time aircraft noise events (ANEs) on subjectively estimated sleep quality, reported in 400 people (211 women, 189 men, aged 20-70y; one per household), were determined by: (i) general sleep questionnaires before and after the main study; (ii) morning sleep logs monitored for 15 nights. Ss lived at one of eight sites adjacent to four UK main airports, having different levels of night flying.

Results: Sleep logs were completed for 95.3% of all nights. 3512 subject nights contained a report of at least one awakening, and a total of 6457 awakenings were documented, of which 6422 either attributed a cause (including aircraft noise) or were ascribed as "don't know". Of all the subjects, 97 (24.2%) reported being awoken by aircraft on at least one occasion on at least one night. This totalled 284 subject nights (less than 5% of nights sampled). Some subjects reported more than one such awakening per night, and the total awakenings attributed to aircraft was 351 (5.5% of all awakenings). Despite large inter-site differences in night-time aircraft movements, inter-site differences in the incidence of reported awakenings due to aircraft were small. Even at the noisiest site the likelihood of being awoken was only about once per 8 nights. The noisiest site had 17 x more ANEs than the quietest, with 50% of the Ss at this site reportedly affected by an ANE on at least one or two nights during the 15 day period. The quietest sites produced proportionately more such awakenings than the "average" noise sites - suggesting that the more unlikely the noise event, the more likely it is to cause an awakening. At all sites, the most likely identifiable causes of awakenings were idiosyncratic (children, toilet, bed partner). Women reported more awakenings in general per night than did men, and the frequency of awakenings increased sig. across the age groups for both sexes. However, this was not the case for awakenings due to aircraft noise, where older (50-70 y) subjects reporting the majority of these specific awakenings. Older Ss reported most awakenings (mostly "toilet") and for younger women it was "children". The cause of awakening also affected its duration, with "illness" and "worry" being worst. 34% of Ss reported occasions of having difficulty getting to sleep. For 58% of this latter group the most common cause was worry and for 17% of them it was aircraft noise. 69% of all Ss reported finding it easy or very easy to return to sleep if woken during the night; 22% reported finding it difficult to get back to sleep, and 6% reported finding it very difficult (can't say = 3%). 69% reported that aircraft never prevented them from getting to sleep at night, 27% reported "sometimes", and 4% reported "frequently".

Conclusions: These results support those from our actimety findings.[1] For the great majority of Ss, and even at the noisiest sites, the most disturbing effects on sleep were not ANEs but more idiosyncratic factors such as children, illness, need for the toilet, and the bed partner. Most Ss were habituated to ANEs during sleep at home.

References:
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1207.I

The Relationship Between REM Sleep Patterns, Intelligence and Performance on Two Procedural Tasks

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Introduction: There is recent support for the idea that REM sleep is related to learning. This support comes from both animal and human studies. Generally, REM sleep increases and/or increases in number of REMs follows successful learning of a task. Further, prevention of REM sleep following acquisition results in long term memory impairment for the task. It has also been reported that "fast learning" rats showed larger increases in REM following acquisition than "slow learning" rats. It has been previously reported in humans that an intensive learning experience is followed by an increase in REM sleep intensity (Smith, 1995). There have been a number of studies attempting to relate intelligence (I.Q.) and sleep architecture. Several reports indicate that profoundly retarded individuals exhibit lower REM density during REM sleep than normal individuals. On the other hand, there are reports of subjects with high I.Q. exhibiting a lower number of REMs per night compared to those with a moderate I.Q. The present study was carried out to examine the possibility that high and low I.Q. individuals might have different sleep architecture and that they might show different sleep responses to the challenge of learning two procedural learning tasks known to be REM sleep sensitive.

Methods: Introductory college students were chosen to be sleep subjects on the basis of their score on the Quick Test I.Q. Test (QT). They were also screened using the Trent University Sleep Questionnaire and paid to participate in the study. Participants were placed in either the high I.Q. group (I.Q. > 126 , n = 5) or in the low I.Q. group (I.Q. < 97, n = 5). All participants were given a baseline sleep night in the lab, using the standard EEG (C3/A2, C4/A1), horizontal EOG and EMG placements for sleep recording. The recording system was an 18 channel Nihon-Kohden polygraph connected to a paperless software system. On the evening of the second night of sleep (Night 2), participants were asked to learn two procedural learning tasks, the Tower of Hanoi and the Mirror Trace tasks. Each individual was asked to complete the Tower of Hanoi (five trials). They were then asked to trace the 4 figures of the Mirror Trace task. Following this, everyone spent a second night sleeping in the lab. Behavioural retesting was done 1 week later at the same time of day.

Results: Learning. A 2 x 2 mixed model ANOVA comparing the I.Q. groups on the number of errors in completing the Mirror Trace task revealed that both groups learned the task [$F(1,8) = 47.42$, $p < .001$]. Further, the High I.Q. groups required less moves than the Low I.Q. group [$F(1,8) = 5.42$, $p < .05$]. Both groups showed learning on the Tower of Hanoi as well [$F(1,8) = 14.25$, $p < .005$]. Sleep. An examination of the states of sleep revealed that the Low I.Q. group had more Stage 2 sleep on both Night 1 ($p = .02$) and on Night 2 ($p < .025$) than did the High I.Q. group. Both groups had more REM sleep on Night 2 than on night 1 [$F(1,8) = 163.99$, $p < .001$]. An ANOVA comparing the actual number of REMs revealed that the Low I.Q. individuals had more REMs than the high I.Q. individuals on both Night 1 and Night 2 [$F(1,8) = 6.80$, $p < .05$]. On Night 2, following training, the Low I.Q. individuals showed a marked increase in number of REMs while those of the High I.Q. group remained unchanged [$F(1,8) = 124.12$, $p<.001$].

POSTER PRESENTATIONS

Conclusions: Individuals scoring either high or low on the Quick I.Q. Test exhibited several basic architectural differences in their sleep patterns. Low I.Q. participants exhibited more Stage 2 sleep than High I.Q. participants. As well, sleep in response to the learning tasks was different, with the Low I.Q. individuals showing a marked increase in number of REMs. These individuals were also the most challenged by the learning tasks. Results support the notion that learning is related to REM sleep and in particular, the phasic component of REM sleep.

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(1) Smith, C: Sleep states and memory processes. Behavioural Brain Research, 1995, 69, 137-145.

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1857.I

An Analysis of the First Night Effect on REM Sleep Quantified EEG

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Introduction: The detrimental effect in healthy participants of having to sleep for a first night in a laboratory is a well-known phenomenon. Very little attention, however, has been given to the analysis of quantified EEG measures. We used REM sleep as an index of the first night effect.

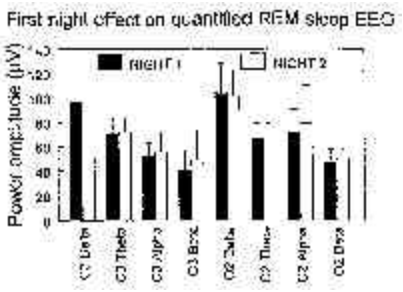
Methods: Eight healthy participants (6 men, 2 women, aged 21.4 ± 4.9 years) were recorded for two consecutive nights in a sleep laboratory. All were free from sleep disorders and from a personal or a familial (first degree) history of psychiatric or neurologic disorders. Subjects were asked to keep a regular sleep-wake schedule for 14 days before coming to the laboratory. Napping was not allowed on days prior to recordings. Both nights were scored according to Rechtschaffen & Kales (1968). Quantified EEG analysis was performed on samples taken from C3 and O2 electrodes, refered to linked earlobes. Twenty-four 4-second artefact free epochs equally distributed over the first three REM sleep periods were selected. EEG samples were submitted to Fast Fourier Transform with a resolution of 0.25 Hz and a cosine window smoothing; power amplitude was extracted. Spectral analysis generated four frequency band windows: Delta (0.75-3.75 Hz), Theta (4.00-7.75 Hz), Alpha (8.00-12.75 Hz), and Beta (13.00-20.25 Hz). T-test for dependent samples was used for between-night comparisons on absolute amplitude power, for each frequency band.

Results: Sleep architecture showed a typical first night effect (see Table 1). EEG spectral analysis however did not reveal any significant difference (see Figure 1).

Table 1. First night effect on sleep parameters

	Night 1	Night 2	P
Sleep onset latency	12.7 ± 3.8	9.6 ± 1.9	ns
SWS latency	35.8 ± 10.9	23.8 ± 5.0	ns
REM sleep latency	106.2 ± 18.1	71.5 ± 6.3	ns
% Stage 1	8.5 ± 1.5	12.0 ± 2.5	p<.05
% Stage 2	55.7 ± 2.2	51.9 ± 2.3	ns
% Stage 3	9.9 ± 1.1	8.8 ± 0.6	ns
% Stage 4	9.2 ± 1.9	7.2 ± 1.1	ns
% REM sleep	16.6 ± 1.1	20.2 ± 1.5	p=.05
REM period	4.4 ± 0.3	5.6 ± 0.4	p<.05
Wake (min)	72.3 ± 13.4	55.3 ± 14.1	ns
% Sleep efficiency	84.9 ± 3.0	89.1 ± 2.4	ns
Total sleep time	410.5 ± 18.5	423.8 ± 20.0	ns

Figure 1. Absolute EEG power amplitude on C3 and O2 leads



Conclusions: Our results show a dissociation between the sensitivity of sleep architecture and quantified EEG analysis to the first night effect in young healthy participants. This does not support the results of Toussaint et al.[1] The absence of a first-night effect on sleep using ambulatory monitoring suggests that variable laboratory conditions,[2] in addition to variable clinical populations, are bound to yield different effects on sleep architecture. This could also apply to quantified EEG measures in REM sleep.

References:
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1869.J

The Impact of Music Upon the MSLT and MWT

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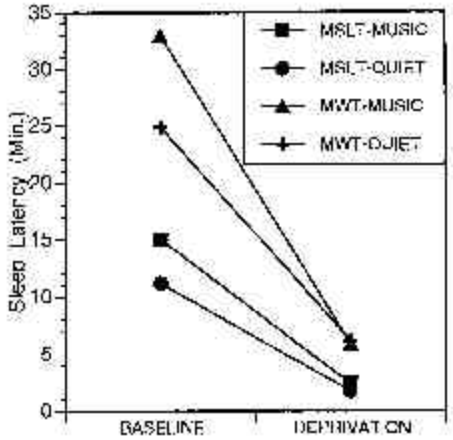
Introduction: Previous work has shown that background noise or music has a small positive impact on performance during sleep deprivation. The current study examined the effect of background music on the ability to fall asleep or remain awake during MSLT and MWT evaluations following baseline sleep and one night of total sleep deprivation. It was hypothesized that the music would help maintain wakefulness in all conditions.

Methods: Twelve normal sleeping young adults (age 25) had an adaptation night to rule out sleep disorders and to document normal sleep. Ss were then scheduled to take Multiple Sleep Latency Tests and Maintenance of Wakefulness Tests after baseline sleep and one night of total sleep deprivation either with background music (compact disks selected by the Ss and played by the technician) or under standard (quiet) conditions in a counter balanced design. Ss also performed the Wilkinson Addition Test (30 min) under similar conditions between sleepiness/alertness tests.

Results: As shown in the Figure, sleep latencies were increased in both MSLT and MWT tests when music was presented, but this effect occurred primarily following normal sleep (a significant Music by Sleep Deprivation interaction). Sleep latencies were 15 and 11 min. on the MSLT (33 and 26 min. on the MWT) during Music as compared to Quiet after baseline sleep, and both differences were statistically significant. However, there was no difference after sleep deprivation. As expected, MWT latencies were significantly longer than MSLT latencies, but this

difference was also reduced after sleep deprivation. Heart rate, used as a measure of physiological arousal, was significantly elevated in MWT and MSLT trials where music was presented ($F = 10.50$, $p < .005$), and there was no significant interaction with sleep condition. Overall, heart rate was higher (69 vs 67 bpm) during MSLT and MWT when music was played. There was also a significant main effect for Music on the Wilkinson Addition Test, but the increase in correct additions in the Music Condition compared to Quiet (126 vs 124 correct) may not be of practical significance.

Figure 1



Conclusions: These data support previous work showing that level of arousal has an impact on measured sleep tendency which is independent of that of the sleep system.[1] On a practical level, these data indicate that music may play a small beneficial role in helping to maintain arousal in sedentary situations.

References:
(1) Bonnet W Arand DL. Sleepiness as measured by the MSLT varies as a function of preceding activity. Sleep 1998;21:477-483.

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1237.J

The Ability to Self-Monitor Performance: The Effects of Acute and Cumulative Partial Sleep Deprivation

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Introduction: The detrimental effects of sleep deprivation on neurobehavioural performance are well documented. In contrast, little is known about the effects of sleep deprivation on individual ability to self-monitor performance. Several recent studies have investigated performance self-monitoring (eg. Baranski et al., 1994; Baranski and Pigeau, 1997). However, to date, studies have solely focused on the effects of continuous periods of acute sleep deprivation. As such, the aim of the current study was to compare the effects of acute and cumulative partial sleep deprivation on the ability to self-monitor performance.

Methods: The protocol consisted of two studies. In the first study, eighteen subjects (19-26yrs), remained awake for a period of 28-hours. In the second study, twelve subjects (19-25yrs) completed seven consecutive 8-hour nightshifts (11pm-7am). In both studies, neurobehavioural performance was measured hourly using three tests from a standardised computer test battery. From these three tests, five performance parameters were obtained including accuracy and response latency measures of logical reasoning and vigilance, and a measure of tracking ability. In addition, before each test, participants completed Visual Analogue Scales which required them to rate their alertness level and predict the speed and accuracy of their performance.

Results: Preliminary analysis indicated that in study one, performance on four of the five parameters significantly decreased ($p<.05$) as hours of wakefulness increased. Subjective estimates predicted significantly decreased performance ($p<.05$) for all five parameters with increasing hours of wakefulness. Furthermore, analysis revealed moderate correlations between subjective performance estimates and actual performance for the four parameters affected by fatigue. Additionally, moderate to high correlations were found between predicted performance and alertness. Further analysis will include a similar investigation of data from study two, with a focus on comparing results from both studies.

Conclusions: Data collection for study two is still continuing. However, results of preliminary analysis indicate that during conditions of acute sleep deprivation, as hours of wakefulness increase, subjects are able to globally assess performance decrements. Furthermore, it is apparent that the global assessment of performance is mediated by subjective alertness levels.

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Research supported by The Australian Research Council

1606.I

Effects of Cumulative Workload on Vigilance Decrement During Total Sleep Deprivation

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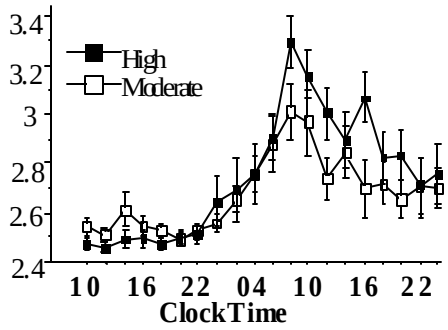
Introduction: Sleep deprivation is known to degrade performance on tasks requiring sustained attention by increasing the vigilance decrement (i.e., time-on-task changes).[1] Current models of sleep/wake regulation account for this decrement as secondary to the effects of homeostatic decline and circadian rhythmicity regulating general arousal level.[2] To test if cumulative cognitive workload might interact with arousal-state to affect vigilance decrement, we evaluated time-on-task changes in a sustained attention task by comparing moderate versus high levels of behavioral testing during 40 hr of total sleep deprivation (TSD).

Methods: A total of n=26 healthy adult subjects were evaluated. Thirteen subjects participated in a 40-hr TSD laboratory experiment involving moderate workload by requiring subjects to engage in 0.5 hr of behavioral testing every 2 hr, including a 10-min version of the psychomotor vigilance task (PVT).[3] Another thirteen subjects participated in a similar TSD study that involved high workload by requiring 1 hr of behavioral testing every 2 hr, including a 20-min version of the PVT. Log-transformed average reaction times (RTs) during the 10-min PVT (moderate workload of study 1) were compared to the first 10 minutes of

the 20-min PVT (high workload of study 2) using a workload x test-time mixed-model ANOVA. Analysis of vigilance decrement used the log-transformed minute by minute mean RTs within each test bout in a workload x minute-on-task mixed-model ANOVA after collapsing the minute by minute data into five 8 hr sleep deprivation periods (I:2h-10h, II:10h-18h, III:18h-26h, IV:26-34h, V:34-40h of TSD). Thus, periods I and IV, and II and V occurred at the same clock time, respectively, and therefore sampled equivalent portions of the circadian cycle before and during TSD.

Results: The workload x test-time ANOVA showed a significant main effect of test time ($F[19,456] = 19.46$, $p < 0.001$) with RTs increasing for both workload conditions across the 40 hr of sleep deprivation. However, there was also a significant workload x test-time interaction ($F[19,456] = 2.17$, $p = 0.003$) such that with increasing TSD, high workload produced longer RTs in the first 10 minutes of the PVT relative to moderate workload (see Figure). In the minute by minute tests for vigilance decrement, a significant main effect of time-on-task was found for periods I, III, IV and V, irrespective of workload condition. Only period IV (26-34 hr of sleep deprivation, i.e., 10am to 4pm of the second day) had a significant workload x time-on-task interaction ($F[9,216] = 2.75$, $p = 0.005$), with high workload causing a larger vigilance decrement than found under moderate workload.

Figure 1. Mean log-transformed RTs (and S.E.) per test bout for both high and moderate workload.



Conclusions: The effect of higher cumulative workload was to further increase sustained attention deficits as sleep deprivation progressed. High cognitive workload was also shown to potentiate the vigilance decrement function after 28 hr of sleep deprivation. As the two studies did not differ with respect to either the degree of TSD or circadian timing, it appears that cumulative performance demands (which may be considered to modulate "intensity" of wakefulness) can have an additional effect on behavioral output, but only when the homeostatic drive for sleep is sufficiently high (i.e., beyond approximately 24 hr of wakefulness), and the circadian drive for wakefulness is sufficiently low. These results suggest that prior workload should be considered when attempting to account for the effects of arousal state on attentional performance.

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1626.J

Behavioral Observations of Sleepiness at National Sleep Meeting

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Introduction: The National Commission Report on Sleep Disorders Research concluded that "a major factor in the pervasive sleepiness found in American society is the failure to educate Americans about the facts related to sleep and sleep deprivation". To determine whether experts within the sleep field were applying their knowledge, attendees were observed during a national conference to assess their level of alertness during the meetings.

Methods: Three observers carefully recorded a sample of attendees in the front of the auditorium during the clinical presentations at the 13th annual APSS meeting. Each observer maintained a direct visual line of sight with the attendees at all times to observe if he or she closed his or her eyes for a period greater than 30 seconds. The attendees were further observed for periods during which their heads would bob. These behaviors are assumed to indicate lapses in attention, resulting from excessive daytime sleepiness. Each attendant was counted once for each display of each individual behavior. For example if a subject closed his/her eyes for longer than 30 seconds and would open their eyes only to close them again later, they would only be counted once for eyes closed. However, if during that same recording period the subject was noted to bob his/her head, that behavior would be counted as both eyes closed greater than 30 seconds and as a head bob. Ambient light intensity was measured with a Sekonic auto-Lumi model L-158.

Table 1

SESSION TIME	N	Eyes Closed	Head Bob
8:30-9:30	69	11 (15.9%)	6 (8.7%)
10:15-11:15	67	16 (23.9%)	7 (10.4%)
11:15-12:15	61	15 (24.6%)	7 (11.5%)
14:00-15:00	58	20 (34.5%)	9 (15.5%)

Results: The results for all three observers are summarized in table I. The morning session had the fewest number of attendants displaying outward indications of excessive daytime sleepiness (15.9%). The excessive sleepiness progressively became more severe as the day progressed with the post lunch session reporting as many as 34.5% of the attendants displaying lapses in attention due to sleepiness. Light intensity was reported to never exceed 60 lux during any of the sessions.

Conclusions: Despite the obvious methodological limits of this study, it does highlight the apparent pervasiveness of excessive daytime sleepiness. The true extent of EDS is likely under reported in this study, as only individuals within the first 15 rows of the auditorium were included. Assuming that individuals sitting in the front are more likely to maintain alertness due to a perceived greater interest as demonstrated by locating a seat up front, the percentage of sleeping attendees in the back of the room would probably be higher. Possible factors contributing to this high incidence of behavioral sleepiness could be partially accounted for by the following factors:1. Jet lag for some of the foreign attendees. 2. The long schedules 3. Late night socialization and consumption of alcohol 4. Low light intensity in auditoriums.5. Presentation style 6. Poor sleep quality. Further documentation and exploration of these possible factors should be conducted to identify the dominant factors involved and for ways to improve these conditions so that experts with the sleep field can lead the general population by example.

1631.J

Brief Paradoxical Sleep Deprivation and Sleep Recordings: Results During Treatment and Recovery

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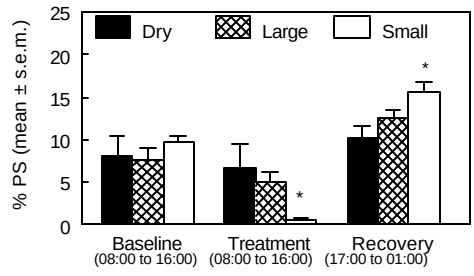
Introduction: Studies using the small platform method for paradoxical sleep (PS) deprivation in rats usually involve long-term treatments (24-96 hours) but sleep structure is seldom reported.[1] We analyzed the sleep of rats exposed to the small platform method for 8 hour, a protocol that induces significant learning impairments in rats.[2]

Methods: Sixteen male Sprague-Dawley rats (280-350g) were implanted with EEG and EMG electrodes and placed in individual homecages lighted from 08:00 to 20:00. One week after surgery, baseline recordings were obtained for 17 hours (08:00 to 01:00). Rats were then submitted for eight hours (08:00 to 16:00) to one of the following conditions: no manipulation (dry control rats remaining in their home cage; n=5), yoked control using a large platform (weight:surface ratio = 1:1; n=5), and PS deprivation using the small platform method (weight:surface ratio = 10:1; n=6). All rats then performed a behavioral task (Morris Water Maze, six 1-minute trials, distributed over 60 minutes, between 16:00 and 17:00; no sleep allowed).[2] Immediately after the last trial rats were returned to their respective homecages and sleep recording was started for a period of eight hours (from 17:00 to 01:00). Vigilance states were scored using 10-s epochs into waking, drowsiness, light slow wave sleep (SWS-1), deep slow wave sleep (SWS-2), and PS. Results were compared to baseline using paired t-tests.

Results: PS was significantly reduced only in rats exposed to the small platform (Figure 1). SWS was not affected but waking was increased in both platform groups. During recovery sleep, rats exposed to the small platform showed significant increases in SWS-2 and PS while drowsiness was decreased. A breakdown of recording time showed that SWS-2 rebound was significant only for the first third while the PS rebound was significant only for the last two thirds of the 8-hour recovery period. Rats exposed to the large platform showed a non significant increase in SWS-2 ($p<.08$) in the first third and a significant increase of PS in the second third of recovery time.

Figure 1. PS ratio in three experimental groups during the three experimental phases. Dry: homecage control rats; Large: yoked control rat, using a large platform; Small: experimental rats, using a small platform.



Conclusions: The quasi-total deprivation of PS observed here is equivalent to what is found upon longer PS deprivation procedures [3]. We observed a PS rebound effect that was not exhausted after a recovery period of a length equal to that of the PS deprivation period. Both homeostatic and circadian factors may be involved.

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1638.J

Neurobehavioral and Somatic Complaints During Chronic Partial Sleep Deprivation

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Introduction: Few studies have systematically explored self-reported symptom complaints during sleep deprivation under controlled conditions. During 7 days of sleep restricted to 4-5 hours per night, two studies have shown that complaints increased during the sleep deprivation period.[1,2] During an experiment in which sleep was restricted to 4-5 hrs per night over 18 nights, the majority reported increased forgetfulness, reduced concentration, loss of interest, sleepiness, and headaches.[3] The purpose of the current report is to describe the course of self-reported symptom experiences associated with three chronic sleep restriction conditions.

Methods: During a 20-day in-laboratory protocol, healthy young adult subjects had 3 baseline nights of 8hr time in bed (TIB), followed by 14 nights (random assignment) of either 4hr (n=10), 6hr (n=11) or 8hr (n=8) TIB, followed by 3 nights of 8hr recovery TIB. Every 2hr throughout all waking periods on all days, subjects were tested on a 30min computerized neurobehavioral assessment battery. At the end of each test battery, subjects completed a Survey of Experiences questionnaire we developed that asked about the presence or absence of 19 specific symptoms. The individual symptoms endorsed each day were averaged to produce a mean score for each phase of the study (baseline, restriction, and recovery). Subjects in the 8hr TIB condition constituted the control group, while those in the 4hr and 6hr conditions were combined to form an experimental group (n=21). A total score from the Survey of Experiences was calculated for each subject, in addition to scores for two symptom subscales: (1) a neurobehavioral subscale score that consisted of reports of tiredness, worry, difficulties concentrating, etc.; and (2) a somatic subscale score that was comprised of physical complaints such as headache, muscle aches, joint pain, etc. Data were analyzed by mixed-model ANOVA.

Results: In the experimental group, symptoms worsened during the 14 days of restricted sleep and returned to baseline over the two days of recovery sleep ($F=12.1$, $p<0.0001$). Subjects in the control condition manifested no change. These effects in the experimental group were almost completely attributable to neurobehavioral subscale factors ($F=11.5$, $p<0.0001$). Subjects in the control condition manifested no change in the neurobehavioral subscale ($F < 1$). On the somatic subscale, neither the experimental nor control group showed significant changes.

Conclusions: Subjects whose sleep was restricted to either 4hr or 6hr per night for a 14-day period reported significantly more symptoms than subjects who were allowed to sleep for 8 hrs. However, consistent with

earlier reports,[1] these complaints were primarily in the realm of neurobehavioral symptoms, as there was no significant change in general somatic symptoms. Recovery to baseline levels was rapid and dramatic when subjects were allowed 8hr sleep for only 2 nights. These results suggest that chronic sleep restriction primarily leads to complaints characteristically associated with CNS impairments rather general physical ailments.

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1300.J

Principal Pattern Analysis of Sleep-Deprived Human EEG

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Introduction: Sleep deprivation is known to lead to an increase in reaction time and to mental lapses on cognitive tests. It has been shown that, after a normal period of 16 hours of wakefulness, EEG power is significantly increased and the interhemispheric correlation is decreased (Corsi-Cabrera et al, 1992). Several studies have looked at the changes in the absolute power of the EEG spectrum of subjects becoming sleepy due to forced wakefulness. These information have many limitations when complex brain activity is investigated. We performed a pattern analysis of sleep-deprived human EEG data, using the Karhunen-Loeve expension method. The primary pattern having the largest eigenvalue was selected as the main EEG dynamic axis. We observed the rotation of the axis as the increase of sleep deprivation time.

Methods: Twenty young adult men, from 21 to 26 years of age, volunteered to participate in the study. All subjects were right handed and were free of neurological or sleep-related disorders. Subjects slept in the laboratory and were recorded just after awakening at 07:00h, after a full night's sleep. Subjects were then kept awake in the laboratory for 36 hours. The wakefulness period started around 07:00h, and the data collection was performed twice: 24 hours into the forced wakefulness period, and at the end of the 36-hour sleep deprivation period, which terminated around 19:00h. Subjects were kept under human supervision while being simultaneously monitored to assure maintenance of wakefulness. Potentials from 16 loci referred to linked earlobe electrodes were recorded for 32.768 secs with 500 Hz sampling. The Karhunen-Loeve expension or singular value decomposition method was then applied to these 16 channels of EEG data. The collected data were decomposed in 16 orthogonal patterns, The stationary of the primary pattern component was checked by ANOVA using SPSS 6.0. Thereafter, the change of the primary pattern component was tested by Paired t test.

Results: During the monitoring, all the primary pattern components lay in their confidence intervals respectively. The equipotential line variation of the primary pattern demonstrate the local variation of electrical activity and the changes in the brain functioning in response to progressive sleep deprivation. The rotation of the dynamic axis of the EEG signals with progressive sleep deprivation is clearly indicated by the color scale. The significant variations of the dominant pattern occurred in P3, T5, P4 after 24 hour of sleep deprivation and C4, P4, F8, Fp1 and T5 electrode sites after 36 h. of sleep deprivation.

Figure 1. 1.Distribution of the primary pattern at baseline. 2. After 24 hour of sleep deprivation 3. After 36 hour sleep deprivation

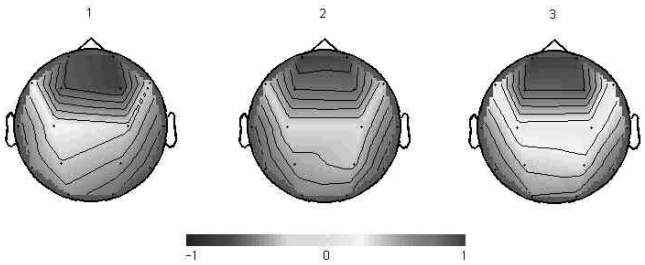
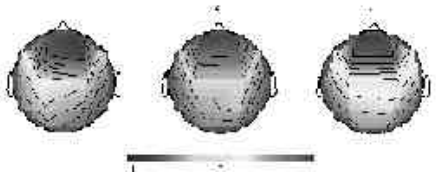


Figure 2. 1.1. Distribution of the primary pattern at baseline. 2. After 24 hour of sleep deprivation. 3. After 36 hour sleep deprivation.



Conclusions: Hemispherically correlated but opposite directional rotation of the main EEG dynamic axis was observed. This result could be viewed as the inter-hemispherical correlation discrepancy increase responding to sleep deprivation. The significant changes in the eigenvector components indicated the relative changes of local activity in the brain with progressive sleep deprivation. This methodology may make the evaluation of dynamic changes in brain activity in normal and pathological conditions possible.

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1303.J

Detection of Electroencephalographic Indices of Drowsiness in Realtime Using a Multi-Level Discriminant Function Analysis

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Introduction: Electroencephalographic (EEG) parameters are sensitive indicators of drowsiness and have proven to correlate with performance on a second-by-second basis (Makeig, 1995). Acquisition of high-quality EEG recordings in workplace environments, such as airplane cockpits, long-haul truck cabins and train-operators' quarters, suggest the feasibility of a real-time EEG drowsiness monitor. In this study, a discriminant function analysis (DFA) model designed to classify one-second epochs of EEG on a continuum from highly vigilant to sleep onset

was validated. This model utilized methods to overcome between-subject variability in alpha generation as well as distinguish theta activity at sleep onset from frontal midline theta during mental performance tasks (Takahashi 1997).

Methods: EOG and EEG (CzPz and CzOz) were recorded in fifteen healthy subjects (5 male, 10 female, ages 19 – 52). When fully rested and seated, subjects engaged in challenging mental performance tasks (MPT) and 10-minute sessions using a finger-tapping task to provide behavioral measures of sleep onset (Casagrande 1997) with Eyes-Open (EO) and Eyes-Closed (EC). Approximately 14 hours after awakening from partial sleep deprivation, subjects completed baseline finger-tapping sessions while seated with Eyes-Open (SD-EO) and Eyes-Closed (SD-EC). Extended-duration finger-tapping sessions were also conducted periodically throughout the night, with subjects reclining in a dimly lit room and attempting to remain awake. Data representing 344 Sleep onsets (SL) were selected from these sessions based on agreement of the finger-tapping procedure and visual scoring conducted blindly by two certified polysomnographers. Procedures were utilized to identify and decontaminate eye blinks in the EEG without the use of EOG recordings, and epochs contaminated with other physiological artifacts were identified and eliminated. Predictive variables were selected from the power spectra of one-Hz bins between 1 and 24 Hz and the EEG band, and median Hz bands using step-wise analysis. Randomly selected data from the MPT, EO, and EC were used to assign each subject to one of three databases using cluster analysis. Individualized DFA coefficients were derived from the respective database inverse-covariances and centroids computed from a sub-set of one-second epochs recorded during the MPT, EO, EC and SL conditions; the DFA then classified each one-second epoch as High-Vigilance(HV) or Low-Vigilance (LV), EC or SL, respectively. A sleep-onset identification rule required either two consecutive epochs to be classified as Sleep (SL) or one epoch classified as Eyes-Closed followed by a Sleep epoch.

Table 1. Distribution of Classifications of One-Sec Epochs

	HV	LV	EC	SL	# Epochs
Fully-Rested Sessions					
MPT	74.8%	21.6%	1.0%	2.6%	7,366
EO	14.9%	76.2%	7.7%	1.2%	4,354
EC	1.4%	11.4%	83.6%	3.6%	4,300
Sleep Deprived Sessions					
SD-EO	22.6%	62.0%	5.2%	10.2%	2,766
SD-EC	1.6%	10.7%	76.1%	11.5%	1,763
P-SO	10.0%	36.2%	34.3%	19.5%	1,834
SL	2.4%	3.6%	0.6%	93.4%	2,723

Results: The distribution of epochs classified as HV, LV, EC or SL for each condition is presented in Table 1. The model correctly classified 97.5% of the fully-rested epochs and 83.6% of the sleep-deprived epochs as awake. 93.4% of the sleep epochs were classified as SL and over 99% of the sleep episodes were accurately identified. Minimal misclassifications occurred between MPT vs. SL and SL vs. HV.

Conclusions: The results from this study provide initial validation for the DFA model, designed to run in real-time using digital signal processing technology and to resolve many of the problems associated with quantifying EEG, thus providing the first step in the development of a portable EEG drowsiness detection device.

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1655.J

Field-based Validations of a Work-related Fatigue Model Based on Hours of Work

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Introduction: Shiftwork, and in particular night work, is associated with decreased quantity and quality of sleep. Such changes to sleep manifest themselves in ways such as increased sleepiness, fatigue and accident risk (e.g., Åkerstedt 1998). To manage these risks, particularly in operational environments, a work-related fatigue model has been developed (Fletcher et al 1998). To date, strong correlations have been observed with a range of measures in empirical and laboratory experiments. This study aimed to determine if the observed relationships between predicted fatigue, alertness and performance also exist in the workplace.

Methods: One hundred and ninety three locomotive engineers (189 male, 4 female) used sleep and work diaries, wore actigraphs, performed subjective alertness and objective performance tests before and after each shift for a period of two weeks during a normal schedule. Work-related fatigue was predicted and then compared to alertness and performance measures using correlation and three-factor ANOVA.

Table 1. Correlations between predicted fatigue, VAS alertness, and performance scores for the beginning and end of shifts.

Predicted fatigue scores	Beginning	End
Alertness scores		
0.22**	0.25**	(n=531) (n=476)
Performance scores		
0.10	0.13*	(n=554) (n=498)

*: $p < 0.05$, **: $p < 0.0001$

Results: The findings of the present study show that there was a stronger relationship between predicted fatigue and self-rated alertness than between predicted fatigue and performance (Table 1). Furthermore, the fatigue model predicted self-rated alertness better in the afternoon and evening hours, when employees worked up to four consecutive shifts.

Conclusions: The strength of the observed relationships are weaker than those determined in the laboratory, where fatigue predictions have correlated very strongly ($r > 0.7$) with measures such as multiple sleep latency test scores, psychomotor vigilance task lapses, sleepiness, vigilance etc. However, the present findings do provide support for validity of the work-related fatigue model. Most significantly, it appears that the fatigue model has predictive ability for self-rated alertness in the field. The strength of the relationships observed, are similar to other published field studies (e.g., $r = 0.2$, Philip et al 1999). With further field validation and refinement of the current model, there is considerable potential for work-related fatigue to be predicted from actual or potential hours of work.

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1024.J

Efficacy of 600 mg Modafinil for the Sustainment of Aviator Performance Throughout 40 Hours of Continuous Wakefulness

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Introduction: Emergency workers and military personnel frequently must perform their duties for extended periods without adequate sleep. This places them at risk for problems associated with sleep deprivation. Although several strategies for overcoming these problems have been explored (i.e., work/rest schedules, behavioral interventions, etc.), few appear feasible or effective for demanding work environments. At present, stimulants may be the most reliable method for sustaining sleep-deprived personnel in certain situations. Caffeine is widely available and socially acceptable, but despite its proven efficacy in laboratory studies (Penetar et al., 1993), questions remain about its effectiveness in persons who regularly consume moderate to high doses (in the form of coffee, soft drinks, etc.). Dextroamphetamine is reliably efficacious (Caldwell et al., 1998), but its history of abuse makes it unpopular. Modafinil (Provigil®) has shown promise for sustaining performance in sleepy personnel, and it has the advantage of purportedly producing fewer side effects while being more politically palatable; however, controlled "real-world" performance studies are virtually nonexistent (Akerstedt and Ficca, 1997). The present investigation sought to address this issue by examining modafinil's capacity to sustain performance and alertness in sleep-deprived pilots.

Methods: Six helicopter pilots were exposed to two 40-hour periods of continuous wakefulness separated by one night of recovery sleep. In one period, three 200-mg doses of modafinil were given (at 2300, 0300, and 0700) and in the other period, matching placebo tablets were administered (the study was double blind and counterbalanced). Testing sessions, which included UH-60 simulator flights, EEG evaluations, Profile of Mood States (POMS) and Visual Analog Scale (VAS) questionnaires, and the Multi-Attribute Task Battery (MATB) were conducted at 0900, 1300, and 1700 at baseline and at 0100, 0500, 0900, 1300, and 1700 during sleep deprivation.

Results: Modafinil significantly attenuated the effects of sleep deprivation on four of the six flight maneuvers. Performance on the straight-and-levels, straight descents, left standard-rate turns, and left descending turn was maintained at or near baseline levels by modafinil, whereas performance suffered under placebo ($p<.05$). In addition, modafinil reduced the amount of delta and theta EEG ($p<.05$), lessened self-reported diminutions of vigor, energy, and confidence ($p<.05$), and curtailed performance decrements (slower response times, increased lapses, and elevated errors) found under placebo ($p<.05$). The most noticeable benefits from the drug were seen between 0330 and 1130 when the combined impact of sleep loss and the circadian trough were most severe. There were no negative effects on recovery-sleep architecture. Side effects including vertigo, nausea, and dizziness were sometimes associated with modafinil administration, but it may be that some of these difficulties would subside under actual flight conditions since simulators have been found to increase the incidence of motion sickness in susceptible individuals (and modafinil may have lowered the threshold for this effect). In addition, it is possible that lowering the drug dosage from 600 to 400 mg would be helpful.

Conclusions: Modafinil was effective for sustaining the performance of aviators in a helicopter flight simulator and for attenuating other detrimental effects of sleep deprivation. Five of six volunteers reported they thought modafinil helped their performance. There were side effects that may have been related to the motion-base testing or the dosages employed, and these must be explored further. In the meantime, it is clear that modafinil holds promise for its alerting effects. Subsequent research is warranted to establish the feasibility of using this medication for sustaining sleep-deprived personnel in "real world" situations.

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1041.J

Performance during Sleep Deprivation: Evidence for State Instability and Trait Vulnerability

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Introduction: It has been frequently reported that total sleep deprivation (TSD) is associated with reduced capability to sustain attention. On a psychomotor vigilance task, this is evident as increased average reaction time (RT), but also as greater variance of RTs with progressive TSD, which has been interpreted as "state instability" as a consequence of TSD. Additionally, a proportionality has been reported between average (AVG) and standard deviation (SD) of RTs.[1] While this within-subject consideration of RT data may certainly have merit, it is also possible that there is an increase in between-subjects variance with increasing AVG of RTs, pointing to individual differences in vigilance vulnerability to TSD.[2] Thus, we hypothesize that there are three variance components contributing to the observed SDs of RTs: (1) within-subject variability (state instability), (2) between-subjects variability (individual vulnerability), and (3) noise. Their respective contributions have not been previously separated. Consequently, neither the claim of state instability nor the claim of individual differences in the vigilance response to TSD could be supported unequivocally thus far. Therefore, the present investigation evaluated the within-subject and between-subjects variance components to psychomotor vigilance performance during TSD.

Methods: Ten healthy adult subjects underwent 40 hours of TSD in a controlled laboratory environment. They were tested every 2 hours on a 20-minute psychomotor vigilance task (PVT-192). This sustained attention RT task presents a visual stimulus at random intervals varying from 2 to 10 seconds, yielding approximately 160 RTs per 20-minute test bout.[1] For each of these test bouts, we computed the AVG and SD of RTs per subject, and also across the combined data of all subjects. RTs exceeding 10 seconds (accounting for less than 2.5% of the data) were not included in this analysis, so as to avoid confounds due to non-

responses (which could last no more than 30 seconds on this task). Linear regression of AVG vs. SD of RTs (considering both AVG and SD as dependent variables) was applied for each individual subject, as well as for the combined data of all subjects.

Results: Overall (i.e., across subjects and over time of TSD), AVGs of RTs ranged from 218 to 2637 milliseconds, and SDs ranged from 38 to 2957 milliseconds, with a near-uniform distribution of AVGs and SDs occurring within these ranges. We found a significant linear relationship between individual subjects' AVGs and SDs (Chi-square tests: $P<0.001$ for all subjects). Across subjects, the mean proportionality constant was 1.6 with a standard error of 0.1 (range: 1.3 to 2.4). This proportionality indicates that substantial variance in the data was due to within-subject variability. Furthermore, if none of the variance were due to between-subjects variability (i.e., all subjects would have the same underlying statistical distribution of RTs for a given test bout), a reduction of SDs would be expected for the combined data of all subjects. On statistical grounds, we would expect a reduction of the proportionality constant between AVG and SD of RTs by a factor of approximately 3.2 (the square-root of the number of subjects), yielding an expected proportionality constant of about 0.5 for the combined data. Contrary to expectation, however, we found a proportionality constant of 1.7 for the combined data of all subjects, indicating that a substantial portion of the variance in the data must have been due to between-subjects variability.

Conclusions: The present demonstration of a linear relationship between AVG and SD of RTs within each individual supports the notion of state instability in sustained vigilance as a consequence of TSD.[1] However, this within-subject variability explains only a small portion of the variance in the data, as the proportionality between AVG and SD of RTs was not reduced, but rather increased, when the combined data of all subjects were considered. This means that there must also be considerable between-subjects variability in the data. Indeed, evidence for consistent individual differences in vigilance vulnerability over time of TSD was found in the relatively large range of proportionality constants across subjects, but there may be other aspects of the data differing among individuals as well. While this between-subjects variability may be stochastic (i.e., noise in the experiment), such individual differences may also be trait-like, as first suggested by the finding that subjects' vigilance responses to TSD were replicable across repeated exposure to TSD.[2] If further studies corroborate this finding, then the consequences for our understanding and modeling of sleep deprivation effects on performance will be considerable.

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1368.J

Sleep Loss and the Relationship Between Confidence and Accuracy of Hospital Interns' Answers to Medical Questions

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Introduction: Although sleep loss causes cognitive deficits, Blagrove and Akehurst (2000) found sleep loss participants had low confidence in their incorrect responses on laboratory cognitive tasks. The question arises of whether sleep loss participants undertaking real-world tasks have low confidence for instances when performance is deficient, or instead have inappropriately high confidence. To investigate this we had intern physicians with varying degrees of sleep loss answer questions of medical knowledge while at work.

Methods: During a day-shift 23 medical interns (M=16, F=7, age 24-35 yrs) completed a sleep questionnaire, which assessed their times of going to sleep and of waking, and the longest period of uninterrupted sleep during the night before testing, which varied due to on-call awakenings. They also rated their confidence and alertness on the Profile of Mood States. They then answered 46 medical knowledge questions, after each of which (unless they had responded don't know) they answered the question 'How certain are you of your answer?' by rating their confidence on a scale of 1 ('extremely uncertain') to 5 ('extremely certain').

Table 1

	POMS		Answers		Don't	Confidence if		C-A
	energ	conf	right	wrong	knows	right	wrong	w-s
Variable mean =	12.1	16.0	30.7	10.7	4.6	4.1	3.6	.22
Max.cont.slp. r=	.81**	.74**	.21	-.14	-.13	.04	.11	.01
POMS conf r=	.89**		.09	.15	-.23	.25	.33	.09
POMS energ r=		.89**	.12	.11	-.24	.14	.16	.13

Table 2

Max. cont.	POMS		Answers		Don't	Confidence if		C-A r_{av}	
sleep	energ	conf	right	wrong	knows	right	wrong	w-s	b-s
< 3.3h	6.7	12.9	29.8	10.8	5.3	4.1	3.6	.22	.18
> 3.3h	18.0	19.5	31.7	10.6	3.7	4.1	3.7	.22	.20
F =	18.1**	6.8*	2.7	0.6	1.4	0.0	0.0	0.0	0.0

Results: Means of number of right, wrong and don't know responses, confidence when right or wrong, and mean (rav) of the 23 within-subject Confidence-Accuracy point-biserial correlations (termed C-A w-s; C-A correlations are a measure of the appropriateness of confidence) are shown in Table 1. Table 1 also shows the correlations of these variables with maximum length of continuous sleep (group mean=3.30 hrs, SD=2.26, range = 0.00 - 8.00 hrs), and with POMS energetic and POMS confidence (df=20 as grade of intern is partialled out). A median split was then used to divide participants into those achieving at least 3.30 hours of continuous sleep on the previous night (n=11, mean=5.17 hrs, range 3.4 - 8.0 hrs), and those achieving less than this (n=12, mean=1.59 hrs, range = 0.00 - 3.00 hrs). Table 2 shows these groups differed significantly on POMS energetic and confidence, but not on response accuracy, response confidence, or mean within-subject (w-s) or between-subjects (b-s, i.e. within-questions) Confidence-Accuracy correlations (ravs). (For all comparisons between the two groups df =1,19, except for the comparison of mean between-subjects correlations, where df=1,32 as the C-A correlations from 33 questions were used.) Number of questions answered correctly was controlled for in that groups did not differ on this variable, this information having been learned prior to sleep loss.(tables should be placed here)*p<.05 **p<.001

Conclusions: Amount of sleep loss was significantly related to deficits in confident and energetic mood, but did not affect the appropriateness of individuals' confidence for answers to questions. This indicates that possible deleterious consequences of sleep loss for real-world tasks could be mitigated by appropriate confidence, which would remain low for incorrect responses, and so more time may deliberately be taken over a task, or more caution exercised, or a second opinion called for, although accidents due to falling asleep could still occur.

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1373.J

Subjective and Objective Measures of Drowsiness in Relation to Sleep Debt

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Introduction: Drowsiness was evaluated by subjective ratings, MSLTs, and vigilance tasks in 6 college-age subjects during experimental conditions of *ad-libitum* sleep, partial sleep deprivation, and sleep satiation.

Methods: Twelve healthy college-age students were screened for sleep disorders and daytime sleepiness. Half of the 12 students were designated observers and the others were subjects, and were further divided into 3 teams, each consisting of 2 observers and 2 subjects. All 12 students completed Stanford Sleepiness Scales (SSS) every half-hour for 2 wks, and noted times when they were at peak drowsiness. They also completed daily sleep logs for the same time period. The 6 subjects each wore actigraphs (Actiwatch model AW-4, Mini-Mitter, Co., Sunriver, OR) to verify the sleep log data, and were placed in 3 conditions for 3 consecutive nights apiece: (a) *ad-libitum* sleep (AL); (b) partial sleep deprivation (SD); and sleep-satiation (SS). The AL condition consisted of each subject's usual sleep-wake patterns. The SD condition consisted of reducing each subject's sleep by 2 hr (i.e., going to bed 2 hr later, awaking at the usual morning time). The SS condition consisted of extending each subject's sleep by 2 hr (i.e., going to bed 2 hr earlier, awaking at the usual morning time). No daytime naps were allowed for any condition. Each condition consisted of a 3-night period in their dormitory, and each subject was then studied in the laboratory following each of the 3-night conditions. Each 4-member team were placed in each condition in random order, and the start of the experiment for each team was staggered, so that only one team was present in the laboratory at the end of each 3-night condition. During the laboratory day, the subjects underwent multiple sleep latency tests (MSLTs) and vigilance tasks. There were 4 MSLTs starting at 10 am, but when the subjects were in the SD condition, they had an extra nap at 8 pm. If the subjects achieved the MSLT research criteria of 3 consecutive sleep epochs, they were awakened to prevent further sleep. Vigilance tasks (SteerClear, 4-Choice) were administered after each MSLT. Lastly, during the days the observers and subjects were in the laboratory, the observers rated the subjects at half-hour intervals using the SSS, and noted times when the subjects appeared at peak drowsiness. Each subject's condition was blinded to the observer.

Table 1

	AL	SD	SS
TST (hr)	6.7* (1.4)	5.0* (1.5)	7.4* (2.1)
SE (%)	88.1 (10.0)	85.3 (14.1)	79.5 (17.2)
Sleep Quality (%)	68.2 (19.3)	78.3 (15.1)	75.4 (17.2)
Refreshed After Sleep (%)	57.5* (16.1)	47.9* (14.8)	73.3* (16.1)
MSLT (min)	15.1 (3.6)	7.9 (4.7)	12.0 (3.2)
SteerClear (#errors)	1.5 (0.7)	1.2 (0.8)	1.0 (1.1)
4-Choice (reaction time in msec)	454.2 (33.2)	492.7 (33.9)	472.4 (23.6)

Results: The table shows the means with standard deviations in parentheses, and asterisks indicate significance levels less than 0.05 by non-parametric Friedman's ANOVA by ranks test. A mean Pearson correlation of 0.14 ± 0.237 between the subjects' SSS ratings and the observers' SSS ratings of the subjects was obtained.

Conclusions: Several comments can be made on these preliminary data: (1) As observed in prior studies, college-age subjects have significant sleep debt (i.e., they have low *ad-libitum* TST and report non-refreshing sleep); (2) Individuals' perception of drowsiness differs markedly from observer ratings of their drowsiness; and (3) Three consecutive nights of increased sleep may not be sufficient to significantly affect sleep debt in this age group.

Special thanks to Drs. Baljit Singh, H.S. Bains, and Mala Ahluwalia for their assistance with this study.

1058.J

Therapeutic Effects of CriticallyTimed Sleep Deprivation in Pregnancy and Postpartum Depression

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Introduction: Sleep disturbances characterize depression and sleep deprivation improves mood in a majority of patients with a major depressive episode. In fact, sleep EEG disturbances that characterize a major depressive disorder predict a therapeutic response to sleep deprivation. Postpartum depression is categorized as an onset specifier for mood disorders in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). Untreated major depressive episodes occurring during pregnancy or postpartum may deter healthy development of the fetus or infant and have potentially long-term ill consequences for the mother and her family. Many depressed pregnant or postpartum women are not willing candidates for pharmacologic interventions given the potential adverse effects of medication on the fetus or brest-fed child. Critically timed sleep deprivation offers the potential to improve mood within a few hours in depressed pregnant or postpartum women without the attendant risks or side effects of pharmacological interventions.

Methods: Nine women who met DSM-IV criteria for a major depressive episode with onset during pregnancy or within 1 year postpartum underwent a trial of either ealy-night partial sleep dprivation (ESD), in which they were sleep deprived in the early part of one night and slept from 03:00-07:00 h, or late-night sleep deprivation (LSD), in which they were deprived of sleep in the latter part of one night and slept from 21:00-01:00 h. Mood was assessed before the night of sleep deprivation, after the night of sleep deprivation, and after a night of recovery sleep (sleep 22:30-06:30 h) by tained clinicians, blind to treatment condition, using standarized scales.

Results: More patients responded to LSD (9 of 11 trials: 82%) compared with ESD (2 of 6 trials: 33%) and they responded more after a night of recovery sleep (9 of 11 nights: 82% than after a night of sleep deprivation (6 of 11 nights: 55%). Pregnant women were the only responders to ESD and the only nonresponders to LSD. Sleep quality (as measured by an increase in sleep efficiency, and delta sleep, and a decrease in wake after sleep onset), improved after LSD more than ESD. The small and heterogeneous sample prevent further and more definitive conclusions based on statistical analyses.

Conclusions: Although the findings are preliminary, the resutls suggest that with further study, critically timed sleep deprivation interventions may benefit women with pregnancy or postpartum mood disorders and potentially provide a viable alternative treatment modality for those

women who are not candidates for pharmacological management. Such interventions are needed to help prevent the devastating effects of depression during pregnancy and the postpartum period on the mother, infant and family.

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1072.J

Sleep-Deprivation-Induced Peripheral Visual Neglect Identified in a Driving Simulator Study

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POSTER PRESENTATIONS

Introduction: We describe here the results of two sleep deprivation studies revealing impairments in performance on a visual divided attention task. We believe impairments of peripheral visual performance represent and suggest a transient peripheral visual field neglect in sleep deprivation. We have shown that sleep deprivation results in decreases in regional cerebral glucose metabolism in frontal and parietal heteromodal regions.[1] Peripheral visual field neglect may be attributed to dysfunction of these frontal and parietal regions. In driving simulations conducted in our laboratory, one task requires dividing attention between driving and registering recognition of a randomly timed peripheral visual field stimulus. We analyzed this divided attention task to ascertain if impairments on this task occurred with sleep deprivation, indicating a possible peripheral visual field neglect.

Methods: In two sleep deprivation studies, both driving and peripheral visual field awareness were measured on the STISIM[2] simulator. STISIM provided a fully interactive audiovisual display responsive to steering, braking, and throttle inputs. Peripheral visual field awareness, referred to as the divided attention task, was measured by presenting at semi-randomized intervals colored triangles in the right or left upper fields of the computer monitor. The driving scenarios were 40 minutes in length and administered every 3 hours during the awake period. In the 64 hour total sleep deprivation study, 12 volunteers were evaluated 8 times per scenario with triangles remaining for 5 seconds or until the driver flicked the directional signal. In the 7 day partial sleep deprivation study, 66 volunteer commercial drivers were evaluated with triangles remaining for 10 seconds or until the driver flicked the directional signal. For the partial sleep deprivation study, the results discussed here will be from the drivers randomly assigned to 7 nights of 3 (n=16) or 9 (n=16) hours per night in bed.

Results: In the 64 hour total sleep deprivation study correct responses to the peripheral visual images remained high (mean 98%) for 20 hours, after which correct responses declined to a low of 77% by 50 hours ($p<.01$ @ 49 hrs). In the chronic partial sleep deprivation study, correct responses to the peripheral visual images dropped significantly ($P<.01$)in the 3-hr partial sleep deprivation group beginning on experimental day 5 and persisted through the third and final recovery day, when compared to the 9-hr sleep group. The volunteers were awake during the driving scenario as determined by polysomnography and microsleep microsleep analysis.

Conclusions: Impairments on a peripheral visual attention task in a driving simulator appeared at 20 hours of total sleep deprivation and achieved significance at 49 hours, while impairments appeared and became significant at 5 days of partial chronic sleep deprivation. Peripheral visual field neglect as demonstrated by impairments on a peripheral visual field attention task during sleep deprivation, may be a behavioral manifestation of sleep deprivation-induced hypometabolism in frontal eye fields and/or posterior parietal heteromodal areas.

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(2) Systems Technology, Inc. Simulator, Hawthorne, CA

Research supported by US Army Medical Research and Materiel Command, US Department of Transportation - Federal Highways Authority

1746.J

The Effect of Total Sleep Deprivation on Muscle Sympathetic Nerve Activity

Kanbayashi T, Ogawa Y, Takahashi Y, Saito Y, Takahashi K, Hishikawa Y, Y. Kaneko, F. Suzuki, M. Abe, Shimizu T

Introduction: It has been demonstrated that sleep deprivation (SD) has profound effect on many aspects of physiological function such as the alertness, cognition, immune function and autonomic function. We report here the effect of overnight sleep deprivation on heart rate (HR), blood pressure (BP) and muscle sympathetic nerve activity (MSNA), which is a direct measurement of post-ganglionic sympathetic efferent innervating vascular bed in the skeletal muscle in man.[1] To elucidate the detailed relationship between MSNA and blood pressure after SD, the relationship between diastolic BP and corresponding MSNA burst incidence was analyzed.

Methods: The subjects was six healthy male students aged from 20 to 28. Each subject gave informed consent about the purpose and the risk involved in the study. Each subject came to the lab at 22pm prior to the experimental day. After wearing the electrodes for recording polysomnogram (PSG), ECGs, the subject maintained supine position one night in the dark (below 50 lux). To keep the subject awake, the subject was allowed to watch video programs on LED monitor (below 15 lux). In the next morning, a tungsten microelectrode for recording MSNA was inserted to the peroneal nerve. The blood pressure at the radial artery was continuously recorded along with MSNA, ECG and PSGs. All experiments was conducted between 9 and 11am. The light intensity was kept below 50 lux all through the experiment. For the control study, the same procedure except for SD was repeated at an intervals of at least 1 week. They also came to the lab at 22pm and allowed to sleep from 23pm to 7am in the next morning. We used burst rate (BR) as a parameter of MSNA which was the number of peaks in the integrated MSNA traces per minute. BR, heart rate (HR), systolic and diastolic BP were compared between those after SD and after sleep using Wilcoxon signed rank test. Sensitivity and set point of baroreflex regulation was also analyzed according to the method of Fagius et al.[2] In brief, we checked the appearance of MSNA for corresponding heart beat for more than 300 heart cycles. Then we calculated the probability of appearance of MSNA burst (burst incidence: BI) corresponding to a given diastolic BP. The calculated BI was plotted against diastolic BP and simple regression analysis was done. If it reached a significant level ($p<.05$), the x-axis intercept (BS) which is a parameter for baroreflex set point and the slope, a parameter for baroreflex sensitivity were obtained. Then, these parameters after SD and control sleep were compared by Wilcoxon signed rank

test.

Results: Diastolic BP after SD was significantly higher than those after sleep (65.2±2.7 mmHg vs 60.3±.7 mmHg, p<.05). BR of MSNA was lower after SD than after sleep (10.6±3.8 mmHg vs 14.6±6.4 mmHg, p<.05). There were no significant differences in systolic BP and HR between two conditions. A statistically significant regression was observed between BI and diastolic BP in every subjects both after SD and after control sleep (Fig1). BS after SD was significantly higher than that of after sleep. The slope showed no difference between these two conditions.

Figure 1

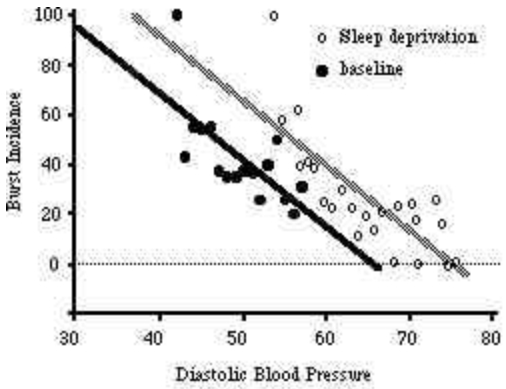

Fig1. Relationships between diastolic BP and probability of the appearance of MSNA burst (burst incidence: BI) in 5 subjects. A significant regression was observed between BI and diastolic BP in all the subjects both after SD and sleep.

Conclusions: Diastolic BP increased significantly and BR decrease significantly after overnight SD. Decreased BR after SD would probably be caused by elevated diastolic BP via baroreflex. However, detailed analysis using in this study demonstrated that the set point for baroreflex shifted to the right (high BP level). The sensitivity of baroreflex seemed not to be changed after SD. It is well known that shift workers, who are chronically sleep deprived, show higher cardiovascular morbidity including hypertension.[3] Our results indicate that even a overnight SD can shift baroreflex set point to higher BP. So resetting of baroreflex set point by SD would contribute to the higher cardiovascular morbidity in shift workers.

References:

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This research supported by a grant from the Japanese Ministry of Health and Welfare, and Special Coordination Funds for Promoting Science and Technology from the Science and Technology Agency.

1758.J

Sleep Deprivation Increases the Number of Neurons that Contain the p65 Subunit of Nuclear Factor Kappa B within the Lateral Hypothalamus of Rats

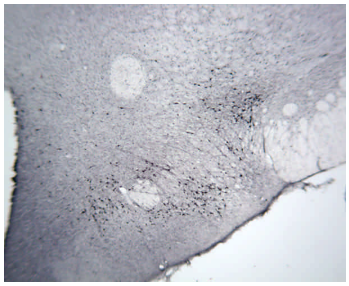
Brandt J, Churchill L, Fang J, Krueger JM

Introduction: Sleep is hypothesized to influence dynamic microcircuitry changes in the brain. Sleep deprivation increases the sleep propensity as well as the production of a number of sleep-promoting factors within specific brain regions. An important transcription factor that is involved in gene activation induced by various sleep-promoting growth factors is nuclear factor kappa B (NFkB). The p65 subunit of NFkB translocates as a heterodimer including p50, p52 or c-Rel subunits into the nucleus of cells and promotes gene transcription. Sleep deprivation increases nuclear translocation of NFkB in the cortex as evidenced by a gel mobility shift assay (Chen et al., 1999) as well as many other brain regions as evidenced by a strain of mice with a NFkB promoter-lac Z transgene (see accompanying abstract-1713). Since the antibody to the p65 subunit of NFkB dramatically labels a population of neurons in the tuberal lateral hypothalamus of rats (Joseph et al., 1996), we evaluated the effect of sleep deprivation on these neurons.

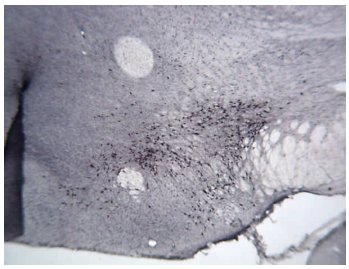
Methods: The rats were kept at 12 hr light/dark cycle (9 am onset)and handled gently for 3 days prior to the experiment. Control rats (n=4) were handled gently and then returned to their home cages and undisturbed for 6 hrs. Experimental rats were sleep-deprived for 6 hrs by gently disturbing the home cage environment occasionally. The sleep-deprived rats were observed continuously to prevent sleep. The rats were anesthetized at 3 pm and cardiac-perfused with 15% picric acid, 2% paraformaldehyde. The brains were removed and postfixed for 30 min prior to sinking in 20% sucrose. The brains were sectioned on a sliding microtome at 50 microns and the sections were incubated with the antibody to the p65 subunit of NFkB (Santa Cruz).

Figure 1. Immunocytochemistry of p65 subunit of NFkB in the tuberal lateral hypothalamus after 6 hrs of sleep deprivation

Control



Sleep-Deprived



Immunocytochemistry of the p65 subunit Of NFkB in the tuberal lateral hypothalamus After 6 hrs of sleep deprivation.

POSTER PRESENTATIONS

Results: The number of p65 subunit-containing neurons that localize in the tuberal lateral hypothalamus adjacent to the medial subthalamus increased dramatically with sleep deprivation. These neurons have been demonstrated to be uniquely different from the orexin/hypocretin-containing neurons that also exclusively localize in this region (Horvath et al., 1999).

Conclusions: These data support the hypothesis that tuberal lateral hypothalamic neurons are important in sleep regulation.

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1425.J

Sleep EEG in the Djungarian Hamster as a Function of Prior Waking Duration

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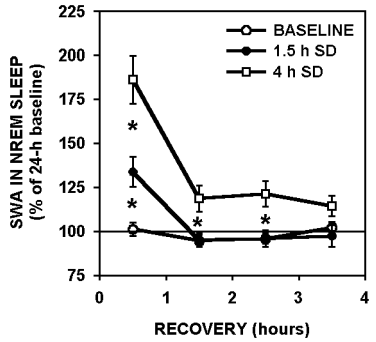
Introduction: It is generally accepted that EEG slow-wave activity (SWA, EEG power density between 0.75-4.0 Hz) in NREM sleep reflects a homeostatic component of sleep regulation. In many species it has been shown that SWA increases after sleep deprivation (SD), but only in few a dose relation between the duration of wakefulness and the subsequent SWA increase was shown. Based on the distribution of sleep and waking, SWA in NREM sleep has been successfully simulated in the human, rat (see Borbély 1994 for review), and 2 mouse strains (Huber et al, in press). In the Djungarian hamster SWA in NREM sleep increases as a function of prior torpor duration (Deboer and Tobler 1996), but the question remained if a similar relation can be found with prior waking duration.

Figure 1



Methods: EEG, EMG and EEG spectral data were obtained from 2 groups of Djungarian hamsters (Phodopus sungorus) well adapted to a short photoperiod (L:D 8:16 h) at 14-16°C ambient temperature. After a 24-h baseline recording the animals were either subjected to 1.5 h SD (n=8) or 4 h SD (n=7). Recovery was recorded for the subsequent 4 h. Vigilance states were scored according to criteria described previously (Deboer and Tobler 1996).

Results: SWA in NREM sleep increased as a function of SD duration (Fig. 1). Neither the amount of NREM nor REM sleep changed as a function of SD duration, although in the first recovery hour the amount of NREM sleep was highest after 4 h SD (data not shown).

Conclusions: Also in the Djungarian hamster the increase in SWA in NREM sleep is a function of prior waking duration, as proposed by the two-process model of sleep regulation (see Borbély 1994 for review). Although the results are similar to the effects of daily torpor, preliminary comparisons with the increase rate of SWA during daily torpor suggest that there may be subtle differences in the increase rate and/or upper threshold of SWA.

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(2) Deboer T, Tobler I: Natural hypothermia and sleep deprivation: Common effects on recovery sleep in the Djungarian hamster. Am J Physiol, 1996, 271: R1364-R1371
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Research supported by Swiss National Science Foundation grant 3100-042500.94 and 3100-053005.97.

1769.J

Sleep Deprivation Interferes with Increased Nuclear Translocation of Nuclear Factor Kappa B After a Whisker Cut: A Model to Test Sleep Function

Guan Z, Churchill L, Ellis G, Rehman A, Memet S, Israel A, Fang J, Krueger JM

Introduction: Sleep is hypothesized to influence dynamic microcircuitry changes at a local network level in the brain. Sleep deprivation increases the sleep propensity as well as the production of a number of sleep-promoting factors. An important transcription factor that is involved in gene activation induced by various sleep-promoting growth factors is nuclear factor kappa B (NFkB). By utilizing a strain of mice with a NFkB promoter-lac A transgene, the anatomical localization of nuclear translocation of NFkB in response to neural adaptations resulting from cutting mystacial whiskers unilaterally can be analyzed by comparing the distribution of nuclear beta-galactosidase activity.

Methods: At light onset (9 am) mice were lightly anesthetized with isoflurane and the long mystacial whiskers were trimmed to the level of the facial hairs on either the left or right side (randomly selected). The control mice were returned to their home cages while the experimental mice were gently disturbed over the next 6 hours to prevent sleep. Videotapes of selected control mice showed that they went to sleep within 2 hrs after the whisker cut. The mice were deeply anesthetized after 6 hrs and cardiac perfused with 2% paraformaldehyde. The brains were removed, postfixed for 30 min and sunk in 20% sucrose overnight. The brains were frozen and cryostat-sectioned and analyzed for beta-galactosidase activity.

Results: Within the brainstem and mesencephalon, a unilateral whisker cut at light onset increases signficiantly the number of cells with NFkB-activated beta-galactosidase activity in dorsal regions of spinal 5, the

principal trigeminal nucleus and mesencephalic 5 nucleus on the side that receives input from the whisker cut at 6 hr after the cut. No differences were observed after the whisker cut in the ventroposteriomedial nucleus of the thalamus or the barrel field of the somatosensory cortex. Sleep deprivation of 6 hr significantly increased the beta-galactosidase activity throughout the somatosensory projection within the brainstem. However, no additional increases were observed in the brainstem on the side that receives input from the cut whiskers.

Figure 1. NFkB-activated beta-galactosidase in the spinal 5 nucleus on the side that receives input from the intact whiskers

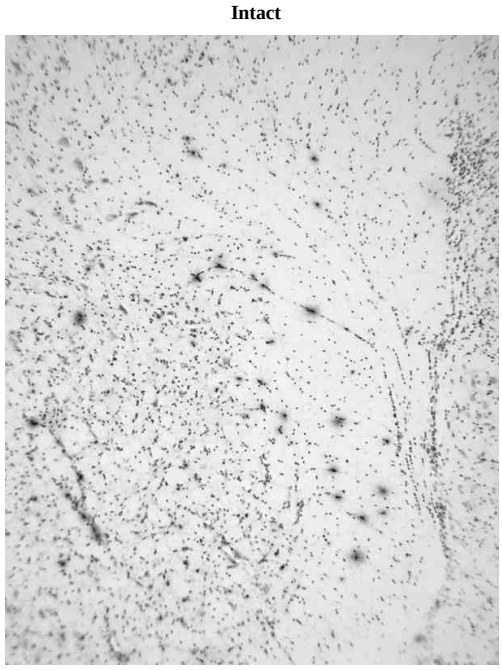
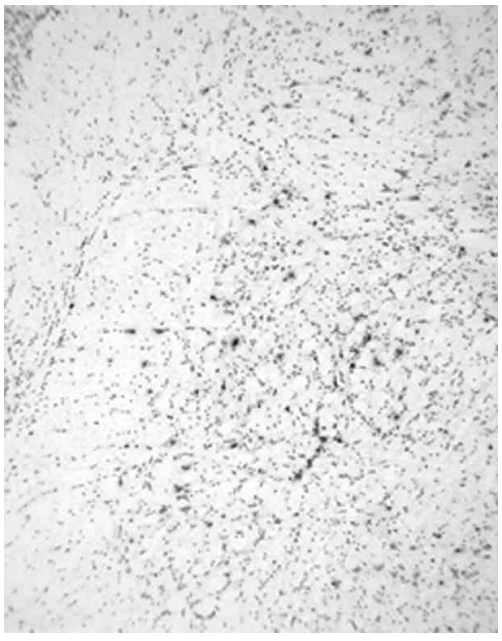


Figure 2. NFkB-activated beta-galactosidase in the spinal 5 nucleus from the side that receives input from the cut whiskers



Conclusions: These data support the hypothesis that sleep functions to maintain, repair or consolidate the neural adaptations to the whisker cut.

Supported by NIH grants HL64245 to J.Fang and HD36520, NS25378 and NS31453 to J.M. Krueger

1772.J

Effects of Total Sleep Deprivation on Corticosterone Plasma Concentrations in Neonatal Rats

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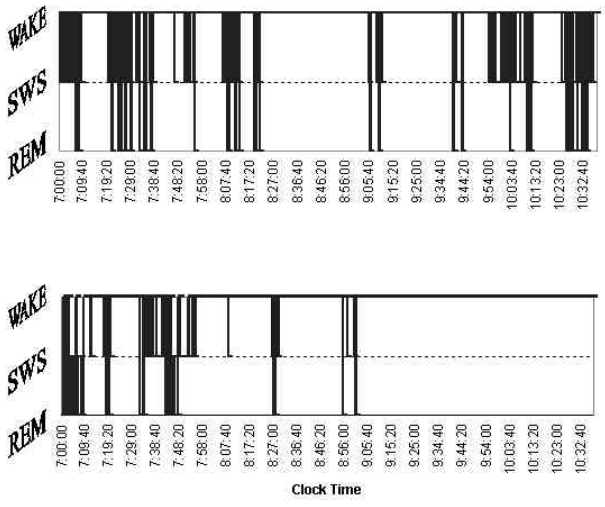
Introduction: Prolonged sleep deprivation in rats increases energy expenditure, initiates hypercatabolism and results in death. Steroid hormones have been implicated in this outcome. Sleep deprived humans exhibit increased evening levels of cortisol and reduced glucose metabolism. In rats selective REM deprivation increases levels of corticosterone (CORT) and corticoptropine releasing hormone. Plasma levels of CORT are regulated mainly via the hypothalamic-pituitary-adrenal (HPA) axis. Increased levels of plasma CORT are associated with response to stress. In neonates, CORT levels are low, and under normal conditions young animals do not express a stress-response. Exposure to exogenous CORT, or initiating a stress-response by extreme measures (e.g., maternal deprivation), have long-term deleterious effects on the function of the HPA axis. Few long-term neonatal EEG recordings have been reported as these usually require isolating the animal. Frank and Heller '97 developed a protocol wherein control of environmental temperature, feeding, and grooming, enabled up to 36 hour recordings from neonatal rats without maternal deprivation-induced stress. This study tested whether this protocol does not induce a stress-response in pups, and assessed the level of stress in young animals sleep deprived by gentle handling.

Figure 1. Hypnogram of non-SD (top) and SD (bottom) animals

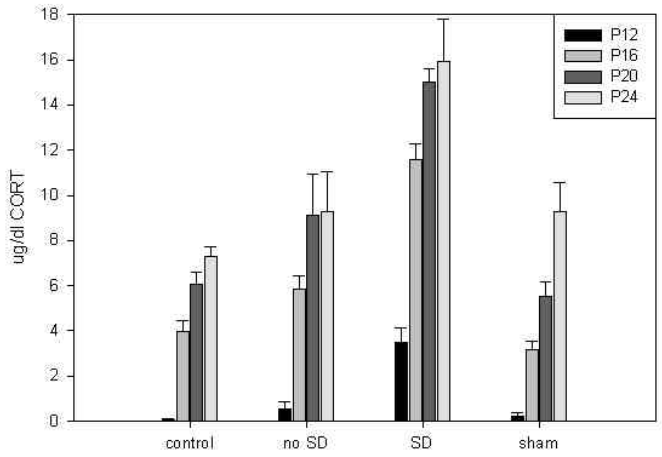


Methods: P9 rat pups were surgically prepared for EEG-EMG recordings. There were four age groups P16, P20, P24, and 4 experimental conditions per age - sleep deprived (SD), non-sleep deprived (non-SD), SHAM surgery and untouched controls (the latter two were not recorded). All pups were handled for 10-15 minutes prior to recording. Recording started the evening prior to sleep deprivation. P12 and P16 animals were fitted with feeding tubes, older animals had free access to food and water. Cage temperature was ~34°C, ~30°C, ~27°C and ~23°C for increasing ages, respectively. P12 and P16 animals were groomed. Sleep deprivation lasted 70, 90, 140, and 360 min for the increasing

ages, respectively. At the end of sleep deprivation animals were decapitated and trunk blood was collected. CORT levels were assessed using a competitive binding assay against a standard curve of CORT (Sigma, USA) ranging from 0.01-5ng/m.

Results: SD animals had no less than 80% wake during the period of deprivation, non-SD animals slept a minimum of 60% of the equivalent period. SD animals had elevated levels of CORT in comparison with age-matched controls (P12: $F(3,22)= 21.34$, $p<0.0001$; P16: $F(3,21)= 42.3$, $p<0.0001$; P20: $F(3,20)= 17.22$, $p<0.0001$; P24: $F(3,18)= 5.68$ $p=0.0064$, N=6 for all groups). Sham CORT levels were similar to controls in all age groups, suggesting that surgery had no long-term effects on this parameter.

Figure 2. Plasma levels of CORT



Conclusions: This study showed that our protocol for sleep recording in neonate rats protects the pups from stress due to maternal deprivation as indicated by levels of CORT. Elevated levels of CORT in the SD P12 animals suggests the HPA system was activated in these animals even though the non-SD animals had low levels of CORT, similar to controls.All SD animals showed a marked increase in plasma CORT suggesting that even this low-level sleep deprivation can act as a stressor.

References:
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(2) Meaney, M. J., J. Diorio, et al. (1996). "Early environmental regulation of forebrain glucocorticoid receptor gene expression: implications for adrenocortical responses to stress." Developmental Neuroscience 18(1-2): 49-72.
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1782.J

Pemoline-Induced Wakefulness and Compensatory Sleep: Assessment of Sensitization and Tolerance

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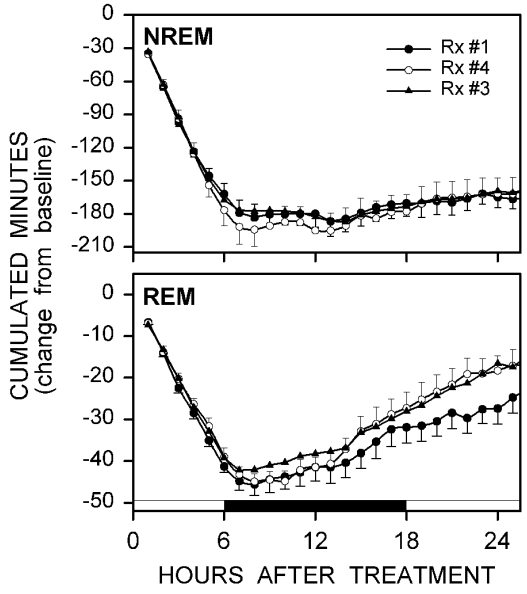
Introduction: Stimulants that increase wakefulness via action at monoaminergic transporters can, upon initial administration, produce sensitization, and with repeated administration, produce tolerance, however these issues have not been systematically explored with respect to stimulant interactions with sleep homeostasis. When administered to naïve rats at 10mg/kg, pemoline dramatically increases wakefulness that is not followed by any appreciable amount of compensatory sleep.[1] Whether sensitization or tolerance impacts the wake-promoting action of pemoline or subsequent compensatory sleep response is not known. For example, it is plausible that the lack of compensatory sleep is a phenomenon limited to drug action in naïve rats. To address this possibility, sleep-wakefulness was monitored continuously for 5 weeks in rats treated every 7 days with a potent wakefulness-promoting dose of pemoline.

Methods: Adult male Wistar rats (N=12) were surgically prepared with a cranial implant that permitted chronic EEG and EMG recording, and with a miniature transmitter in the abdomen for monitoring body temperature and locomotor activity. Sleep-wake states were discriminated using SCORE,TM an on-line sleep-scoring system validated for rodents, which also collected the concurrent telemetry data. Animals entrained to LD 12:12 lived continuously in separate chambers and were injected i.p. (1 ml/kg) 5 h after lights-on with 10 mg/kg pemoline dissolved in sterile 0.25% methylcellulose once per week for four consecutive weeks. Hourly group means for all variables were computed for 30 hours before and after treatment. In addition, for each hour post-treatment, the change-from-baseline value for NREM sleep was computed, the baseline value being the minutes of NREM during the same circadian time 24 hours earlier. This cumulative change-from-baseline value was determined for each hour post-treatment. The "maximum NREM deficit" was defined as the most-negative point in the cumulative NREM deficit profile. REM sleep was similarly analyzed.

Figure 1. Cumulative deficit in NREM and REM sleep after the first, third, and fourth acute treatments with pemoline



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Results: The maximum NREM deficit averaged -183±12 minutes, was reached 7 hours after injection, and did not differ between treatments (see Figure). Thirty hours post-treatment there was no significant recovery of the NREM sleep (NREM deficit = 167±8 minutes). Maximum REM sleep deficit was –45±2 minutes and did not differ with repeated treatment. REM sleep recovery 30-h post-treatment #3 and #4 were 14±5 minutes as compared to -24±4 after the first pemoline treatment, but hour-by-hour differences were not significant. Interestingly, there was evidence of sensitization in body temperature increase, but not locomotor activity level, with repeated pemoline treatment that was independent of sleep-wake effects.

Conclusions: Repeated administration of pemoline once weekly produces no sensitization or tolerance, as measured by wake-promoting efficacy and the compensatory sleep response to drug-induced wakefulness, in the rat.

References:
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Research supported by NIH grant HL61594

1789.J

Impact of Short Sleep Duration on Sleepiness, Performance, Mood and Glucose Metabolism.

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Introduction: Chronic sleep loss is an increasingly common condition, which affects millions of individuals in industrialized countries. The current consensus is that sleep deprivation is only deleterious to the brain and has no effect on peripheral functions. A study performed with 11 young men in a clinical environment indicated otherwise (Spiegel, et al., 1999). The results showed that sleep curtailment is associated with negative alterations of glucose tolerance and endocrine function, which could have adverse health affects under chronic conditions. We are investigating whether similar results are found in individuals who voluntarily chronically curtail their sleep in their normal environment.

Methods: Twenty six healthy non-obese adults, 13 chronic short sleepers (sleep duration < 6.5hrs) and 13 "normal" sleepers (sleep duration >7.5hrs and <8.5 hrs), aged 24-40 years old, were studied in their normal environments. The subjects wore a wrist activity monitor for one week to verify their usual sleep duration. Subjects who met the inclusion criteria then recorded their sleep at home using the Nightcap, an ambulatory sleep recording system, for two nights. On the final day of the study, the subjects were admitted to the Clinical Research Center after an overnight fast and underwent an intravenous glucose tolerance test (IVGTT). Paper and pencil scales of sleepiness (Stanford Sleepiness Scale) and mood (Visual Analog Scale for Global Affect), and a computerized test of cognitive performance (perceptual cueing task) were administered hourly, before and during the IVGTT.

Results: Based on the mean of the two nights of Nightcap recordings, the mean (±SEM) sleep time was 306 ± 17 min in the short sleepers and 486 ± 5 min in the normal sleepers ($p<0.0001$). Subjective sleepiness across the 4-hour IVGTT study period did not differ significantly between the two groups. However, short sleepers had significantly decreased reaction times on the performance task ($p< 0.02$) and tended to have lower scores on the Global Affect scale ($p<0.08$). First phase insulin secretion and insulin sensitivity (SI) were calculated using the Bergman minimal model. Glucose levels before and during the IVGTT were similar in both groups. However, on average, short sleepers secreted 65% more insulin than normal sleepers (371 ± 52 versus 225 ± 41 pmol/ml) to maintain similar glucose profiles. Consistent with this observation, insulin sensitivity was reduced by nearly 40% in the short sleepers as compared to the normal sleepers (5.66 ± 1.05 10-5*min-1*pM-1 versus 9.06 ± 1.47 10-5*min-1*pM-1, $p<0.08$).

Conclusions: Voluntary chronic sleep curtailment is associated with cognitive and metabolic alterations but not with increased self-reported sleepiness.

References:
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Research supported by grant DK-41814 and AG-11412 and by the MacArthur Foundation. The University of Chicago Clinical Research Center is supported by NIH grant M01-RR00055.

1469.J

Residual Effects of Call on Sleep and Mood in Medical Residents

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Introduction: Research has documented that medical residents on call have decreased total sleep time (TST) and increased dysphoria (Akerstedt et al, 1990). We evaluated the mood effects following a night on call and the time course of recovery.

Methods: Thirty-four residents from the departments of Internal Medicine at two universities participated in this study. Each morning at about 0800 hours, residents completed the Profile of Moods Scale (POMS), estimated TST and completed the Epworth Sleepiness Scale. An actigraphy device (Minimitter®) worn throughout the study monitored sleep. An ANOVA was performed to evaluate group differences between the morning following call (On-Call), and the three post call days (Post Call +1, Post Call +2, and Post Call +3).

Table 1

Measure	Call	Post Call +1
Reported Sleep (hr.)	3.7 + 2.4(101)	7.6 + 2.3(81)
Actigraph Sleep (hr.)	3.8 ± 2.5(74)	7.3 ± 2.4(58)
POMS Fatigue	11.8 + 8.1(102)	7.5 + 6.3(82)*
POMS Confusion	6.9 ± 5.1(102)	5.5 ± 3.9(82)*
POMS Vigor	10.8 + 6.6(102)	14.5 + 7.2(82)*
Epworth	14.6 ± 7.4(102)	9.1 ± 5.8(81)*

Measure	Post Call +2	Post Call +3
Reported Sleep (hr.)	7.1 ± 1.6(73)	7.1 ± 1.4(78)
Actigraph Sleep (hr.)	6.8 + 1.5(55)	6.9 + 1.7(63)
POMS Fatigue	5.0 ± 6.1(69)	3.8 ± 4.6(78)
POMS Confusion	4.3 + 4.8(70)	4.2 + 3.7(78)
POMS Vigor	17.1 ± 7.5(70)	15.0±7.2(78)
Epworth	7.6 + 5.6(71)	6.1 + 5.6(77)

* = Post Call +1 diff. from Post Call +2 & +3 ($p <.05$)

Results: Self-reported sleep and actigraphy monitored sleep both indicated significantly decreased TST On-Call than for Post Call (Table, all $p < .05$). Post Call nights +1, +2 and +3 TST did not differ from one another. Post call TST recovered on the first night post call but without rebound. Decreased TST was associated with decreased POMS Vigor

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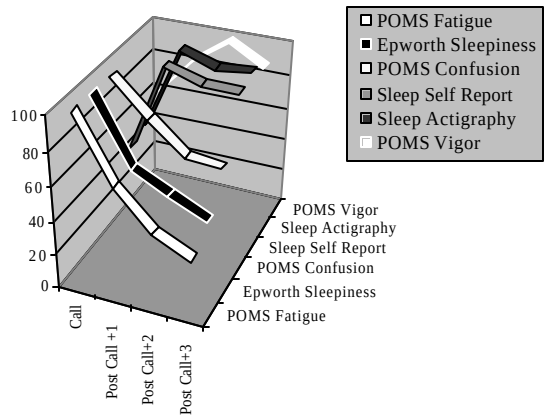
that improved over the three post call days. POMS Fatigue, POMS Confusion, and Epworth Sleepiness were also greater On-Call and improved over the three post call days. These data are displayed in the Figure as a percentage change.

Figure 1



Conclusions: Although TST recovered within one day Post Call, mood effects measured by the POMS (Vigor, Fatigue and Confusion), and Epworth measured sleepiness take at least two days to recover. The lingering effects from the residents sleep deprivation may affect their interaction with patients and supervisors. An important question is whether or not a scheduled rebound sleep time would reduce more quickly the lingering effect of call.

References:
(1) Akerstedt T, Arnetz B. B, Anderzen I. Physicians during and following night call duty-41 hour ambulatory recording of sleep. Electroencephalography and Clinical Neurophysiology, 1990, 76, 193-196.

1830.J

Peptidoglycan Recognition Protein (PGRP) Transcripts Increase During Sleep Deprivation

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Introduction: Muramyl peptides (MPs) are components of bacterial cell wall peptidoglycan; MPs were also identified as sleep promoting substances isolated from human urine and from brain of sleep-deprived rabbits (reviewed Krueger and Majde Crit. Rev. Immunol. 14:355, 1994). Although it was assumed that the sleep-promoting MPs were derived from bacteria of gut origin and that they elicited their effects on the brain via cytokines, it remained unknown how MPs or peptidoglycan induced cytokines. Recently PGRP was characterized as a normal brain product and its mRNA and protein levels are upregulated by bacterial infection (Kang et al PNAS, 95:10078, 1998). We showed (unpublished) that the transcripts of PGRP are identical to a novel cytokine described as TAG7 (Kiselev et al. JBC, 273:18633, 1998). TAG7 mRNA and protein are also induced by bacterial infections. We determined if PGRP is upregulated in brain during sleep deprivation.

Methods: We used semi-quantitative RT-PCR to compare the level of PGRP transcripts in cortex, brainstem, hippocampus, and hypothalamus of six control rats and equal number of rats subjected to 8 hour of sleep deprivation. All rats were kept at 12:12 hour light/dark cycle in a controlled ambient temperature and the sleep deprivation was started at the onset of the light cycle.

Results: A 75% increase in PGRP transcripts was observed for the hypothalamic region ($t10 = -2.63$, $p<0.03$) in sleep deprived animals compared to controls and the brainstem region exhibited a 26 % increase in PGRP transcripts in sleep deprived group ($t10 = -2.62$, $p<0.03$).

Conclusions: These experiments raise some very interesting questions such as: Why should a bacterial product recognition protein be in normal brain: Why should it up regulation in response to changes in sleep? The current data provide evidence for the notion that MPs and PGRP play a role in sleep regulation.

References:
(1) Krueger, Majde, Crit Rev Immunol, 14:355, 1994.
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Research supported by NIH grants HD 36520, NS 27250, NS 31453

1527.J

Cognitive Function After Severe Sleep Restriction

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Introduction: A fund-raising event provided an opportunity to investigate the effects of marked sleep restriction. We chose to study executive function, including learning, memory and creative thinking in this opportunistic sample.

Methods: Approximately two-hundred individuals participated in a "stand-a-thon" at five sites in the St. Louis Metropolitan area to raise money for charity. Stand-a-thon rules restricted subjects from sitting, lying down or leaning except when taking a scheduled break. Subjects were given four 15-minute breaks per 24-hour period, taken ad libitum. Thirty-nine subjects between the ages of 18 and 60 participating in the stand-a-thon agreed to complete cognitive testing. Subjects included were self-reported normal sleepers with no significant medical or psychiatric problems. Cognitive performance was assessed by a battery of standardized psychometric tests administered on Day 1, 3, 4 or 5, between 1600 and 2300 hours. Because of logistical problems (staff time, subject refusal to participate, and exclusion of individuals because of medical conditions), testing was completed on 20 subjects on day 1. Subject attrition in the stand-a-thon resulted in no subject being tested more than one time, yielding independent groups for days 1, 3, 4 and 5. The testing battery included the Torrance Tests of Creative Thinking – Verbal Form A (TTCT-V) and the Wechsler Memory Scale III subtests Logical Memory (LM) I and II, Letter Number Sequencing (LNS), Spatial Span (SS), and Digit Span (DS). The TTCT-V measures verbal creativity by assessing verbal fluency, flexibility, and originality. LM-I assesses learning and memory of conceptual material by having the subject immediately recall details of a short story, and LM-II assesses retention of learned material via delayed recall of the same story. LNS assesses auditory working memory by requiring the subject to sequentially order a random series of numbers and letters presented orally. SS taps the subject's ability to hold a visual-spatial sequence in working memory via the subject tapping out visual sequences forward and backward on a 3-dimensional board. DS assesses processing speed and working echoic memory by having the subject repeat a series of digits forward and backward. For statistical analysis, the data were grouped as baseline group (day 1) and sleep deprived group (days 4 and 5 combined). Multivariate analysis of variance tests (MANOVAs) were performed on verbal creativity and working memory measures, and repeated measures ANOVAs were performed on logical memory measures.

Results: The multivariate F was significant for verbal creativity ($F(3,28$

= 3.90, p = 0.019) and there were main effects for time (F(1,30) = 16.15, p = 0.000) and group (F(1,30) = 10.28, p = 0.003) for LM units and a main effect for group for LM themes (F(1,30) = 5.8176, p = 0.022). Group differences were found for LM %retention (t (df 30) = 2.58, p = 0.015). Descriptive statistics revealed increasing cognitive performance impairment as sleep restriction increased. There appears to be a linear trend of deteriorating cognitive performance on most measures as there was an average 13.4% decline in performance between days 1 and 5 on all subtests. Specifically, verbal creativity declined 14.4%, logical memory fell 18.9% and there was an average 7.0% decrease in working memory.

Table 1

Domain	Subtest	Day 1 (n=20)	Day 3 (n=8)	Day 4 (n=6)	Day 5 (n=5)
Verbal Creativity	Fluency*	69.8	67.3	62.4	58.4
	Flexibility*	65.7	65.5	59.9	56.2
	Originality	72.1	70.4	68.3	63.2
Logical Memory	LM-1 themes*	5.7	4.4	3.9	4.8
	LM-2 themes*	5.5	4.3	4.3	4.8
	LM-1 units*	13.0	11.0	8.4	11.2
	LM-2 units*	12.0	10.1	6.0	8.4
	% retention*	92.3	92.3	70.5	71.8
Working Memory	LNS*	10.8	10.9	7.4	8.8
	SS forward*	8.6	8.3	7.1	7.8
	SS backward	7.5	5.3	6.6	6.4
	DS forward	10.2	9.4	8.7	9.8
	DS backward	7.0	6.3	5.0	7.8

* p < 0.05

Conclusions: Higher level cognitive abilities became increasingly impaired as duration of participation increased. As individuals remaining in the competition on days 4 and 5 are likely to have been more motivated and/or more tolerant to severe sleep restriction, these results may underestimate the effects for the entire population.

1540.J

The Effects of Prolonged Sleep Deprivation on Verbal Fluency

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Introduction: Many behavioral studies have shown that decrements in higher order cognitive function are incurred with sleep deprivation. After one night of sleep deprivation, performance on verbal fluency tasks declines significantly, including an increase in perseveration-type errors. (Horne 1988). Verbal fluency is a standard neuropsychological test that is highly sensitive to cerebral lesions in the left hemisphere of the prefrontal cortex (PFC) (Walsh 1978). A brain imaging study has shown significant decreases in cerebral glucose metabolism in the PFC over prolonged sleep deprivation (Thomas et al. 1998). In this report, we evaluate the extent of further decline in verbal fluency as sleep deprivation continues from 24 to 48 hours. We hypothesized that with continued sleep deprivation, total word count would decrease, and intrusions (spelling errors), nonsensical words, and perseveration errors (repeated words) would increase.

Methods: Seventeen normal, healthy, right-handed male volunteers with a mean age of 24.7 (± 2.8 yr.) participated in the eight-day experimental study. The main purpose of the original study was to assess brain glucose metabolism imaged by positron emission tomography (PET) at 24-h intervals during an 85 h sleep deprivation period. We assessed verbal fluency was evaluated by the Thurstone Word Fluency Test (TWFT). The TWFT was first given on the fourth day (baseline day) of the study after three nights on a fixed sleep schedule (10 p.m.-5:45 a.m.), and then given approximately every two-to-four hours until the final evening of sleep deprivation (Day 7). During TWFT administration, each subject was assigned a letter and asked to write down as many words as possible within a 5 min period.

Results: Analyses were performed using univariate analysis of variance (ANOVAs) for each dependent measure for the 24 h and 48 h periods of sleep deprivation (72 h of sleep deprivation was not assessed due to insufficient data). Significant differences were found for total word count: F (1, 102) = 8.192, p < .005, and intrusion: F (1, 102) = 4.751, p < .05, between these two days of sleep deprivation. There were no significant differences for nonsensical words and perseveration errors.

Conclusions: Prolonged sleep deprivation results in a decline of verbal fluency, thus suggesting also a decline in neuronal activity in the left hemisphere of the PFC. The left PFC has been shown by previous research to be sensitive to the TWFT and to have decreased brain activity with prolonged sleep deprivation. In this study, we found that word generation and spelling errors were significantly affected by two nights of sleep deprivation. Nonsensical words and perseveration errors, however, were not affected as prior research would suggest.

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(3) Walsh KW: The frontal lobes. In: Neuropsychology: A Clinical Approach. New York, Churchill Livingston, 1978, 109-152.

1209.J

Sleep Deprivation and School Performance

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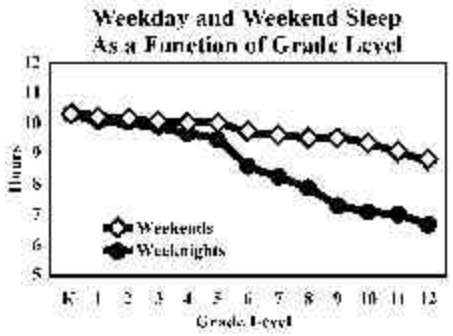
Introduction: Intriguing findings in the sleep literature suggest that the gradual decline in the average need for sleep is not nearly as steep as is the decline in the actual amount of sleep obtained. The most striking divergence between sleep needed for optimal functioning and that obtained occurs during adolescence when many children begin staying up considerably later at night. Since the demands of school usually require an early awakening, this habit of delaying bedtime sets the stage for chronic sleep deprivation. The data reported here are based on a survey of the sleep habits of the children and adolescents from an entire school district.

Methods: A total of 13,150 students from grades 6-12 and parents of children from grades K-5 filled out questionnaires concerning students' sleep habits and various aspects of their daytime functioning. The data reported here focus on the weeknight and weekend sleep habits of high school students, their school performance and attendance, their moods, daytime sleepiness, and academic self-efficacy, and their involvement in sports, work, and extracurricular activities. For some analyses, students were categorized as Low (<= 6 hours) vs. High (>= 9 hours) Sleepers.

Results: The mean number of hours of sleep on weeknights fell from 7.3 hours in grade 9 to 6.7 hours in grade 12 and the percentage of students who slept at least 8 hours per weeknight fell from 16.9% to 6.1%. Applying a higher criterion than 8 hours for "adequate" sleep, the percentage of students who slept 9 or more hours per weeknight ranged from 2.7% in grade 9 to 1.6% in grade 12. MANOVA analyses revealed that while there was no significant difference between Low and High Sleepers on academic self-efficacy, Low Sleepers were significantly

sleepier during the day (higher Epworth scores, more frequent episodes of falling asleep in school, and more hours of additional sleeping on weekends), scored higher on a measure of negative moods, and had poorer school attendance and lower school grades. Similarly, those who worked more than 10 hours per week got significantly less sleep during the week, had higher Epworth scores, were more likely to fall asleep in school, and had poorer attendance and lower grades.

Figure 1



Conclusions: It is highly likely that a large proportion of the adolescents studied here suffer from chronic sleep deprivation and it appears that this lack of sleep is directly related to key indicators of school success, namely, attendance, grades, sleepiness, and moods.

1032.K1

Relationship Between Depressive Symptoms and Sleep Latency in Subjects with and without Obstructive Sleep Apnea

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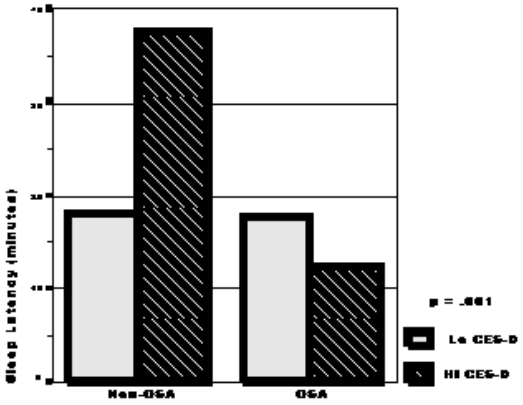
Introduction: This study examined the relationship between depressive symptoms and sleep latency in subjects with and without obstructive sleep apnea (OSA). OSA patients generally have short sleep latencies, likely secondary to their sleep deprivation. Many depressed patients experience disturbed sleep, including delayed sleep onset (Idzikowski, 1994). We wondered if the relationship between depressive symptoms and sleep latency would differ between subjects with and without OSA.

Methods: Subjects (n=106) were recruited by advertising and word of mouth, were between 100 and 150% of ideal body weight and free of major illness other than OSA. Subjects were studied for two nights with polysomnography. Sleep latency was defined as the time from lights out to the first epoch of stage 2 sleep. OSA was defined as a respiratory disturbance index (RDI) ≥ 15. For OSA subjects (n=67), RDI ranged from 15 to 142 (mean = 51.5); for Non-OSA subjects (n=39), RDI ranged from 1 to 14 (mean = 5.8). Subjects completed the Center for Epidemiological Studies-Depression (CES-D) scale and were divided into Hi/Lo groups using a commonly-accepted cut-off score of 16 (Hi CES-D indicates more depressive symptoms). Data were analyzed using a 2-way analysis of variance: OSA/Non-OSA and Hi/Lo CES-D.

Results: Main effects emerged for both OSA and CES-D: OSA patients had shorter sleep latency than Non-OSA patients (15.7 vs. 26.0 minutes, p<.001); and, Hi CES-D subjects had longer sleep latency than Lo CES-D subjects (22.9 vs. 17.5 minutes, p=.043). However, a significant OSA X CES-D interaction emerged (p=.001). Post-hoc analyses revealed that Non-OSA/Hi CES-D subjects had sleep latency twice as long as Non-OSA/Lo CES-D subjects (37.6 vs. 17.9 minutes, p=.012) and OSA/Lo CES-D (37.6 vs. 17.3 minutes, p=.010) subjects, and three times as long as OSA/Hi CES-D subjects (37.6 vs. 12.2 minutes, p=.002). Sleep latency differences between OSA/Lo CES-D and OSA/Hi CES-D and between OSA/Lo CES-D and Non-OSA/Lo CES-D subjects were not significant. CES-D scores for OSA and Non-OSA subjects did not differ significantly (12.6 vs. 13.7, p=.601). Results did not differ significantly after controlling for response bias, age, weight, blood pressure, and social class.

Figure 1



Conclusions: Depressive symptoms may in part account for differences in sleep latency between subjects with and without OSA. Depressed subjects with no apnea experienced longer sleep latency than normals (non-depressed, non-apneic subjects) and all apnea patients. There is a high degree of comorbidity between depression and OSA. Depressive symptoms and OSA have opposite effects on sleep latency. Because of these opposing effects, depressed patients with OSA may have their extended sleep latency masked. In other words, it is possible that the sleepiness experienced by OSA patients overrides the delay in sleep onset often associated with depression.

References:
(1) Idzikowski C: Insomnia and depression: sleep EEG changes. Journal of Psychosomatic Research, 1994;38(Suppl 1): 27-40.

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1034.K1

Multiple Cardiovascular Risk Factors in Obstructive Sleep Apnea Syndrome

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Introduction: To clarify the clinical characteristics of cardiovascular risk factors in patients with obstructive sleep apnea syndrome (OSAS), the patients suspected of OSAS due to heavy snoring and/or daytime sleepiness were investigated.

Methods: The subjects consist of the 339 outpatients, 277 men and 62 women, with a mean age of 49.9?}13.1 years. In all of the subjects, a blood sample was taken when they were hungry in the morning, and the portable polygraphic recordings were obtained. In addition, plasma catecholamine and 75 g oral glucose tolerance test were measured in 86 inpatients who was studied with the polysomnography.

Results: The prevalence of OSAS (respiratory disturbance index , RDI?†5) was in 219 of the subjects (64.6%). The OSAS patients classified by RDI level into mild group of 5?…RDI?ƒ20 (28.0%), moderate

group of 20?…RDI?ƒ40 (17.1%), and severe group of RDI?†40 (19.5%). Complications of obesity, hypertension, erythrocytosis, value increased hematocrit, diabetes, and smoking gradually increased with the severity of OSAS group. Although there was no difference of total cholesterol between OSAS groups, the prevalence of hypertriglyceridemia and a low level of high density lipoprotein-cholesterol was significantly higher in severe group. Hematocrit, hypoxemia, and body mass index (BMI) gave RDI significant effects in Stepwise regression analysis. There was a significant correlation between RDI and noradrenaline in the inpatients. In severe group, the existence of hyperinsulinemia (insulin resistance) was suggested because of higher insulin level during glucose tolerance test. It seems that the majority of moderate or severe group has the disease background of the multiple cardiovascular risk factors.

Conclusions: The severe OSAS patients showed hypertriglyceridemia, a low level of high density lipoprotein-cholesterol, and higher insulin level during glucose tolerance test. Not only a specific OSAS treatment as continuous positive airway pressure (CPAP) but also the aggressive examination and treatment to multiple cardiovascular risk factors are necessary in OSAS patients with RDI of 20 and over.

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1043.K1

Compliance of CPAP in Patients with Obstructive Sleep Apnea who are enrolled in a CPAP Clinic

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Introduction: Problematic compliance with CPAP has been well documented in patients with obstructive sleep apnea syndrome. A large percentage of patients are unable to tolerate CPAP and reports of CPAP compliance are gernerally low. The Lahey Clinic Sleep Center has a CPAP Clinic which is managed by our Sleep Technologists and Physicians. This study is to assess weather our CPAP clinic has a positive influence of patient's compliance with CPAP as compared to a control population of patients with OSA.

Table 1

Patient Demographics	Study	Control
# patients	17	17
Sex (M/F)	15/2	13/4
Age (yrs)	52.3	50.2
AHI (events/hr)	48.2	40.1
CPAP (cm H2O)	9.2	10.0
E.S.S.	11.7	12.1
Avg. desaturation (%O2)	90.1	91.9

6 Month Data	Study	Control
# dropouts/total	1/8	7/8
Avg. use (hrs) all days	4.6	0.6
Avg. use (hrs) days used	5.0	0.7
% days used	79.2	11.3
% days used >= 4 hrs.	57.9	9.2

Methods: 50 patients with polysomnographic and clinic diagnosis of OSA will be randomized into a study (CPAP clinic) or control (non-CPAP clinic) groups. Both groups are followed at 1,3 and 6 month intervals. The study group is seen in the CPAP clinic whereas the control group is seen as a follow-up appointment in the sleep physicians office. Each patient is provided with a CPAP machine (Aria LX) which has a microprocessor that is capable of storing a variety of complicance information. Complicance data is downloaded at each patient visit.

Results: Preliminary data includes results of 34 patients thus far enrolled in our study (see demographic chart). Many of these patients have not yet completed the 6 month follow-up. Our preliminary data suggests that regular visits to our CPAP clinic significantly improve CPAP compliance at 6 months. More patients in the study group were regularly compliant with CPAP as expressed in average hours of use per night, percent of days CPAP was used and percent of days CPAP was used for greater that 4 hours per night (see 6 month data table) as compared with the control group.

Conclusions: Regular attendance in a CPAP clinic can improve compliance with CPAP.

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1048.K1

Sleep-Disordered Breathing in Twenty Consecutive Crime Victims Presenting for Nightmare and Insomnia Treatment: A Preliminary Report

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Introduction: Sleep complaints are common in posttraumatic stress disorder (PTSD) and are allegedly caused by stress, hyper-arousal and psycho-physiological conditioning. Nonetheless, sleep-disordered breathing (SDB), e.g., obstructive sleep apnea (OSA) or upper airway resistance syndrome (UARS) can present atypically as insomnia. Treatment with CPAP in such cases may alleviate insomnia. Two recent case reports have described improvements in sleep, nightmares, and posttraumatic stress symptoms following CPAP treatment for SDB in patients with chronic nightmares and PTSD. In the current study, we hypothesized that prevalence of SDB (primarily UARS) would be higher than expected in a sample of crime victims in comparison to the general population.

Methods: Twenty consecutive crime victims who enrolled in an insomnia and nightmare treatment program were assessed for SDB. Mean (SD) age was 39 (8.3) and mean BMI was 26.5 (5.0). Seventeen were diagnosed with nightmare disorder and PTSD. All participants were diagnosed with psycho-physiological insomnia. Participants underwent two sleep tests: a full (in lab) polysomnogram (Grass Heritage Colleague, Astro-Med, Inc.) and a home monitoring test (Autoset Portable II Plus, ResMed Ltd). The SleepScan nasal pressure transducer (Bio-logic Systems Corp) assessed flow limitation on the PSG. In addition to apneas (AP) and hypopneas (HYPO), Sleep Breathing Related Arousals (SBRAs) were scored with flattening of the nasal pressure tracing coupled with EEG micro-arousals on the PSG. A positive diagnosis for SDB was 20 events/hour of any type (i.e., Total Events = AHI + SBRA). Flattening indices were calculated automatically by Autoset based on the device's 0.15 threshold. An SDB diagnosis required a flattening index $\geq$ 20% of study time spent below the 0.15 cutoff.

Results: On PSG, 17/20 participants, and on Autoset, 13/20 met diag-

nostic criteria for SDB. UARS diagnoses occurred twice as frequently as OSA on either test. Nineteen of 20 (95%) patients demonstrated SDB on at least one test. Table 1 lists events/hour and flattening indices for the group.

Table 1

SDB Indices	AP	HYPO	AHI	SBRA	Total Events	Autoset Flattening % <0.15
Mean (SD)	6.6 (11.4)	9.7 (12.4)	16.3 (21.4)	24.9 (12.5)	41.2 (23.6)	29.8 (22.6)

Discussion: A high prevalence of SDB, notably UARS, was confirmed in this select group of crime victims. General population rates of SDB are lower, although there are no UARS rates for comparison. Future investigations with these crime victims will evaluate the impact of SDB treatment on insomnia, nightmares, and PTSD. We hypothesize that SDB will prove to be an integral component of the sleep disturbances of certain PTSD patients, and expect treatment outcomes in which nightmares, insomnia, and PTSD improve following CPAP use. The study is limited by the absence of validity and reliability data for Autoset and nasal pressure transducers. Selection bias may limit generalizability. Notwithstanding, the most common type of insomnia complaint in an undiagnosed SDB patient is sleep maintenance difficulties; and, this was reported by 90% of our patients. Sleep specialists who treat crime victims and other PTSD patients may find that objective sleep testing is an essential component of the work-up for those presenting with insomnia and nightmares.

Research support: Oxnard Foundation, New Mexico Crime Reparations Commission (Victim of Crime Act), NIMH (MH 53239), Astro-Med, Inc., Resmed Ltd., and Bio-logic Systems, Corp.

1068.K1

Asynchronous Breathing During Non-REM, Non-Supine Sleep in Patients with Supine Positional Obstructive Sleep Apnea

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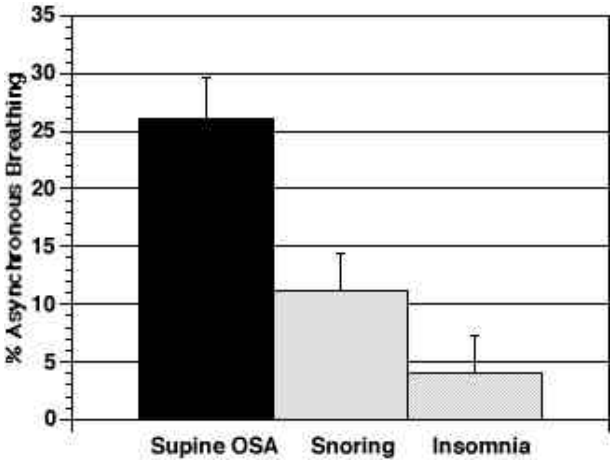
Introduction: Asynchronous breathing (ASB) during REM sleep is frequent and may be related to REM sleep physiology. ASB during non-REM sleep, however, appears to be of pathological significance. Previous studies have demonstrated that ASB during non-REM sleep is increased in adults with the upper airway resistance syndrome (Castriotta et al 1998) and in snoring children (Castriotta et al 1999). There is further evidence that ASB is increased during the non-REM sleep of patients with REM-related obstructive sleep apnea (OSA). These findings suggest that ASB during non-REM sleep is a form of sleep-disordered breathing. To further explore this hypothesis, in this study we evaluated ASB during non-REM, non-supine sleep in patients with supine positional OSA (SP-OSA).

Methods: Sixty five (65) subjects were evaluated in the Memorial Hermann Hospital Sleep Disorders Center by standard nocturnal polysomnography (NPSG) with quantitative scoring of ASB in minutes as well as all other NPSG parameters. All apneas and hypopneas were excluded from ASB scoring. Of these, 30 subjects (26 men, 4 women, age 49.5 ± 12.1 years) had SP-OSA with supine apnea+hypopnea index (S-AHI) ≥ 10 apneas+hypopneas/hor of supine sleep and at least 60 minutes of supine sleep. These were compared to 27 subjects (16 men, 11 women, age 42 ± 13.5 years) with primary snoring disorder (PSD) and to 8 subjects (4 men, 4 women, age 50.2 ± 13.4 years) with persistent psychophysiological insomnia (PPI). The PSD subjects all had no significant sleep apnea or hypopnea in any sleep stage or position with < 10 arousals/hour of sleep and denied excessive daytime sleepiness.

Results: The SP-OSA subjects had a S-AHI = 30.7 ± 2.9 apneas+hypopneas/hour of supine sleep. **Subjects with SP-OSA had ASB in 26 ± 3.7% (SEM) of non-REM, non-supine sleep, compared to 11.2 ± 3.2% in PSD subjects (p = 0.0018) and 4 ± 3.3% in PPI subjects (p = 0.0001).** There was no significanct difference in total sleep time (TST) between those with SP-OSA (398 ± 7.8 minutes) and PSD (387 ± 11 minutes, but the PPI subjects had less TST (289 ± 30 minutes, p = 0.0066). Those with SP-OSA had significantly higher Epworth Sleepiness Scale scores (13.2 ± 1.3) than those with PSD (4.9 ± 0.4, p < 0.0001) or those with PPI (3.9 ± 1.9, p = 0.0007).

Figure 1. % Asynchronous Breathing in NOn-REM, Non-Supine Sleep



Conclusions: This study further strengthens our hypothesis that ASB during non-REM sleep is a form of sleep-disordered breathing associated with pathological conditions such as UARS, REM-related OSA and SP-OSA. ASB in non-REM sleep may contribute to the excessive daytime sleepiness seen in patients with low overall apnea+hypopnea indices.

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1163.K1

The Vestibular In-line Pressure System (VIPS); Oral Delivery of Continuous Positive Airway Pressure (CPAP)

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Introduction: Since the original description by Sullivan et al., CPAP via the nose (nCPAP) has been the mainstay of therapy for obstructive sleep

apnea syndrome (OSAS).[1] With increased patient demand, mask designs have improved. Nevertheless, many patients dislike nCPAP; complaints include skin abrasions, leaks, conjunctivitis, sinus irritation, claustrophobia, and limitation of sleeping position. Such negative experiences may contribute to the 20% of patients who abandon therapy within the first three months. Accordingly, we wondered if an oral CPAP delivery system would be feasible and efficacious. This study reports our first experiences with the VIPS.

Methods: Phase 1: 5 patients with OSAS (initial RDI>15/h.), on nCPAP, came to the laboratory for titration with the VIPS. The first rendition of the VIPS was a strapless butterfly-shaped device, fashioned of medical silicone. The interface rests in the oral vestibule between the lips and teeth. To avoid nasal breathing via tongue occlusion of the oral cavity, a small protrusion was added to the mouthpiece. The VIPS was attached to a CPAP unit with a heated humidifier (Fisher & Paykel, HC200). Patients underwent polysomnograhy (PSG) and CPAP titration with the VIPS. Airflow at the nose and mouth was monitored with a thermister and pneumotachograph, respectively. Humidification was adjusted for maximal comfort. Phase 2: 7 CPAP naïve patients referred for OSAS underwent "split-night" PSGs. The first half of the study established OSAS (RDI>15/h.), with subsequent nCPAP titration occurring during the later half. Within a week, another PSG titration with the VIPS was completed. The device was altered by adding a single head strap to prevent dislodgment. All PSGs were scored with focus on the therapeutic pressure, arousal index (AI; arousals/h.), and SaO2 nadir. Statistical comparisons were achieved with t-tests.

Results: In Phase 1, all nCPAP users (initial RDI 34+7/h.) slept the full night with the VIPS. For 4 of 5 patients, the VIPS reversed respiratory events without a significant difference in the set pressure (nCPAP, 8+1 cmH2O; VIPS, 8+2 cmH2O, p>.05). One patient on 10 cmH2O nCPAP was not controlled with the VIPS (peak 12 cmH2O); nasal breathing was dominant. 2 of 5 patients complained of drying with the VIPS, requiring an increase in humidification. The AI and SaO2 nadir were not different with either device (nCPAP, AI 12+11/h., SaO2 nadir 93+2%; VIPS, AI 9+8/h., SaO2 nadir 94+3%; p>.05). In Phase 2, 7 patients slept with the modified VIPS, with good response. Minimal nasal breathing was observed. Pressures were similar (VIPS, 9+3 cmH2O; nCPAP, 11+4 cmH2O, p>.05). One patient required 14 cmH2O nCPAP, and 6 cmH2O with the VIPS. 3 of 7 patients preferred nCPAP; only one noted excessive drying with the VIPS. The AI and SaO2 nadir were not different with either interface (nCPAP, AI 14+8/h., SaO2 nadir 93+2%; VIPS, AI 16+14/h., SaO2 nadir 94+3%; p>.05).

Conclusions: An oral interface that delivers CPAP is both feasible and effective. Modifications were necessary to prevent nasal breathing and dislodgment. Drying of the oral cavity necessitated higher humidification levels in several patients. With further revisions, the VIPS will provide patients with a new and comfortable alternative for CPAP therapy.

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1177.K1

Comparison of Ricketts Analysis and Downs-Northwestern Analysis for the Evaluation of Obstructive Sleep Apnea Cephalograms

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Introduction: Among over 200 cephalometric analyses, we selected and compared Ricketts method and Downs-Northwestern method as the most popular analysis to determine which analysis is suitable to examine the skeletal pattern characteristics of the obstructive sleep apnea syndrome (OSAS) patients.

Methods: The lateral cephalograms of 34 OSAS patients and 34 non-OSAS controls were analysed by both Ricketts method and Downs-Northwestern method.

Results: There were significant differences (p<0.005) between OSAS patients and non-OSAS controls on Facial Axis (OSAS 79.4° ±}4.0, non-OSAS 84.3° ±}4.8), Lower Facial Height (OSAS 56.6° ±5.5, non-OSAS 50.8° ±4.7) and Total Facial Height (OSAS 70.0°±5.9, non-OSAS 64.8° ±5.2) by Ricketts analysis. According to the Ricketts analysis, the OSAS patients indicated Dolico facial pattern. However we could not find any significant differences between OSAS patients and non-OSAS controls by Downs-Northwestern analysis.

Conclusions: Most of the analyses for facial pattern are based on Sella-Nasion reference like Downs-Northwestern analysis. However Ricketts analysis is based on Basion-Nasion reference, because point of Basion is more stable than point of Sella which has a tendency to move upward during the growth of period. Furthermore Ricketts analysis could clearly address how to determine vertical skeletal characteristics of OSAS patients which was Dolico facial pattern. We should not apply Downs-Northwestern method to analyse the skeletal pattern characteristics of OSAS patients. Ricketts method is supposed to be better than Downs-Northwestern method to analyse the skeletal pattern characteristics of the obstructive sleep apnea patients.

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1181.K1

Oral Appliance Treatment: Polissonographic and Nuclear Magnetic Resonance Imaging Results in 9 Mild to Severe OSAS Subjects

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Introduction: Obstructive sleep apnea-hypopnea syndrome ranges from increased upper-airway resistance manifested as respiratory-related arousals to recurrent airway collapse with apneas and hypopneas. OSAHS is a potentially life-threatening disorder and it causes daytime sleepiness, diverse cognitive deficits, social disadjustments, motor vehi-

cle accidents and cardiovascular morbidity and mortality.[1] Therefore, even mild degree OSAHS demands effective treatment. Although nasal CPAP is therapeutically effective, its compliance rate is poor even for more severe OSAHS cases. Hence, removable intraoral appliances have become a treatment alternative for selected OSAHS patients. The objective of this study is to correlated the sleep studies-based MLRD[2] treatment effectiveness with NMRI-imaging UAW volumes with and without the fitted MLRD.

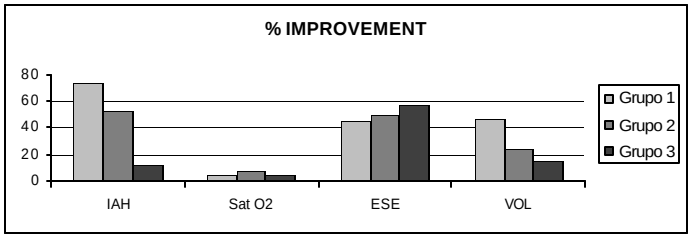
Methods: A group of nine patients (descriptive data are shown in table I) were divided in three distinct groups: group one (n=4): 3>RDI>10; group two (n=3): 10>RDI>26 and group three (n=2): 40>RDI>80. Post-treatment indexes were obtained at approximately 4 months and included: RDI (events/hour), Epworth Sleepiness Scale (ESS) subjective daytime sleepiness scores, min.SatO2% and UAW volume (mm3) NMR imaging were obtained with and without the MLRD in place. The UAW volume was calculated taking into consideration upper limit set at the tip of the hard palate down to the tip of the epiglottis.[3] Student's t-test was employed to pre- and post-treatment conditions.

Results: See Table and Graphic

Table 1

G	AGE	BMI	RDI 1	RDI 2	O2 1	O2 2	ESS 1	ESS 2	Vol1	Vol2
1	49.25	24.09	6.04	1.61	87.50	91.50	10.50	5.75	4837.76	7099.66
2	54.00	26.32	22.51	10.54	79.00	88.00	19.67	10.00	3783.88	4697.57
3	56.00	32.96	61.15	53.91	71.50	77.50	15.00	6.50	2696.25	3122.83

Figure 1



Conclusions: Pre- and post-treatment RDI, ESS, min Sat O2.% and UAW volumes were statistically different confirming the clinical and polissonographic efficiency. UAW significant volume difference confirmed the anatomic effect of the MLRD in this patient population. MLRD-induced Improvement in ESS-measured subjective daytime sleepiness has been reported before and relates to the reduction of the brief respiratory-related arousals. The degree of minimum oxygen desaturation improvement primarily relates to abnormal respiratory event duration rather than to its rate number. This is suggestive the ARML is more efficient in reducing the number of arousals, and in reducing the number than the duration of abnormal respiratory events.

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1191.K1

Breathing-Related Sleep Disorders and Hypertension in Patients with Rubinstein-Taybi Syndrome

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Introduction: Rubinstein-Taybi syndrome (RTS) is a multiple congenital anomaly syndrome characterized by typical craniofacial features, small stature, broad thumbs and toes, and mental retardation. The craniofacial features include microcephaly with reduction in upper, mid-, and lower facial depths, as well as narrowing of the skull base. These findings suggest that the pharyngeal airway might also be abnormally small. We therefore hypothesized that individuals with RTS may be at high risk for sleep-disordered breathing and subsequent cardiovascular complications.

Methods: To address this hypothesis, RTS patients attending two RTS International Family Conferences held in Cincinnati, Ohio were evaluated: two groups of patients (A and B) of national and international representation were studied. Group A (N=42, 16 female and 26 male, age = 10.1 ± 7.1 years (mean ± SD)) was evaluated by two separate questionnaires, one completed by each patient's primary care physician or a developmental pediatrician (PMD questionnaire) and one completed by the child's parents concerning sleep apnea (SA questionnaire). Group B (N=44, 21 female, 23 male, age = 8.3 ± 5.6 years (mean±SD)) was evaluated by a survey focused on sleep apnea and hypertension. Patients in Group B also underwent measurement of blood pressure (BP) by a trained nurse from the hypertension clinic, who followed the national guidelines for BP measurement in children. The mean of two BP measurements was compared to normal values according to age, sex, and height. Regression analysis was performed for Group A results to determine the correlation between history of sleep apnea and history of hypertension.

Results:

Group A	
PMD Questionnaire	N = 42
IQ < 50	49%
IQ < 75	97%
Height ≤5th P*	71%
Head Circumference < 3rd P	63%
High arched Palate	93%
Snoring	76%
Sleep apnea	45%
Anesthesia problems	27%
Hypertension	21%
Parent Questionnaire	N = 42
Snoring	64%
Labored breathing during sleep	33%
Sleep apnea	20%
Excessive daytime sleepiness	60%
Suddenly falling asleep	30%

Group B	
Parent survey	N = 44
Snoring	89%
Sleep apnea	32%
Excessive daytime sleepiness	68%
BP measurement	N = 41
Systolic > 90th P	2 (5%)
Diastolic ≥95th P	10 (24%)
Diastolic 90th P– 95th P	5 (12%)

*P = percentile

Conclusions: This study suggests that a history of breathing-related sleep disorders and a history of hypertension are highly prevalent in patients with RTS. Single measurements of BP also suggest that there might be a higher prevalence of hypertension in this patient population. Further studies are needed to determine the exact prevalence of breathing-related sleep disorders and sustained hypertension in this population and to evaluate the contribution of sleep apnea to the elevation of blood pressure.

1200.K1

REM Related Apnea: Risk Factors and Subjective Response to Treatment

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Introduction: Much is known about the risk factors and treatment of Obstructive Sleep Apnea (OSA). What is less clear is the significance of when OSA is confined to REM sleep.

Methods: We conducted a retrospective review of 10 months of polysomnographic studies and selected cases demonstrating apnea restricted to REM sleep. Of the 1,629 polysomnograms performed at the Cleveland Clinic between November 15th 1998 and September 15th 1999, 117 (7.18%) demonstrated a REM index greater than 5, a non REM index less than 5, and at least 20 minutes of REM sleep. Follow up telephone interviews were conducted that included current weight, treatment received, a subjective improvement score, and a repeat ESS assessment. The subjective improvement score was a ranking of perceived improvement on a scale of 1 to 5 where 1 was no improvement and 5 was greatly improved. Analyses focused on the correlation of age, weight, and sex on the initial diagnosis of REM related apnea and the correlation of treatments chosen with subjective improvement scores and changes in the scores of the ESS.

Results: 89 patients were successfully interviewed. Of these, 53 (60%) received no treatment, 13 (15%) lost weight to decrease their BMI by at least 5%, 8 (9%) received CPAP, 11 (13%) received surgery, and 6 (7%) received REM suppressing medications. 8 patients were treated with more than one modality. The mean REM index was 17.7 with a range from 5.35 to 52.6. Among males, significant positive correlations were observed between REM index and age (R=0.29 and p=0.038) and between REM index and BMI at the time of the polysomnogram (R=0.43 and p=0.001). A similar but not statistically significant positive correlation existed for females between REM index and age (R=0.28 and p=0.09) and between REM index and BMI (R=0.16 and p=0.13) at the time of the polysomnogram. No statistically significant correlation existed for either sex between subjective improvement ranking and change in the ESS or between the change in BMI and change in the ESS. A notable significant difference was seen in the subjective improvement ranking between treatment and no treatment (p<0.001). This was shown for each type of treatment as follows: weight loss (p=0.013), CPAP (p=0.001), and surgery (p<0.001), but not for REM suppressant medications (p=0.88).

Conclusions: As in OSA that is not restricted to REM sleep, REM related Apnea demonstrated a significant positive correlation for both age and BMI for males. A similar but not statistically significant pattern was seen for females. The majority of patients diagnosed with apnea restricted to REM sleep were not treated. Of those who were, there was a significant correlation between subjective improvement ranking and treatment with weight loss, CPAP, and surgery, but not for REM suppressant medications. The Epworth Sleepiness Scale was not useful for assessment of overall subjective improvement.

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1100.K1

Nasal CPAP Compliance in Japan

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Introduction: Although nasal continuous positive airway pressure (nCPAP) is known to be the first choice of the treatment for obstructive sleep apnea hypopnea syndrome (OSAHS), number of prescribed CPAP was quite small in Japan, mainly because it was not covered by the social insurance. Since the April, 1998, when nCPAP treatment was authorized by the government, the number of prescription has been dramatically increased. In addition, monthly visit to the clinic has become a duty for the patients, intensive support was enable to maintain compliance. We hypothesized that present CPAP compliance is good in Japan, we studied OSAHS patients who are now on nCPAP treatment.

Methods: We studied 98 consecutive patients (90 males and 8 females, mean age; 50.1• }11.5 years, mean body mass index; 27.4• }5.7 kg/m2), who visited Sleep Breathing Center, Komagamine Clinic, were diagnosed as having OSAHS, and were prescribed nCPAP for the initial treatment from April, 1998 to October, 1999. Diagnosis was made by the overnight polysomnography, and nCPAP titration on the following night. Symptom, time of use and adverse effects were checked, then education, adjustment of mask fitting and treatment of side effects were performed at every visit. We defined good compliance is more than 5 hours daily use. CPAP compliance was calculated in every three months.

Results: Mean apnea hypopnea index are 55.9• }28.5 /hr, and mean CPAP pressure was 8.9}2.2 cmH2O. Subjective compliance at 6 months periods was 90.2%. Only 6 paitients could not tolerate nCPAP, and failed to use within the first month, and changed to the other alternative treatment. Number of good compliant is 69 (63.5%).

Conclusions: Compliance rate with nCPAP in Japan has reached the same level as in USA and Europe since April, 1998, it is appeared to be mainly due to the coverage by social insurance, and in part the monthly care.

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1155.K1

Oculopharyngeal Muscular Dystrophy and Sleep Apnea

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Introduction: Oculopharyngeal muscular dystrophy (OPMD) is a rare form of autosomal dominant adult onset muscular dystrophy with a predilection for the muscles of the oropharynx (Weitzner 1969). Since this disorder can profoundly affect the upper airway dilator muscles, the prevalence of obstructive sleep apnea(OSA) in this population should be very high, but thus far remains unreported. We present the case of a

patient of Spanish American descent with OPMD and OSA documented by nocturnal polysomnography (NGSP).

Methods: Case Report.

Results: The patient is a 75-year old Spanish American female that came to medical attention due to her bilateral ptosis, dysphagia and strong family history of OPMD. Sleep consultation was sought due to complaints of snoring, daytime somnolence and nocturnal coughing/choking. She had a history of low back pain, depression and hypertension. Medications included lisinopril, lansoprazole and paroxetine. On examination she was 5 feet tall and 120 pounds with obvious ptosis but otherwise normal cranial nerve findings, oropharyngeal appearance and function in the awake state. Ancillary investigation showed no response to a tensilon challenge, normal swallowing study, normal TSH and no acetylcholine receptor binding antibodies. Nocturnal polysomnography showed a markedly reduced sleep latency of 30 seconds and a normal REM latency of 1 hour 52 minutes. Sleep efficiency was 81% (TST 6 hours 12 minutes); sleep architecture was divided as follows - stage 1, 17.7%; stage 2, 65.0%; stage 3, 6.0%; stage 4, 0.0%; stage REM, 11.3%. Respiratory disturbance index was 37 (apnea index, 2; hypopnea index, 35; total number of events 227). The apneas were predominantly obstructive (11 obstructive, 4 central). The respiratory events overall were twice as likely to occur in REM sleep compared to NREM sleep and there was no supine predominance. Twenty-five desaturations to less than 90% were noted. Periodic limb movements with arousal was only 3, without arousal zero. She responded well to a CPAP of 8 cm water demonstrating an RDI of zero at this pressure.

Conclusions: Oculopharyngeal muscular dystrophy is a rare form of autosomal dominant adult onset muscular dystrophy with a genetic predominance in the French Canadian and colonial Spanish American population. Symptoms usually begin in the sixth or seventh decade of life and include ptosis, dysphagia, temporal wasting and varying amounts of peripheral weakness. The diagnosis is made clinically with supportive evidence from family history, electromyogram, muscle biopsy, normal creatine kinase and a negative tensilon test. The differential diagnosis includes myasthenia gravis, Lambert-Eaton syndrome and inflammatory myositis. The pharyngeal muscles are often profoundly affected (Weitzner 1969), raising the question of whether obstructive sleep apnea occurs more often in this disorder than in other muscular dystrophies. However only one previous report of probable OSA in OPMD has appeared (Lacomis et al 1991). An unequivocal diagnosis of OPMD was made in our patient, and OSA of moderate severity responsive to nasal CPAP was documented. Although awake pharyngeal muscle fucntion appeared normal, the patient was not obese and therefore pharyngeal dilator muscle dysfunction appearing during sleep and attributable to OPMD is suspected. Apparently normal awake upper airway funciton, with deterioration during sleep leading to obstructive sleep apnea has been reported in other neuromuscular disorders, e.g. Shy-Drager syndrome (Williams et al 1979). This report represents the second case of OSA in OPMD appearing in the literature, and further epidemiological investigation of the prevalence of OSA in this population is warrented.

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1407.K1

CPAP-Related Changes in Cognitive Functions in Patients with Obstructive Sleep Apnea

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Introduction: Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder. Cognitive impairment reportedly occurs in individuals with OSA. Treatment intervention paradigms may be useful to investigate OSA-related cognitive impairments. Some studies report dramatically improved neuropsychological functions after treating OSA with continuous positive airway pressure (CPAP). By contrast, when CPAP-treated groups are compared to untreated or placebo-treated groups only modest or no improvements in neuropsychological test scores are typically found.

Methods: This prospective, randomized, trial compared changes from baseline at 2-week follow-up in treated vs. untreated parallel groups. Subjects were 29 men, age 33-64 years (mean=52 years) with OSA randomized into CPAP treatment (n=17) or untreated (n=12) groups. Mean apnea+hypopnea index at baseline for the treated group was 45.5 compared to 39.7 for the untreated group (not significantly different). Diagnosis and optimal CPAP was determination with comprehensive polysomnography. Neuropsychological test battery included California Verbal Learning Test (CVLT), modified Wisconsin Card Sorting Test (WCST), Paced Auditory Serial Addition Task (PASAT), Bedside Assessment of Executive Cognitive Impairment (EXIT), Tower of Toronto (TOT), Stroop-color test (Stroop), Wechsler Adult Intelligence Scale – Revised Digit Span (WAIS-R Digit Span), and Trail-making test (TMT).

Results: The experimental design can be represented as main effects for GROUP (Treated vs. Untreated) X SESSION (baseline vs. follow-up). The interaction GROUP X SESSION provides a test for the differential effect of CPAP therapy on outcome measures. Additional analyses were conducted with a trifurcated GROUP factor (treated compliant {>5 hours usage per night}, treated noncompliant, and untreated). Practice effects were robust and pervasive; however, few CPAP-related changes were found. There were significantly decreased perseverations on CVLT Tuesday List, significantly decreased omissions on PASAT, marginally fewer violations on 4-disc TOT trial 2, and near significant improvement on TMT-A. No other significant improvements beyond practice were found for any other measures.

Conclusions: One explanation for lack of CPAP-related neuropsychological improvements is that OSA is marked by partial, not total, sleep deprivation. Although fragmented, intervening sleep may allow cognitive abilities to remain intact. Patients may become sleepy, irritable, and distractible; however, sleep deprivation evolves gradually. Therefore, adaptation may occur that allows time-limited "best effort" performance. Another explanation relates to linguistic ambiguity in self-report. Our patients frequently complain about having "difficulty remembering things". As clinicians we focus on the words remembering things, interpreting this as memory impairment. In such cases the keyword may be difficulty that may be overcome. Cognitive and psychomotor "slowing" often occur with sleep loss and when performance is overtaxed, test outcome may suffer (e.g., more PASAT omissions in untreated group). Alternatively, the paucity of findings may simply reflect a differential time course for sleepiness, mood, and cognitive improvement. Previous work indicates self-reported sleepiness improves within the first week and mood improves within 3 weeks. CPAP trials vary with respect to

interval between treatment initiation and follow-up testing with no apparent differential effect of time course. However, this does not rule out the possibility that cognitive improvement requires more time. Nonetheless, most standardized neuropsychological tests appear insensitive to CPAP treatment outcome.

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1250.K1

Compliance of Nasal Continuous Positive Airway Pressure (nCPAP) Treatment in Korean Patients with Obstructive Sleep Apnea Syndrome

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Introduction: Patients with the obstructive sleep apnea syndrome (OSAS) who have initiated nasal continuous positive airway pressure (nCPAP) treatment are strongly recommended to use nCPAP on long-term basis in order to prevent recurrence of symptoms. It is thus important to evaluate long-term nCPAP compliance in patients using the device and factors influencing it.

Methods: We reviewed the records of 120 consecutive patients with OSAS referred to Division of Sleep Studies for nocturnal polysomnography with nCPAP pressure titration during the period of March 1994 through April 1999. And we performed a telephone interview with each of them on October 1999 and obtained data from 83 patients. Sociodemographic factors, severity of sleep apnea, body mass index(BMI), subjective daytime sleepiness, prescribed nCPAP pressure, presence of earlier uvulopalatopharyngoplasty (UPPP), and presence of coexisting disease (hypertension, chronic obstructive pulmonary disease) were compared in compliant and noncompliant patients. Compliant patients were defined as those who had continued to use a nCPAP device regardless of the frequencies of use.

Results: Out of 83 patients, 23 patients(27.7%) refused the recommended nCPAP treatment (these were more often low-educated). Of the remaining 60 patients, 34 patients (56.7%) had discontinued nCPAP treatment, primarily because of discomfort of use, while 26 patients(43.3%) were still using nCPAP device at the time of the telephone interview (the 24.6th ¡¾14.5 months, mean¡¾SD). Only 15 patients (25%) were using CPAP device everyday. Out of 34 patients who discontinued nCPAP use, 25 patients (73.5%) did within the first 3 months and 31(91.2%) within the first 1 year. There were no statistically significant differences between the compliant and noncompliant patients in age, sex, baseline respiratory disturbance index(RDI), BMI, oxygen saturation data, prescribed nCPAP pressure, presence of earlier UPPP, and presence of coexisting disease. Subjective daytime sleepiness was present before nCPAP application in 22 of the 26 compliant patients and in 21 of the 34 noncompliant patients (Kaplan-Meier method, $p<0.05$).

Conclusions: In our study, the nCPAP compliance rate is relatively lower than those in the previous studies done in other countries. Increased long-term compliance with nCPAP treatment appears to be associated with the subjective presence of daytime sleepiness before nCPAP application. Long-term compliance with nCPAP may be mostly predicted from the usage pattern within the 3 month of use.

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1255.K1

AutoSet Nasal CPAP Titration: In-home Validation Using Comprehensive Portable Polysomnography

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Introduction: Obstructive sleep apnea (OSA) is common and is associated with significant morbidity, but often remains unrecognized in the primary care setting (Young et al. 1997). Continuous positive airway pressure (CPAP) therapy is an effective treatment for OSA. Laboratory titrations are considered the gold standard, but are labor intensive, costly and not always available. Home polysomnography (PSG) and CPAP titration are means to increase accessibility. Compared to manual laboratory titrations, the AutoSet (AS) is equally effective in reducing the respiratory disturbance index (RDI). Fixed pressures are prescribed from the AS, and these effective pressures continue to ameliorate OSA over time (Teschler et al. 1997). This study validates the effectiveness of AS in the patient's home using the Digitrace Home Sleep System (DHSS).

Methods: Thirty nine patients (30 men and 9 women, mean age = 46.5 yrs ± 11.7, mean BMI = 33 kg/m-2 ± 6.8) underwent simultaneous AS titration and comprehensive portable polysomnography using the DHSS. The AS is a self-setting positive airway pressure device. Pressure increases occur in response to closed airway apneas lasting longer than 10 sec, snoring and changes in inspiratory airflow limitation; pressure is decreased when no further abnormalities are detected. The DHSS is a digital recording system with established validity, capable of multi-channel recording, including EEG (Fry et al. 1998). The AS and DHSS were interfaced with an analog-to-digital converter, and pressure level was displayed during post-acquisition review. All patients had a DHSS diagnostic PSG confirming OSA (mean RDI = 41.5, range = 5.5 - 118) an average of 52 days prior to titration. When patients returned for the AS titration, they were given detailed verbal and written instructions in its use, and the results of the diagnostic study and rationale for CPAP were discussed with the patient. Patients did not require supplemental oxygen or BiPAP, and were capable of following equipment instructions.

Results: A successful titration was defined as a significant reduction in RDI, mean oxyhemoglobin saturation > 90%, a minimum of four hours total sleep time (TST), sleep efficiency ≥ 75%, minimal mask leak (< 0.4 l/sec for ≥ 50% TST), and the occurrence of REM and SWS. Ninety percent of titrations (35/39) were successful. There was close agreement between the AS RDI and the DHSS RDI, as scored by a technician blind to the AS data ($r = 0.67$, $p < 0.001$). There was a significant difference between the diagnostic RDI and the DHSS RDI ($t=8.4$; $p < 0.001$), representing an average 88 percent reduction in sleep disordered breathing severity. Means and (std dev) are presented for the following variables: TST = 363.3 min (61.2), Sleep Efficiency = 84.5% (6.9), Number of Awakenings = 17.5 (7.8), Stage 1% = 5.8 (3.4), Stage 2% = 55.6 (10.4), SWS% = 15.1 (8.2), REM% = 23.4 (5.7), DHSS RDI = 4.3 (5.1), AS RDI = 5.5 (3.8), Mean SaO2 = 96.3% (1.5), Median Pressure = 7.5 (2.2) and 95th Pressure Centile = 10.4 (2.8).

Conclusions: Home AS titration is a viable alternative to laboratory titration in patients with uncomplicated OSA. Nearly all patients had successful titrations and effective pressures were prescribed. The use of portable diagnostic and treatment techniques, in combination with valid

self-report screening tools, may facilitate the recognition and treatment of OSA in the primary care setting. Patients with documented OSA may be prescribed fixed-pressure therapy or maintained on auto-titrating CPAP.

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1274.K1

Preliminary Report on the Comparison Between Automatic and Manual Positive Airway Pressure Therapy in the Home Using the AutoSet T

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Introduction: Continuous positive airway pressure (CPAP) is the treatment of choice for moderate to severe obstructive sleep apnea (OSA); however, compliance is less than optimal (Kribbs et al. 1993). A self-adjusting CPAP device has the potential to increase compliance by regulating optimal air pressure. The AutoSet T (AST) greatly attenuates sleep disordered breathing and improves sleep continuity in the laboratory setting (Teschler et al. 1997). The AST provides lower mean pressures during therapy and compensates for night-to-night variability in sleep disordered breathing. The following is a preliminary report of a larger study designed to determine if self-adjusting CPAP improves compliance, quality of life and reduces unwanted side effects in OSA patients who require higher fixed pressure levels.

Methods: Eight patients (7 men and 1 woman); mean age 51.4 yrs ± 8.1; BMI ≤ 40) with polysomnographically-confirmed OSA (mean RDI = 52 ± 37.3) were included. All patients were titrated manually in the laboratory, and required ≥ 10 cwp. A randomized crossover design was employed; following the manual laboratory titration patients used the AutoSet T device set in manual mode or automatic mode for 6 weeks and then switched to the alternate mode. Patients maintained a sleep diary for the duration of treatment, daily for the first week and weekly thereafter. Patients completed the Epworth Sleepiness Scale (ESS), the SF-36 Health Survey and Trails A & B prior to and following each treatment arm.

Results: Table 1 presents means and standard deviations for selected outcome measures. Objective compliance, ESS score, Trails B and the Physical Functioning (PF) and Vitality (VT) scales of the SF-36 Health Survey. The PF and VT scores were standardized, range 0-100. Two items from the sleep diary were included: "How well did you sleep?" and "How much discomfort did you get from the pressure?" These questions were assessed with a 100mm visual analog scale; higher numbers indicating better sleep and less pressure discomfort. Values for the first week of each treatment mode are presented. A trend toward increased compliance with automatic therapy was observed ($t=1.8$; $p=0.11$). A significant reduction in ESS score ($F_{2,7}=29.6$; $p<0.001$) and increase in Vitality ($F_{2,7}=12.5$; $p< 0.001$) was observed with therapy, but no differences were noted between automatic and fixed pressure. Patients reported less discomfort from the pressure during automatic therapy ($t=2.8$; $p=0.03$). At the conclusion of the study, patients were maintained on the therapy of their choice; seven patients preferred the automatic mode and one patient preferred the manual mode.

Table 1

	Compliance (minutes)	ESS	Trails B (sec)	Physical Function
Pretreatment		12.6 ± 3.6	62 ± 16.4	70.9 ± 28.1
Automatic	366 ± 54	6.9 ± 2.3	56.1 ± 18.4	80 ± 22.7
Manual	320 ± 99	7.0 ± 1.8	56.8 ± 21.5	75 ± 23.8
	Vitality	**Slept Well**	**Pressure**	
Pretreatment	36.3 ± 25			
Automatic	70 ± 17.9	77.1 ± 8.1	91.9 ± 3.3	
Manual	71.3 ± 19	69 ± 15.5	78 ± 12.4	

Conclusions: These preliminary results suggest the utility of AutoSet T in patients who require higher pressures during manual titration. A trend toward increased compliance with automatic therapy may be the result of less pressure discomfort, and a reduction in other adverse side effects. Quality of life and daytime sleepiness are likely to be improved in all patients using CPAP; some scales of the SF-36 may show differential improvement during automatic therapy. Subsequent analyses with a larger sample size are required to confirm these preliminary results.

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1276.K1

Comparison of Morning Nap Split-Study Versus Nocturnal Split-Study CPAP/BiPAP Titration

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Introduction: Current standard of treatment for obstructive sleep apnea and hypopnea syndrome (OSA) is continuous positive airway pressure (CPAP) or Bi-level positive airway pressure (BiPAP). The therapy is typically administered in patients with moderate to severe OSA. Accepted practice is to perform overnight observation in which a "full-night titration" study or "split-night titration" study is performed. Both protocols remain the "gold standard" for determination of optimal treatment pressures, with a minimum of 6 hours suggested by the American Sleep Disorders Association Task Force.[1] This study compared the same patients who received both a nap study and an overnight study during which nasal CPAP or BiPAP was titrated. We determined if the nap CPAP/BiPAP titration differed from nocturnal CPAP/BiPAP titration

pressures and whether a nap split-study CPAP titration was a satisfactory procedure in patients with moderate to severe OSA.

Methods: Forty patients (19 females; 21 males) underwent both nap CPAP/BiPAP titration and nocturnal CPAP/BiPAP titration. Overnight studies were performed an average of 12.5 months after nap studies and all patients were treated with CPAP/BiPAP between evaluations. Nap and nocturnal protocols were designed as split-studies to determine a baseline Apnea Hypopnea Index (AHI) and overnight studies were performed blind to the nap titration . Naps began at 6:30 am following a night of sleep deprivation with an average of 64.0 (± 3.7 SE) minutes used to determine the AHI, while nocturnal split-studies started at 11:00 pm, and had an average of 70.0 (± 5.1 SE) minutes to determine the AHI. Baseline data acquisition was followed by CPAP/BiPAP titration. Optimal CPAP/BiPAP therapy under both protocols was determined while patients slept supine and each was effective in eliminating snoring and obstructive respiratory events while maintaining oxygen saturation > 93% in sleep.

Results: Nap total study time (TST) (MEAN 190.50 min. ± 4.2 SE) and nap sleep time (MEAN 136.7 min. ± 6.7 SE) resulted in a mean nap sleep efficiency of 73.5% (± 2.7% SE). Overnight studies' TST (MEAN 386.1 min. ± 6.7 SE) and sleep time (MEAN 325.7 min. ± 10.0 SE) resulted in a mean overnight sleep efficiency of 84.2% (± 2.0% SE). A mean nap AHI was 58.5 (± 7.3 SE) and the nocturnal AHI was 53.9 (± 5.5). The therapeutic pressures (nap: 11.9 ± 0.6 and overnight: 12.4 ± 0.8 cm H2O) were not statistically different and highly correlated ($r = .82$; $p < .001$).

Conclusions: A nap split protocol may be utilized to effectively titrate CPAP in patients with OSA. Integration of the protocol into a sleep lab's practice could increase productivity.

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1286.K1

Does Cervical Positioning with Auto-titration Effectively Reduce Pressures Delivered to Patients with Obstructive Sleep Apnea?

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Introduction: Extension of the uppermost part of the cervical spine has been shown to increase the width of the pharyngeal airway. Cervical positional effects on snoring and reduction of mild obstructive apneic events have recently been reported using a custom-designed cervical pillow which promotes neck extension. Likewise, studies using auto-titration for the treatment of Obstructive Sleep Apnea (OSA) have reported a lowering of the median pressure delivered to patients over the course of a night of therapy, thereby increasing patient comfort and compliance. The purpose of our study is to show if cervical positioning in conjunction with auto-titration will allow therapeutic pressure levels to be effectively reduced in a group of patients who have been sleeping at home with nCPAP for greater then one year.

Methods: Fourteen patients, 9 males and 5 females, with mild to severe OSA were chosen from our nCPAP program patient data base (Mean Age = 47.86, Mean BMI= 41.15, Mean Diagnostic RDI= 45.91, Mean Pre-treatment Epworth Sleepiness Score =12.93, Mean Epworth Sleepiness Score after 12 months of nCPAP treatment= 6.07, Mean Quality of Life Score after 12 months using nCPAP= 3.2). Patients were queried regarding interest in participating in our three week study using the Pillow Positive #61668; LifeSleep Systems, Inc. and an auto-titration system, the Tranquility #61666;Auto by Respironics, Inc. or the AutoSet-T #61666; by ResMed Corporation. Patients were custom fitted to their pillows using three measurements of the head and neck. During the first week of study, the patients slept at home with their assigned auto-titration system. Assignment of an auto-titration system was based on patients preference for mask interface as well as need for humidification during therapy. During the second study week the patients slept at home with both the pillow and the assigned auto-titration system. The second week was considered to be a period of adjustment to sleeping with the new pillow and data collected during this time was not included in the study results. During the third and final study week, the patients again slept with the pillow and their assigned auto-titration system. Median and Peak pressures were compared with and without cervical positioning. In addition, auto-titration pressures were compared with each patients pre-study fixed level of CPAP. Patients also provided subjective data regarding adjustment to sleeping with the new pillow, sleeping with auto-titration and a nightly rating of their quality of sleep. Additional patient comments were encouraged.

Results: Eleven patients completed the study; 2 patients could not adjust to sleeping with the pillow and 1 patient could not adjust to sleeping with auto-titration. The mean prescribed fixed nCPAP = 9.7 cmH2O , mean Median pressure with auto-titration = 8.0 cmH2O, mean Peak pressure with auto-titration = 13.5 cmH2O, mean Median pressure with auto-titration and pillow = 8.0 cmH2O, mean Peak pressure with auto-titration and pillow = 13.4 cmH2O. The mean average usage time with auto-titration = 7.7 hours and with auto-titration and pillow = 7.8 hours. On a scale of 1-5, the patients provided a mean Quality of Sleep rating of 3.2 with auto-titration alone and 3.6 with auto-titration and the pillow. On a scale of 0-4, the patients provided a mean rating for adjustment to sleeping with auto-titration of 3.4 and adjustment to sleeping with the pillow of 3.5.

Conclusions: From this limited study, we conclude that there is no change in median pressures and an insignificant reduction in peak pressures delivered to patients sleeping with the Pillow Positive. The patients who completed the study reported an improvement in their quality of sleep and little difficulty adjusting to sleeping with the pillow.

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1289.K1

MWT in Patients with Obstructive Sleep Apnea: Comparing Three Scoring Criteria for Sleep Onset

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Introduction: Excessive daytime sleepiness is typically quantified by either the tendency to fall asleep (Multiple Sleep Latency Test, MSLT), or the ability to resist sleep onset (Maintenance of Wakefulness Test, MWT). Scoring involves calculating the latency from lights out to the occurrence of unequivocal sleep onset, typically defined as either the

first 30-sec epoch of sleep,[1] or the first of three consecutive epochs (90 sec) of stage 1.[2] In obstructive sleep apnea (OSA), apneic events may interrupt the continuity of the sleep onset process, creating inflated sleep latency scores when the 30-sec or 90-sec scoring criteria are used. An alternative may be to calculate the latency from lights out to the first occurrence of a 5-sec microsleep.[3] Five-second, 30-sec and 90-sec scoring criteria were compared on the MWT in patients with OSA before and after 5 weeks of treatment with continuous positive airway pressure (CPAP).

Methods: To date, seven male patients diagnosed with OSA (mean AHI=29; mean age=55 years) have been studied. A randomized crossover design was used, consisting of two 5-week CPAP limbs, with each limb preceded by a 1-2 week washout period. Two forms of CPAP treatment were compared: conventional titration using overnight polysomnography followed by treatment at the determined optimal pressure, and self-adjustment of CPAP pressure according to subjective comfort and efficacy. MWT testing was performed before and after each limb, with trials occurring at 0900, 1100, 1300 and 1500 hrs. Each trial was scored using 5-sec, 30-sec and 90-sec criteria for sleep onset. Mean sleep latency and frequency of sleep onset were calculated for each testing day and analysed using repeated measures ANOVAs with treatment order as the between-subjects factor, and scoring criterion, treatment type and pre/post CPAP as within-subjects factors.

Results: Main effects of scoring criterion were significant for sleep latency [$F(2,10)=45.8, p<.001$] and frequency of sleep onset [$F(2,10)=31.5, p<.001$]. Matched t-tests showed that the 5-sec criterion produced significantly shorter latencies and more frequent sleep onsets compared to the 30-sec criterion [$t(6)=6.3$, $p=.001$; $t(6)=3.6, p=.012$], and the 90-sec criterion [$t(6)=5.7$, $p=.001$; $t(6)=5.0, p=.002$]. Similarly, the 30-sec criterion produced significantly shorter latencies and more frequent sleep onsets than the 90-sec criterion [$t(6)=3.8, p=.009$; $t(6)=3.2, p=.018$]. The criterion x treatment type and criterion x pre/post interactions were not significant. The criterion x type x pre/post interactions were significant and their interpretation is consistent with the main effects.

Table 1

	5-sec Criterion Mean (Std. Error)	30-sec Criterion Mean (Std. Error)	90-sec Criterion Mean (Std. Error)
Sleep Latency	21.1 min (2.9)	26.7 min (2.7)	31.3 min (2.2)
Frequency of Sleep Onset	76.8% (7.0)	60.7% (9.8)	42.0% (9.0)

Conclusions: On average, sleep onset was almost twice as frequent and sleep latency was reduced by 10 min when MWT trials were scored using the 5-sec criterion versus the 90-sec criterion. Therefore, in patients for whom the sleep onset process may be fractured due to apneic events, a more sensitive index of sleepiness may be obtained by scoring the occurrence of microsleeps on the MWT.

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1298.K1

Increased Upper Airway Collapsibility and Decreased Ventilation in Men vs Women in Response to Resistive Loading During NREM Sleep

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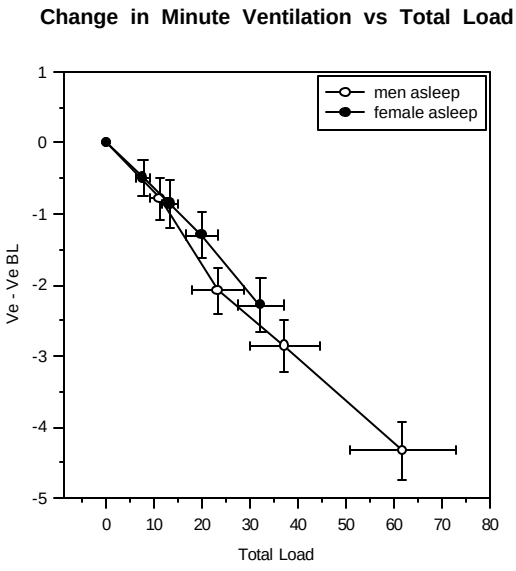
Introduction: The male predominance of Obstructive Sleep Apnea (OSA) is currently poorly understood. A previous study suggested that inspiratory resistive loading (IRL) during NREM sleep may lead to more marked hypoventilation in men than women. However, the underlying mechanism was not tested. We hypothesized that the gender-related differences in load response resulted from differences in upper airway collapsibility (greater total load in men), rather than differences in central drive.

Methods: Upper airway (UA) collapsibility and load responsiveness were assessed in both genders awake and asleep. We studied 16 normal subjects (8 men, 8 women) awake and during NREM sleep while measuring UA resistance (Millar pressure catheters @ choanae and epiglottis). We performed breath-by-breath analysis (first 3 breaths per condition, 3 trials per load) during baseline and 4 IRL conditions (5, 10, 15, and 25cmH2O/l/sec).

Results: · During wakefulness, women increased minute ventilation (VE) during IRL, while VE decreased in men (+21±5% vs -23±3% @ max load, $p<0.05$). · During NREM sleep, when given identical external loads, UA resistance increased more in men than women (+36.6±3.9 vs +7.2±1.7 cmH20/l/sec @max load, $p<0.05$). · Men hypoventilated to a greater extent than women in response to IRL (Ve decreased by 45±2% vs 29±2% @max load, $p<0.05$). · Hypoventilation in response to IRL was solely explained by decreases in tidal volume, with respiratory rate relatively remain unchanged. Inspiratory time increased similarly in both genders.· When total load was determined (applied + intrinsic), the ventilatory response to IRL during NREM sleep was similar between genders (see fig), namely hypoventilation in men can be solely explained by increased UA resistance in response to IRL.

Figure 1



POSTER PRESENTATIONS

Conclusions: The increased ventilation seen in women awake is likely behaviorally mediated. During NREM sleep, the pharyngeal airway of males was considerably more collapsible than that of females. Thus, men were exposed to a greater total load. The ventilatory response to total load was similar between genders. A more collapsible airway may predispose men to sleep apnea.

Research supported by NIH HL 48531 and HL 60292 and NCRR RR02635

1304.K1

Detection of Obstructive Sleep Disordered Breathing Events Utilizing Peripheral Arterial Tonometry and Oximetry.

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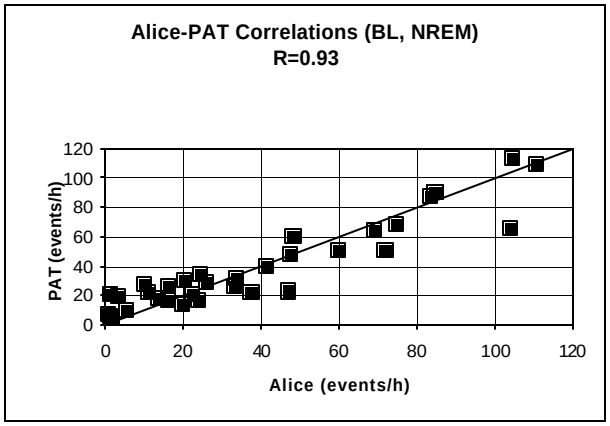
Introduction: The termination of obstructive sleep disordered breathing events is associated with an increased heart rate, blood pressure, and sympathetic activation. We hypothesized that these periodic increases in sympathetic activation could result in periodic peripheral vasoconstriction, which would be detectable by a peripheral arterial tonometer (PAT).

Methods: We studied 40 patients referred to the sleep lab with suspected OSA, comparing standard PSG with PAT+oximetry (all data obtained simultaneously). The PAT is a modified finger plethysmograph specially designed for overnight studies. It was inflated with a subdiastolic pressure (continuously throughout the night) to inhibit retrograde venous shock wave propagation and partially unload arterial wall tension. Pulse volumes were measured on 2 fingers. The recordings (PSG vs PAT+oximetry) were scored blindly. On PSG, events were scored using recent AASM criteria. On PAT+oximetry, an event was scored if one of the following occurred: PAT attenuated by >50%, SaO2 dropped by >4%, or PAT attenuated by >30% plus either SaO2 dropped by >3% or heart rate increased by >10%. Only epochs with EEG document sleep were scored and compared.

Figure 1



Results: Data are available on 35 patients. The remaining 5 had either poor signal quality (n=2) or asked to remove the PAT device after less than an hour (n=3). Based on a categorization of OSA as mild (RDI<20), moderate(20<RDI<40) and severe (RDI>40), PAT and PSG had 86% agreement (in 5/35 categorization was different). PAT could distinguish OSA from non-OSA (based on RDI cutoff =10/h) with sensitivity of 100% and specificity of 80%. The correlation between RDI measured by the 2 methods was R=0.93 during NREM sleep (Fig), and R=0.79 during REM sleep (P<0.01 for both). During REM sleep there was a substantial attenuation of the PAT signal, likely representing an increase in baseline tonus of the vasculature of the finger.

Conclusions: These results support previous findings showing that sleep disordered breathing events are associated with bursts of sympathetic activation. They also indicate that OSA can be diagnosed accurately utilizing PAT and oximetry (assuming sleep could be distinguished from wakefulness). As both devices can be easily placed on the finger, PAT + Oximetry has the potential to be a simple, effective ambulatory diagnostic tool.

Research supported by NCRR GCRC RR02635, NHLBI HL48531/HL60292

1306.K1

Can Heart Rate Variability Differentiate Between Obstructive and Non Obstructive Apnoeas?

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Introduction: Heart rate variability (HRV) is recognised as a measure of autonomic regulation of cardiac function. It has been demonstrated that the high frequency (HF) band of the HRV frequency spectrum reflects vagal tone, while the low frequency (LF) is mainly associated with the influence of the sympathetic nervous system. The ratio of these measures LF/HF reflects the sympatho-vagal balance.

Methods: 10 normal subjects, 20 patients with obstructive sleep apnoea (OSA), 10 patients with neuromuscular disease and non- obstructive sleep hypoventilation (NOSH) and 7 patients with neuromuscular disease and mixed OSA & NOSH participated in this study. All subjects underwent an overnight full polysomnography including ECG recording (sampling rate=100 Hz). Sequential segments of 256 seconds were extracted and analysed using power spectral analysis. Out of the 4970 segments recorded, 1870 were excluded after visual revision, due either to interference or arrhythmia. From the remaining 3100 segments, spectral power in the LF band (0.002-0.15 Hz) and HF band (0.15-0.4Hz), and LF/HF ratio were calculated.

Table 1

HRV	LF ($msec^2$)	HF ($msec^2$)	LF/HF
Wake	5141	834	11.8
NREM stage 1	7352*	1009*	14*
NREM stage 2	4524*	1184*	7.3**
NREM stage 3	2930**	1209**	4.6***
NREM stage 4	2108**	2585**	1.5***
REM	5295*	859*	11.8*

* NS ** P < 0.01 ***P < 0.001

Results: In all subjects, age decreased spectral power significantly (p<0.001) in both LF and HF to 96% (94-98%) and 93% (90-95%) respectively [mean change per year (95% confidence interval)]. LF/HF ratio significantly increased with age (p<0.01) to 104% (101-107%). Men did not differ significantly from women in any of the three measures. Sleep stage1 and REM did not differ significantly from wake. Uninterrupted sleep stages 2, 3 and 4 showed a significant decrease in LF & LF/HF and increase in HF (see table).The presence of OSA or NOSH produced distinct changes in HRV. Compared with uninterrupted sleep, OSA increased HF to 115% (111-118%), LF to 135% (130-140%) and LF/HF to 117% (113-121%). In NOSH, HF remained the same, LF increased to127% (118-137%) and LF/HF increased to 133% (124-143%) [mean change per 10 seconds apnoea / segment (95% confidence interval), p<0.01]

Table 2

	Normal	PLM with Arousals	95% Conf Interval		PLM with no Arousals	95% Conf Interval	
LF(msec^2)	1575	2000*	1764	2268	1890*,***	1670	2142
HF(msec^2)	164	213*	202	223	210*,***	189	233
LF/HF	16.8	28.2*	23.5	33.6	25.7**,***	21.8	30

*** P<0.001,** compared to normal **** P<0.01,** compared to normal
***** NS,** compared to PLMS with arousals

Conclusions: 1. Uninterrupted NREM sleep stage 2-4 is associated with a decreased LF and LF/HF ratio and an increased HF as compared to the wake and REM sleep. 2. There is an immediate sympathoactivation during any type of apnoea as evidenced by the increase in LF & LF/HF ratio. 3. A simultaneous increase in the HF suggests an obstructive apnoea, while no change or a decrease suggests a non-obstructive apnoea.

1307.K1

Assesssment of Heart Rate Variability During Periodic Leg Movements in Sleep

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Introduction: The other physiologic changes that occur with periodic leg movements during sleep (PLMS) might be more sensitive indices of sleep fragmentation than EEG arousals. Arousals from sleep are associated with transient increases in blood pressure, heart rate and ventilation. It has become increasingly clear that non-EEG (autonomic) arousals are associated with daytime consequences. HRV can be used as a measure of these autonomic arousals. High frequency (HF) band of the Heart rate variability (HRV) frequency spectrum reflects vagal tone, while the low frequency (LF) is mainly associated with the influence of the sympathetic nervous system. The ratio of these measures LF/HF reflects the sympatho-vagal balance.

Methods: 10 normal subjects and 10 patients with a PLM index of >10 events per hour participated in this study. All subjects underwent an overnight full polysomnography including ECG recording (sampling rate=100 Hz). Sequential segments of 256 seconds were extracted and analysed using power spectral analysis. Out of the 1467 segments recorded, 426 were excluded after visual revision, due to either interference or arrhythmia. From the remaining 1041 segments, spectral power in the LF band (0.002-0.15 Hz) and HF band (0.15-0.4Hz), and LF/HF ratio were calculated.

Results: Normal subjects age [mean (range) of 46.4(17-66) years] did not differ from PLMS patients [50.4(21-70)years]. Men did not differ significantly from women in any of the measures of HRV. Compared to the segments of normal sleep, the segments with PLMS had higher LF, HF and LF/HF ratio than normal (see table). Periods with arousals had higher values than those without arousals, but the difference was not statistically significant.

Table 1

HRV	LF (msec^2)	HF (msec^2)	LF/HF
Wake	5141	834	11.8
NREM stage 1	7352*	1009*	14*
NREM stage 2	4524*	1184*	7.3**
NREM stage 3	2930**	1209**	4.6***
NREM stage 4	2108**	2585**	1.5***
REM	5295*	859*	11.8*

* NS ** P < 0.01 ***P < 0.001

Conclusions: There is an increase in the autonomic output to the heart during PLMS, being more prominent in the sympathetic axis. This is independent of the presence of cortical arousals.

1334.K1

Clinical Predictors of Obstructive Sleep Apnea

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Introduction: Obstructive sleep apnea (OSA) is a fairly common condition affecting 24% of male and 9% of female middle-aged adults. Currently, the condition is diagnosed through history, physical exam, imaging studies, and polysonmography. Despite the large volume of literature on OSA, there is a lack of consensus in describing physical findings associated with OSA- The anatomic abnormalities associated with difficult endotracheal intubation might be associated with OSA. It may be logical, therefore, that the clinical factors that predict difficult intubation can also predict OSA- One hundred seventy-two patients who answered questionnaires with responses that suggested they might have OSA were included in this prospective study to identify physical findings that can be standardized to predict the presence and the severity of obstructive sleep apnea (OSA).

Methods: All patients underwent a physical examination and polysomnography. The physical exam included the measurement of 4 parameters used by anesthesiologists to identify patients likely to have difficult intubation to determine if these same parameters predict OSA. We recorded modified Mallampati grade (MMP), tonsil size, body mass index (BMI) and measured thyroid-mental (TMD) and hyold-mental (HMD) distances in the study population.

Results: When the physical findings were correlated singly with the RDL we found that NEAP (p<.001), tonsil size grading (p=0.008) and BMI (p=0.003) were reliable predictors of OSA. A greater correlation with OSA emerged when an "OSA score" was formulated by factoring the MMP, tonsil grade, and BMI grade (RDI=7.8l6*MMP+3.988 *Tonsi1 Size+4.675*BMI-7.544). A high score was not only predictive of OSA but also correlated well with OSA severity. Neither HMD nor TMD correlated with the severity of RDI.

Conclusions: Most diseases have identifiable symptoms, signs and laboratory corroboration. OSA has been traditionally identified by symptoms and laboratory test results without identification of physical abnormalities, except for the known correlation with BMI. This study has identified the correlation between modified Mallarnpati grade, tonsil size and BM1 with levels of severity of OSA. This data provides substantial initial clinical evidence that will alert the clinician, while examining the patient, about the strong possibility of the existence of OSA and may help identify those patients who should have a full sleep evaluation.

References:
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(2) Friedman M et al: Quantifiable physical findings in obstructive sleep apnea. Poster presentation at the 1999 annual meeting of the American Academy of Otolaryngology - Head and Neck Surgery.

1342.K1

The Effect of Improved Nasal Breathing on Obstructive Sleep Apnea

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Introduction: Correction of an obstructed nasal airway is considered an important component in OSA treatment Clinical reports document nasal

obstruction induced OSA, but controversial data exists regarding the role of improved nasal breathing in treating OSA. If nasal obstruction can result in OSA, it would be logical to assume that correction of an obstructed airway can improve OSA. Experimental data exists regarding the role of increased nasal resistance and nasal occlusion in OSA. Objective analysis of the effect of nasal surgery alone may provide novel information about the impact of nasal airway obstruction on OSA. Our goal is to compare the effect of an improved nasal airway on obstructive sleep apnea (OSA) by using subjective and objective measures. The results of this study may allow a more tailored approach to the treatment of OSA.

Methods: A prospective study was designed to accrue 50 adult patients with OSA who required surgical treatment for nasal airway obstruction between July 1, 1997 and June 30, 1998. Patients were required to have symptomatic subjective documentation and OSA documented on an 18-lead PSG. A second night PSG with titration of continuous positive airway pressure (CPAP) was performed on patients who were able to tolerate CPAP treatment Postoperative PSG and CPAP titration were performed 6 weeks post-operatively or later. This study was designed to collect data from standard treatment only and did not alter any treatment plans.

Results: Subjectively, nasal breathing improved in 49 (98%) patients, while snoring decreased or disappeared in 17 (34%); the remaining 33 (66%) patients did not notice any significant change in their snoring, Daytime energy levels increased in 39 (78%) patients and remained unchanged or worsened in 11 (22%). In review of the polysonographic data, the group overall did not have significant changes in respiratory disturbance index (RDI) or lowest oxygen saturation levels ($LSaO_2$). Continuous positive airway pressure (CPAP) levels needed to correct OSA, however, decreased afternasal surgery ($p<0.01$). Mild OSA patients showed significant worseningin RD1 ($p<0.05$), while $LSaO_2$ levels were improved in the moderate OSA group ($p<0.05$). In patients with severe OSA neither the RDI levels nor the $LSaO_2$ changed, but CPAP levels required to alleviate the obstruction post-operatively was reduced ($P<0.01$).

Conclusions: The majority of patients report improvement in nasal and sleep symptoms after correction of nasal airway obstruction. However, nasal surgery alone does not consistently improve OSA when measured objectively. Depending upon the seventy of OSA, nasal airway reconstruction may contribute to a decrease in CPAP level and improvement in oxygen saturation. Correction of the obstructed nasal airway should certainly be included in the overall treatment plan for OSA.

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(1) Papsidero MJ, The role of nasal obstruction in obstructive sleep apnea. Ear Nose Throat J, 1993, 82-4.
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(3) Atkins M, Taskar V, Clayton Net al: Nasal resistance in obstructive sleep apnea. Chest, 1994,1133-5.

1349.K1

Chronic Treatment with Nasal Intermittent Positive Pressure Ventilation (NIPPV) and Daytime Gas Exchange in Different Patient Groups with and without Sleep Apnea.

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Introduction: Chronic treatment with NIPPV at night may improve daytime blood gases in a number of patients with chronic respiratory insufficiency and/or sleep apnea (Simonds AK et al 1995; Jones DJ et al 1995). It is not established which factors may contribute to the improvement in blood gases when the whole spectrum of the diseases is taken into account.
Methods: The aim of the present study was to determine these factors in patients with chronic obstructive pulmonary disease (Gr1), restrictive lung disease (Gr2), obstructive sleep apnea with normal lung function (Gr3), OSA with obstructive lung disease (Gr4), OSA with restrictive lung disease (Gr5). All patients got a standard polysomnographic evaluation, arterial blood gas analysis and lung function testing at baseline. Blood gases were repeated after 12 months NIPPV treatment.

Table 1

	Age y	FEV_1 %pred	TLC %pred	AHI #/h
Whole group	57 (1)	58 (3)	86 (2)	61 (6)
Gr 1 (n=10)	55 (2)	39 (4)	105 (7)	5 (2)
Gr 2 (n=11)	56 (3)	48 (6)	62 (4)	8 (2)
Gr 3 (n=14)	56 (3)	102 (3)	100 (3)	85 (16)
Gr 4 (n=27)	59 (2)	49 (4)	96 (3)	77 (11)
Gr 5 (n=27)	61 (2)	56 (3)	72 (2)	75 (10)

	$PaCO_2$ mmHg	PaO_2 mmHg	$DPaO_2$ mmHg	$DPaCO_2$ mmHg
Whole group	45 (1)	64 (1)	3.2 (1.3)	-1.1 (0.7)
Gr 1 (n=10)	47 (2)	58 (3)	-3.6 (2.9)	-1.9 (1.6)
Gr 2 (n=11)	43 (2)	66 (4)	-1.4 (5.0)	2.1 (1.3)
Gr 3 (n=14)	39 (1)	72 (4)	3.8 (2.9)	-0.6 (1.0)
Gr 4 (n=27)	46 (2)	63 (2)	2.2 (2.2)	0.8 (1.1)
Gr 5 (n=27)	47 (2)	62 (2)	7.3 (2.2)	-4.1 (1.6)

Results: 89 patients were included into the study. Baseline characteristics and mean changes in daytime blood gases (after 12 m) are given in the table (Mean/SEM). Multiple regression analysis indicates that the changes in PaCO2 are significantly influenced by initial PaCO2 (BETA -0.64, $p<0.01$), while changes in PaO2 are significantly influenced by

initial PaO2 (BETA -0.57, p<0.01), FEV1 (BETA 0.38, p=0.03) and diagnostic category (GR 1-5) (BETA 0.23, p=0.02).

Conclusions: After chronic treatment with NIPPV at night, daytime gas exchange (especially PaCO2) improves mainly in patients who also have underlying obstructive sleep apnea.

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1513.K1

Epilepsy and Obstructive Sleep Apnea

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Introduction: Recent publications document the coexistence of epilepsy and obstructive sleep apnea (OSA) (Devinsky et al 1994; Malow et al 1997). The extent, nature, and clinical relevance of this association remains poorly known.

Methods: A diagnosis of epilepsy was made in 21 (3.4%) of 615 patients (pts) with OSA seen at our Sleep Center over the last six years. Characteristics of epilepsy, sleep history, presence of excessive daytime sleepiness (Epworth Sleepiness Score=ESS), and response to continuous positive airway pressure (CPAP) were assessed. Clinical follow-up was obtained in all pts at a median of 26 months (range: 5-102 months) after the diagnosis of OSA.

Results: There were 19 men and two women with a median age of 50 years (range: 35-76). The median Apnea-Hypopnea-Index was 44 (range: 13-85) and 67% of pts had an ESS >10. Epilepsy was generalized in 8 pts and focal in 13 pts. In 11 pts epilepsy was idiopathic, and in three pts seizures were state-dependent. In 20 pts epilepsy appeared one month to 35 years before the diagnosis of OSA. In 14 pts the onset of OSA-symptoms coincided with a clear increase in seizure frequency or first appearance of a status epilepticus. Treatment with CPAP was continued with good compliance in 11 pts and led to a significant reduction of both ESS and seizure frequency in four pts.

Conclusions: 1) The frequency of pts with epilepsy and OSA is greater than expected by pure coincidence, 2) a detrimental effect of OSA on seizure frequency was likely in >50% of our pts with OSA and epilepsy, 3) treatment with CPAP improved seizure control in at least 1/3 of pts, all of whom had an excessive daytime sleepiness.

References:
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1356.K1

Expiratory Flow Limitation and Bilevel Titration

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Introduction: Since introduction of nasal pressure by Rappaport, flow limited breath is becoming a more recognized aspect of SRBD. There has been a large amount of data in regard to inspiratory flow (IF)but much less attention has been given to expiratory flow limitation (EFL). If apnea began with recurrence of events that start at the end of expiration, one may postulate that IFL is the result of the change in the flow dynamics during expiration. Bilevel improved not only IFL but also EFL although at the expense of the higher level of inspiratory pressure (IPAP). Theoretically, improving EFL by adjusting expiratory positive airway pressure (EPAP) decreases the amount of pressure required by inspiration (IPAP).

Methods: We examined 15 PSGs titrated on Bilevel who failed maximum pressure of IPAP after improving apnea with EPAP. Adjustment of EPAP improved OH and led to further down-regulation of IPAP. Of the 15 patients, 3 were female, 12 male, age 26-72, all overweight with BMI of 35-40. All patients were monitored with full PSG montage including EEG, EOG, submental EMG, EKG, snoring microphone, nasal pressure, nasal/oral thermistor, pneumotachograph with separate inspiratory-expiratory flow, bilevel plotting of the pressure-flow, uncalibrated RIP, surface diaphragmatic EMG, and oximetry. Bilevel titration was performed according to standard technique in our sleep laboratory. IPAP/EPAP began at 4 cm and increased 1 cm, alternating until OSA was eliminated. Thereafter, IPAP was increased in increments of 1 cm until the difference between the IPAP-EPAP reached 4 cm. The difference was kept constant with further increase in IPAP/EPAP at increments of 1 cm according to pneumotachograph tracing of either IFL or EFL.

Results: Successful level titration was performed on 12 of the 15 patients. Three of the patients required maximum allowable IPAP level.

Conclusions: Adjustment of the IPAP/EPAP based on inspiratory/expiratory flow limitation can give a better titration of bilevel pressure. We monitored both inspiratory/expiratory flow by pneumotachograph as it has been shown to be a Gold Standard technique to measure flow in the sleep laboratory. Partition of the inspiratory versus expiratory flow by pneumotachograph also gives additional advantage of analyzing flow limitation both during inspiration and expiration. Due to inherent difference of the pressure-flow (hysteresis) during inspiration versus expiration, the contour of the inspiratory versus expiratory flow limitation may differ. In this study we did not intend to correlate nasal pressure vs pneumotachograph, however, a good correlation was found for IFL with discrepancy in 3 patients' EF with normal tracing by Pn and EFL by pneumotachograph. EFL in OSA is similar to COPD, which can cause auto-PEEPor PEEPi. Similar to COPD, application of external PEEP and/or EPAP equal to the PEEPi and/or 2-3 cm above improve auto-PEEP. Starting resistor applies not only during inspiratory phase but also during expiratory phase in OSA with critical closing pressure during expiration, perhaps in the vicinity of + 4 cm. Theoretically, the reduction and/or decreased flow at the end of the expiration may lead to a lack or reduction of the flow at the beginning of the ensuing inspiration resulting in increased effort and IFL and asynchrony. Increasing the flow by the IPAP eventually not only improves IF but also EFL, but at the expense of higher IPAP. Improving EFL by adjusting the EPAP may lead to further reduction of IPAP not only by improving the flow at the end of the exhalation but also improving synchrony with flow triggering breath on ensuing inspiration. Furthermore increasing EPAP also improves oxygenation which otherwise could be accomplished only with higher pressure of IPAP. We kept the difference between IPAP-

EPAP at 4 cm/H2O in non-hypercapnic OSA patients due to the fact that increasing IPAP-EPAP > 4 cm may lead to collapse of the airway at the end of the expiration.

References:
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1364.K1

Quality of Life in Sleep Apnea Patients Using Intraoral Mandibular Repositioner.

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Introduction: Quality of life is evaluated through socioeconomic and cultural factors. Obstructive sleep apnea syndrome (OSAS) is one of clinical disorders that affects these parameters once it interferes with life relationships. Our study utilizes an efficient and simple method to evaluate improvement in the OSAS patients´ quality of life, when intraoral mandibular repositioner is used as a treatment.Objective: Our goal in the present study is to verify how much the treatment with mandibular repositioner can improve the OSAS patients´ quality of life.

Methods: 11 male patients with mild and moderate OSAS were evaluated through the Calgary Sleep Apnea Quality of Life Index (SAQLI); which was developed to estimate the OSAS patients´ quality of life. Calgary SAQLI is organized into four domains: daily functioning, social interaction, emotional functioning and symptoms; a fifth domain, treatment-related symptoms, is added after clinical intervention. This questionnaire was applied before and after a 4-week treatment. We called no improvement (<1.0), mild improvement (1.0-1.49), moderate improvement (1.50-1.99) and great improvement on quality of life ( 2.0), taking account the difference between the pre and post intervention score. The mandibular repositioners were fabricated with acrylic polymer, provided with an adjustable mechanism and Adams clasps to maintain the mandible in a forward position during sleep.

Results: Four out of eleven patients (36.3%) reached a mild improvement, 2 (18.2%) a moderate improvement and 5 (45.5%) a great improvement in quality of life. On the daily functioning domain: 2 (18.2%) reached a mild improvement, 5 (45.5%) a moderate improvement and 4 (36.3%) a great improvement. Regarding to social interactions, 4 patients (36.3%) obtained a great improvement, 3 (27.3%) a moderate improvement, 3 (27.3%) a mild improvement and one (9.1%) didn't have improvement. In the emotional functioning domain, 3 patients didn't have improvement, 3 (27.3%) had a mild improvement, 2 (18.2%) a moderate improvement and 3 (27.3%) had a great improvement. Regarding to the symptoms domain, where we obtained the most important results, 10 patients (90.9%) had a great improvement and 1 (9.1%) a moderate improvement

Conclusions: Calgary SAQLI application has indicated a clear improvement in OSAS patients´ quality of life in this study, with a systematic use of the intraoral mandibular repositioner. Separated analysis of the four domains of the Calgary SAQLI has shown that the symptoms domain is the major responsible for the improvement in these patients´ quality of life. The change to a better outcome on daily functioning domain also endorses the intraoral mandibular repositioner as an instrument of great value in the treatment of mild and moderate obstructive sleep apnea syndrome.

1376.K1

CPAP-Related Changes in MWT Sleep Latency in Patients with Obstructive Sleep Apnea

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Introduction: Excessive sleepiness is a cardinal symptom of obstructive sleep apnea (OSA). Continuous positive airway pressure (CPAP) improves sleep-related breathing and relieves self-reported sleepiness. The maintenance of wakefulness test (MWT) is designed to evaluate an individual's ability to overcome sleepiness and remain awake. Previous research examined MWT in patients with sleep apnea and narcolepsy. To our knowledge, however, CPAP-related changes in MWT have not been evaluated in a randomized trial using untreated controls.

Methods: This study was a prospective, randomized, outcome trial comparing improvement from baseline at 2-week follow-up in treated vs. untreated parallel control group. Subjects were 29 men, age 33-64 years (mean=52 years) with obstructive sleep apnea randomized into CPAP treatment (n=17) or untreated (n=12) groups. Diagnosis and optimal CPAP was determination with comprehensive polysomnography.

Figure 1. CPAP-related MWT Changes

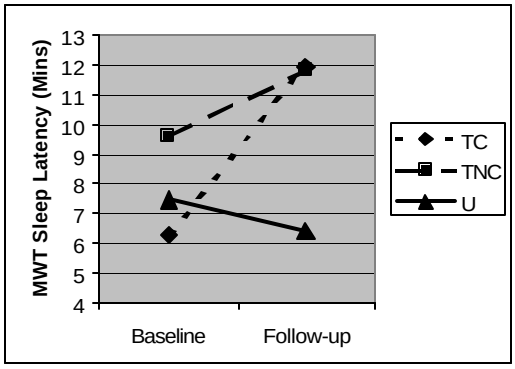
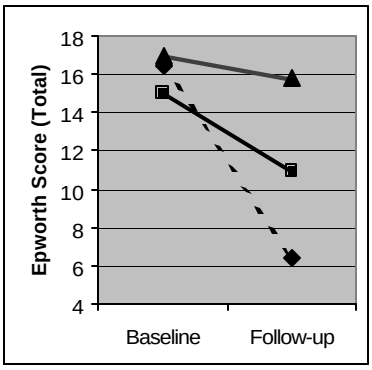


Figure 2. CPAP-related ESS Changes



Results: The overall experimental design can be represented as main effects for GROUP (Treated vs. Untreated) X SESSION (baseline vs. follow-up). The interaction effect for GROUP X SESSION provided a test for the differential effect of CPAP therapy on an outcome measure. Mean apnea+hypopnea index at baseline for the treated group (T) was 45.5 compared to 39.7 for the untreated group (not significantly different). Additional GLM analyses were conducted with a trifurcated GROUP factor (treated compliant with 5 or more hours usage per night

{TC}, treated noncompliant {TNC}, and untreated {U}). All significance testing was performed at the $p<0.05$ level. MWT sleep latency did not differ between T and U groups at baseline; however, group TNC was less sleepy at baseline than group TC. At follow-up, MWT was higher in both treated groups than the untreated group (which did not improve). ESS did not differ at baseline between groups. There was a stepwise significant improvement with group TC showing the most improvement, followed by group TNC, and finally U (no improvement).

Conclusions: Our results show that 1-2 weeks of CPAP therapy improves MWT-measured alertness in patients with SRBD. Mean MWT sleep latency for patients randomized into the untreated group did not differ between baseline and follow-up sessions. Both compliant and noncompliant treated groups reached a MWT sleep latency endpoint of 12 minutes. Interestingly, 12 minutes is the lower boundary of MWT's 95th percentile in normal subjects. It is possible that some patients only used CPAP enough to improve alertness to this level. By contrast, self-reported sleepiness declined as a function of CPAP usage, from a common starting point. Nonetheless, both MWT and ESS positively reflected treatment outcome.

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POSTER PRESENTATIONS

1379.K1

Cyclic Alternating Pattern and Continuous Positive Airway Pressure Titration

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Introduction: The biphasic pattern consisting of transient arousals (phase A) that periodically interrupt the tonic delta/theta activities of NREM sleep (phase B) is known as the cyclic alternating pattern (CAP). Absence of A phases for at least 60 consecutive seconds is scored as non-CAP (NCAP). Arousal phenomena linked to sleep apnea, PLMS, epilepsy are associated with A phases of CAP.[1-3] We hypothesized that during CPAP titration, flow limitation would be stable in NCAP and unstable in CAP even at sub-therapeutic pressure settings.

Methods: The polysomnograms of 12 patients with severe obstructive sleep apnea who underwent CPAP titration were reviewed. Inspiratory and expiratory flow profiles were monitored by measuring nasal mask pressure through a differential pressure transducer (Grass PT5). Periods of unstable (progressive worsening of inspiratory flow-limitation terminating in an arousal) and stable (non-progressive inspiratory flow limitation) airflow with the following characteristics were selected for detailed review: 1. Duration of 10 minutes or longer. 2. Suboptimal CPAP. 3. No positional change during the period. 4. No REM sleep within 2 minutes of the beginning or end of the period. Sleep was staged during these periods as delta/non-delta [conventional R & K scoring] or as CAP / NCAP [Terzano]. Pressure changes and the resulting change in flow-limitation were also noted as improvement or no improvement.

Results: Patient (mean) characteristics were as follows: age: 44, RDI: 76, minimum oxygen saturation: 78%. There were a total of 50 periods fulfilling the above criteria, totaling 1113 minutes of titration time. 30 periods (757 minutes, 68% of total) showed a stable flow-limitation pattern. 29/30 periods showing a stable flow pattern during sleep was scored as NCAP, and only a single 18-minute period of stable flow was scored as CAP. 19/20 periods showing an unstable flow pattern was in sleep with CAP characteristics, the exception being a single 14-minute period where unstable flow was noted in NCAP. Conventionally scored delta sleep made up 192 minutes (17.3%) of total tabulated titration time, and was always co-scored as NCAP. There were 53 upward pressure adjustments during the periods evaluated for study, 34 during CAP periods and 19 during NCAP periods. Pressure (1-2 cm each) increases during NCAP never resulted in a discernable change in the inspiratory flow profile, while 23/34 (68%) of pressure increments during CAP periods improved inspiratory flow. On 12/19 occasions, the pressure had to be decreased to the previous setting following a change during NCAP, at the end of the stable period.

Conclusions: The conceptualization of NREM sleep as "stable" or "unstable" has practical implications during pressure titration for the treatment of sleep-disordered breathing. Characterizing NREM sleep as CAP or NCAP is one practical method to do this. CAP periods are associated with unstable flow limitation and recurrent arousals, while relatively stable flow and undisturbed sleep irrespective of the actual pressure used are seen during NCAP periods. Pressure increases in NCAP rarely improve flow-limitation, and may result in pressure intolerance at the end of the NCAP period. Optimal pressure normalizes flow during CAP or NCAP. These findings have implications for manual titration, research on upper airway physiology and auto-titration algorithms.

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1388.K1

An Investigation of Sleep Apnea Variables as Predictors of Sleep Continuity and Sleep Architecture

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Introduction: It is well-established that individuals with Sleep Apnea Syndrome (SAS) have diminished sleep quality; specifically, SAS is associated with increased nocturnal arousals and stage 1 NREM sleep, as well as a reduced amount of slow-wave sleep.[1] The present study investigated the relation of various sleep continuity and architecture variables to respiratory event frequency and severity variables. Additionally, the study sought to determine whether respiratory event frequency and severity variables effectively predicted sleep continuity and architecture indices.

Methods: Subjects underwent a full-night standard polysomnographic (PSG) assessment of SAS, from which 4 respiratory event indices were obtained: Apnea + Hypopnea Index (AHI), mean SaO_2 during events, mean apnea/hypopnea duration, and Respiratory Event Arousals (REA). Sleep continuity indices were stage 1 periods per hour of sleep, stage changes per hour of sleep, spontaneous transient arousals per hour of sleep, total arousals per hour of sleep, and number of awakenings per hour of sleep; sleep architecture variables were % Stage 1 NREM, % REM, and % slow-wave sleep (SWS). Subjects were excluded from the analyses if their total sleep time was less than 5 hours, or if they showed evidence of Periodic Limb Movement Disorder or any other diagnosable sleep disorder in the PSG.

Table 1. Significant correlations of apnea variables and sleep continuity and architecture variables

	AHI	*Mean SaO_2*	*Mean Dur.*	*REA*
Stage 1 periods/hr.				r =.293 p =.003
Stage changes/hr.				r =.215 p =.029
Spont. transient arousals/hr.		r =-.197 p =.048		r =.372 p =.001
Total arousals/hr.	r =.459 p =.001	r =-.218 p =.028		r =.800 p =.001
Number of awakenings/hr.				
% Stage 1 NREM	r = .247 p = .012		r =.203 p =.039	
% REM	r =-2.66 p =.007			
% SWS	r =-.203 p =.040			

Results: Preliminary analyses included data from 103 subjects (65M, 38F; mean age = 51.03 ± 12.66). Pearson product-moment correlations yielded a number of significant associations between respiratory severity and sleep continuity and architecture variables (See Table 1). These analyses showed that each apnea severity measure correlated significantly with one or more of the sleep quality/restorativeness variables; AHI and REA correlated the most frequently and strongly with these indices.

In order to determine which apnea severity variables were the best predictors of sleep continuity and architecture variables, the 4 apnea severity indices were entered into a forward stepwise multiple-regression analysis; the criterion for entry of an independent variable into a regression equation was $p < .05$. For sleep continuity variables, REA was the primary predictor for stage 1 periods/hour ($R = .29$; $R^2 = .08$), stage changes/hour ($R = .20$; $R^2 = .04$), spontaneous transient arousals/hour ($R = .41$; $R^2 = .17$), and total arousals/hour ($R = .80$; $R^2 = .64$). SaO_2 was a significant factor in the prediction of total arousals/hour, and with REA removed from the predictors, mean SaO_2 was the only predictor for spontaneous transient arousals/hour. In regard to sleep architecture, AHI emerged reliably as the only, or chief predictor, for % stage 1 NREM ($R = .26$; $R^2 = .07$), % REM ($R = .25$; $R^2 = .06$), and % SWS ($R = .21$; $R^2 = .04$).

Conclusions: The regression analyses confirm prior conclusions that arousals caused by respiratory events is the variable most clearly associated with poor sleep continuity (stage 1 periods, stage changes, and arousals). But, the analyses also showed that AHI best predicts deficits in REM and SWS, and excesses in stage 1 NREM sleep. Most of the AHI effect is shared with REA, since they correlated at .76 ($p = .001$); however, that still leaves 42% of the variance accounted for by something else, perhaps SaO_2 and duration of respiratory events, though neither correlated significantly with either AHI or REA. Further analyses of these data will control for possible medication effects.

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1412.K1

Predictors of Rejection of Nasal CPAP in Patients with Obstructive Sleep Apnea

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Introduction: Nasal continuous positive airway pressure (CPAP) is the most effective nonsurgical treatment for obstructive sleep apnea (OSA). CPAP eliminates apneas and hypopneas due to upper airway obstruction and reduces the fragmentation of sleep that leads to excessive daytime sleepiness (EDS). CPAP requires the use of a well-fitting nasal mask that maintains positive pressure in the upper airway during sleep. Nasal congestion, facial discomfort, claustrophobia and failure to relieve the symptom of EDS are associated with rejection of CPAP. OSA is confirmed by polysomnogram (PSG). Some patients undergo a single split-night PSG during which the first part of the night is diagnostic. If the patients meet certain criteria for OSA, then CPAP is applied during the second part of the night. Alternatively, other patients have a full night diagnostic PSG and a second night for application of CPAP. Both programs of diagnosis and treatment lead to elimination of EDS and improvement in functional status (Smolley et al 1999). Some patients have difficulty accepting CPAP in the sleep lab, despite their introduction to it prior to the sleep study. The purpose of this study is to determine which patients are more likely to reject CPAP.

Methods: A retrospective analysis of the available clinical and polysomnographic data from the series of patients who underwent PSGs in the Cleveland Clinic Florida sleep laboratory since September 1996 (n=415) yielded 226 with OSA who were treated with CPAP. These patients included those who had split-night PSGs (n=69) and those who had two-night PSGs (n=157). The Epworth Sleepiness Scale (ESS) was used to assess daytime sleepiness. ESS is a simple, self-administered questionnaire which rates a person's tendency to doze off in situations encountered in daily life (Johns 1991). The Functional Outcomes of Sleep Questionnaire (FOSQ) was used to evaluate the impact of EDS due to OSA on activities of daily living. FOSQ is a self-report assessing the effects of sleepiness on activity level, vigilance, intimacy and sexual relationships, general productivity and social outcome (Weaver et al 1997). All patients received education regarding CPAP and had opportunities to try it prior to application in the sleep lab.

Results: For the split-night (14f/55m) and two-night (40f/117m) groups respectively, the means±S.D. were: age (yrs.) 66±12 vs. 62±14, BMI (kg/m2) 37±9 vs. 33±8, ESS 14±6 vs. 13±6, FOSQ 74±24 vs. 76±29, AHI (apneas + hypopneas / hrs. of sleep) 58±32 vs. 52±30, AI (apneas / hrs. of sleep) 25±28 vs. 22±25, SL (sleep latency) 18±23 vs. 21±32. Those in the split-night group were significantly older ($p=0.03$) and had higher BMIs ($p=0.005$) than those in the two-night group. Rejection rates were 20.29% in the split-night group vs. 9.55% in the two-night group ($p=0.03$). Within the split-night group, no statistically significant difference was found between those patients who rejected and those who accepted CPAP. Within the two-night group, those who rejected CPAP were older ($p=0.04$) and tended to have a lower BMI ($p=0.06$) than those who accepted. T-tests and Wilcoxon tests were used to compare the groups. Further analysis using logistic regression showed similar results. If the group differences were ignored and all the data put together, no statistical difference could be found between the demographic and polysomnographic factors and rejection rates.

Conclusions: 1. Patients who have split-night PSGs are more likely to reject CPAP than those who have two-night PSGs. 2. Older patients who undergo two-night PSGs are more likely to reject CPAP. 3. There is no significant correlation between severity of illness (AHI, AI, SL, ESS, and FOSQ) and rejection of CPAP. This data suggests that older patients,

and those who are undergoing split-night PSGs, may benefit from more extensive preparation to help them accept CPAP.

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1415.K1

Survey of the Effects of Alcohol on the Sleep of College Students

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Introduction: Little is known about the effects of alcohol on the sleep of college-age individuals. Even low doses of alcohol can adversely affect the sleep of young adults,[1] and snoring worsens with alcohol consumption.[2] Interestingly, a recent study showed that subjects with mild to moderate sleep-disordered breathing had worse test reaction time performance parameters than healthy, alcohol-impaired subjects.[3] However, the effects of combining alcohol and individuals with sleep disorders are less clear. The present study uses questionnaire data to evaluate sleep and the effects of alcohol in college students.

Methods: The questionnaires were administered to 100 randomly selected college students at or above the age of 21 years (51 men, 49 women, 21-26 years). The questionnaire was composed of 24 questions concerning social activities and the consequent effects of alcohol on sleep. The study required approximately 5-10min of each participant, and subjects were provided a consent form reviewed by the human subjects panel at our institution.

Results: The mean BMIs (calculated from self-reported height and weight) for the women and men were 20.7 ± 1.6 and 23.9 ± 2.3 kg/m-squared, respectively, with the men reporting a mean neck circumference of 16.4 ± 0.8 in. With respect to snoring, 16.3% of the women reported snoring, versus 41.2% of the men. Awaking with respiratory complaints were reported by 4.1% of the women and 9.8% of the men. Although 39.4% of the respondents reported that they felt non-refreshed in the morning, 89.9% reported that they noted daytime sleepiness. Further, they felt sleepy, on average, one to two times during the day, with 36.6% reporting sleepiness on a daily basis. Seventy-six percent took daytime naps, with an average of two to three times per week. With respect to driving, 44.9% reported drowsiness while driving, with 52% of this subgroup reporting the drowsiness as occasional. A medium to very low energy level was reported by 61.6% of the respondents.Alcohol was reportedly consumed by 85.8% of the respondents, with an average of approximately 4 alcoholic drinks (1 drink = 12 oz beer, 4 oz wine, 1.25 oz 80 proof liquor) twice per week. These drinks were typically consumed about 2 hr prior to bedtime. Social activities accounted for 92% of the reasons for consuming alcohol. An average of 4.5 years of alcohol use was reported. The majority (73.6%) reported that their sleep was affected by alcohol, with 65% reporting worsened sleep. Not surprisingly, 81.3% reported feeling different the next day after consuming alcohol (98.5% felt worse), with 68.8% reporting that alcohol the previous 24 hrs affecting their performance (97.8% adversely). On the average, the subjects reported sleeping 7 hours per night, with an additional hour of sleep each night after consuming alcohol.

Conclusions: As in prior studies, college-age subjects suffer from significant sleep debt. There may also be undiagnosed sleep disorders in this population, particularly sleep apnea, which contributes to this sleep debt. Further complicating this issue are the effects of alcohol, which independently worsens sleep and daytime performance in young adults.

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1416.K1

Polysomnographic Characteristics of the First Half-Night Versus Full-Night in Moderate to Severe Obstructive Sleep Apnea

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Introduction: In normal subjects, slow wave sleep (SWS) predominates in the first third of the night and REM sleep in the last third of the night. In obstructive sleep apnea (OSA), both SWS & REM sleep are reduced secondary to frequent arousals caused by episodes of upper airway obstruction. Our aim was to compare the polysomnographic features of the first half-night (HN) and full-night (FN) in these patients.

Methods: We selected 52 consecutive patients with apnea-hypopnea index (AHI) >20/hr on standard FN PSG performed for suspected OSA. The HN (=the first 50% of total recording time) of the same PSG was separately analyzed to determine sleep efficiency (SE), sleep stages, number of obstructive events and arousals, and the time with oxygen saturation <90% (O2<90%, as % of total sleep time, TST). The results were compared to the analysis of FN PSG for each patient.

Results: These 52 patients included 45 men & 7 women with mean (+SD) age 53 (+12) years, AHI 58.5 (+24.1), BMI 34.3 (+9.7) kg/m2, and Epworth Sleepiness Scale (ESS) 12.4 (+5.4). In HN PSG (vs. FN PSG), REM sleep% was lower, whereas SWS% and SE% were similar (Table). AHI for HN correlated significantly vs. AHI for FN ($r = 0.91$, $p<0.05$), but it was higher (Figure, Table). ArI for HN was also higher and O2<90% was similar. On FN PSG, 22 patients had moderate OSA (AHI>20 & <50; range 24.2 to 49.2) & 30 had severe (AHI>50; range 51.3 to 124.3). When categorized by HN PSG, 32% (7/22) of moderate OSA were severe, and only 3% (1/33) of severe OSA were moderate. On HN PSG, only 1 moderate OSA, and none of the severe, was categorized as mild (AHI < 20) with AHI = 9.5. Thus, only 2% (1/52) of all moderate to severe OSA patients were categorized as mild on HN PSG.

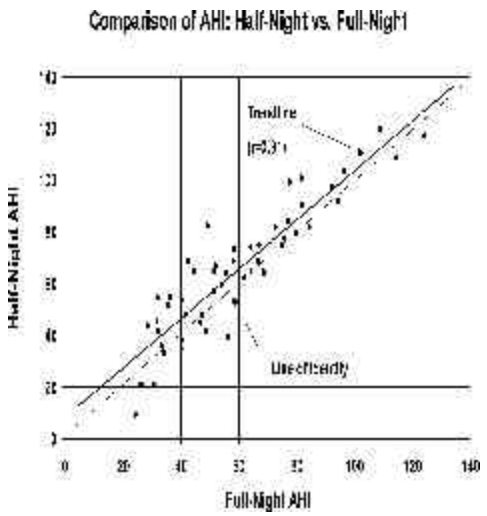
Table 1

Comparison of Analysis of the first half-night (HN) and full-night (FN) PSG:

n=52	Half-Night	Full-Night	Difference	P
SE %	79.4 +16.1	80.8 +16.0	-1.4 +16.2	**0.52**
SWS %	2.6 +6.6	3.0 +10.0	-0.5 +8.5	**0.70**
REM %	7.3 +9.3	12.2 +8.6	-4.8 +6.6	**<0.0001**
AHI (n/hr)	64.2 +25.3	58.5 +24.1	5.7 +10.5	**0.0003**
ArI (n/hr)	53.4 ±25.4	49.6 ±24.6	3.8 ±8.8	**0.0029**
O2<90%	43.0 +33.1	43.5 +31.8	-0.6 +6.6	**0.55**

SE, SWS and REM% = % of TST. ArI = Arousal Index.
Difference = HN - FN value.

Figure 1



Conclusions: Patients with moderate to severe OSA have less REM% and SWS% (vs. normals). In the first half-night (vs. FN) REM% is less. AHI and ArI are statistically increased; however, the increases are too small to be clinically significant. HN PSG slightly overestimates overall severity of OSA. It underestimates OSA only in a few (2%) moderate to severe OSA patients. Therefore, half-night PSG study with CPAP titration in second half-night appears to be adequate in the evaluation of patients with moderate to severe OSA (AHI >20). The split-night protocol may not be appropriate for evaluating sleep disordered breathing for all degrees of OSA1. Although, split-night CPAP titration is more likely to be unsuccessful than FN study (48% vs. 12%)2, when it is successful, the compliance to CPAP at 4 to 6 weeks is similar to patients with FN titration3.

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1418.K1

Improvemet in Snoring by Laser-assisted Uvulopalatoplasty Analyzed with Automated Computer Program

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Introduction: Laser assisted uvulopalatoplasty (LAUP) is a surgical treatment for snoring. The surgical procedure consists of a reduction and reshaping of the uvula and soft palate using local anesthesia and a Laser system to release the collapse in the retropalatal space. However, subjective self-reported evaluations of snoring by patients are sometimes questionable and unreliable. The purpose of this study is to objectively analyze the improvement of snoring by the LAUP procedure using an automated computer program.

Methods: Snoring sounds of all patients who entered this study, were analyzed preoperatively and 2 months after the LAUP procedure. Tracheal sounds were recorded continuously during 6 hours of sleep via a microphone which was located on the suprasterna notch connected directly into a personal computer or using a digital audio tape corder. Tracheal sounds were digitized and a computer was used to calculate short time power spectra (400-600 Hz) every 0.2 seconds by the fast Fourier transform. The moving averages (18 seconds) of the logarithms of the power spectra were calculated every 2 seconds. Snoring sounds appeared as a soundspectgram on the computer display, and snoring index, frequency curve, duration and mean power of snoring were automatically caluculated.

Results: Twenty patients were examined, 3 were women and 17 were men. The patient ages ranged from 20 to 71 years, with a mean of 46.7 years. Polysomnography (Alice 3: Healthdyne Technologies, Marietta GA, USA) was performed preoperatively. Ten were simple snorers [apnea hypopnea index: (AHI) ƒ5], 6 were mild obstructive sleep apnea syndorme (OSAS) (5…AHI ƒ20), 2 were moderate OSAS (20…AHI ƒ40), and 2 were upper airway resistance syndrome (AHI ƒ5, 30 ƒArousal Index, 90% ƒSpO2 and esophageal pressure ƒ-10cmH2O).The snoring index was 495.0 preoperatively and decreased to 150.3 postoperatively.The snoring duration was 22.1% pre-LAUP and declined to 2.6% post-LAUP. The mean power of snoring was 87.2 preoperatively and decreased to 71.9 postoperatively. All of three objective parameters of snoring were significantly reduced by the LAUP. The pattern of the frequency curves did not show significant difference between before and after LAUP surgery.

Conclusions: Automated computer analysis of all- night records of tracheal sounds demonstrated that the LAUP procedure improved the snoring index, duration and mean power of snoring significantly.

1428.K1

Comparison Between Non-Snoring and Snoring Subjects in Upper Airway Resistance Syndrome

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Introduction: It has been demonstrated that a reduction in the size of the upper airway during sleep can cause an increased upper airway resistance(Guilleminault et al 1993). Patients with UARS usually complain of isolated EDS and snoring(Patrick et al 1993; Levy P et al 1996). However, not all UARS patients report snoring(Guilleminault et al 1993). This study aims to compare demographic and polysomnographic parameters between snoring group and non-snoring group in UARS patients.

Methods: This is a retrospective study of 66 UARS patients(34 men, 32 women) who had completed nocturnal polysomnography including esophageal manometry at the Stanford Sleep Disorders Clinic. UARS patients met the following criteria: RDI< 5, characteristic findings of an elevated esophageal pressure(< -10 cmH2O), frequent arousals secondary to increased respiratory efforts and symptoms of daytime fatigue and sleepiness. The presence of snoring(n=48) was determined by the technician's report during nocturnal polysomnogrphy.Demographic data and polysomnographic variables between snoring group and non-snoring group were compared by unpaired t-test.

Results: (1) Demographic findings of snoring group showed older age(p=0.022), more heavy weight(p=0.012), higher body mass index(p=0.000), higher systolic blood pressure(p=0.019) than non-snore group.(2) Polysomnographic findings of snoring group showed a less

stage 4 sleep(p=0.028), more esophageal pressure(p=0.038) than non-snoring group.

Conclusions: (1) Snoring in UARS could be a factor to indicate more upper airway resistance.(2) Snoring seems to be part of a continuum of upper airway dysfunction

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1460.K1

Desensitization of a Claustrophobic Response to Nasal CPAP

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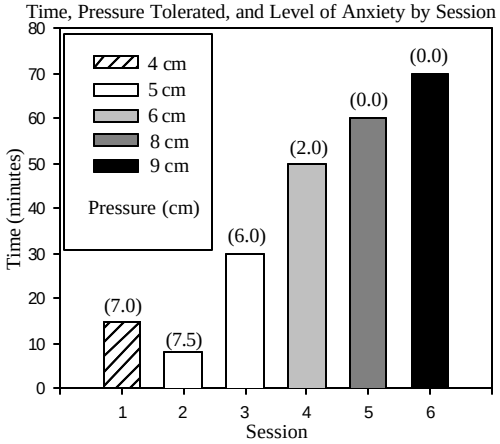
Introduction: Nasal continuous positive airway pressure (CPAP) compliance rates are low (30-40%) [e.g., Rauscher et al., 1991]. One commonly reported reason for noncompliance is a claustrophobic response to the nasal mask. Although behavioral desensitization therapy is a well-documented, effective treatment for phobic reactions, a literature review revealed only one study documenting the use of desensitization to treat a claustrophobic response to CPAP (Edinger & Radtke, 1993). The present report describes a claustrophobic case involving several unique features: 1) desensitization was accomplished in only six sessions without homework assignments, 2) neuropsychological testing revealed our patient's intellectual abilities were in the borderline retarded range, and 3) our patient was a male veteran whose claustrophobic response was due to his reported association of the nasal mask with gas masks worn during combat.

Methods: The patient was an obese, 48 year old, married, Hispanic male who reported a 10 year history of excessive daytime somnolence, snoring, and frequent nocturnal awakenings. A 6 hour diagnostic polysomnogram (PSG) revealed brief sleep onset latency (4.0 min.), normal REM latency (112 minutes), and 328 apneic events (primarily mixed). His typical O2 desaturations were from 94% to 84%. Periodic limb movements and cardiac arrhythmias were absent. Following baseline recording, nasal CPAP therapy was attempted. The patient did not tolerate nasal CPAP, complaining of both difficulty tolerating the air pressure and anxiety associated with the placement of the mask. Desensitization therapy was provided in six, 60-75 minute outpatient visits over a 3-month period. During treatment, the patient was encouraged to relax, but no specific relaxation technique was used. The pace of treatment was dictated by patient progress. Because the patient had not been issued a CPAP machine for home use, there were no homework assignments. The goal of treatment was to gradually increase the time and the amount of pressure tolerated. After each session, the patient rated his level of anxiety on a scale of 0 (not at all anxious) to 10 (extremely anxious).

Results: The patient progressed from tolerating 15 minutes of 4 cm pressure (anxiety rating = 7) during the first session to tolerating 70 minutes of 9 cm pressure (anxiety = 0). At the conclusion of treatment, the patient was issued a CPAP machine and nightly home use was encouraged. One week later, the patient reported using the CPAP nightly without anxiety. At 4-months and 6-months follow-ups, the patient reported continued CPAP compliance without anxiety. (figure should be placed here)

Figure 1. In Vivo Desensitization of a Claustrophobic Response to Nasal CPAP



Note: Reported anxiety levels are noted in parentheses: 0 = not at all anxious, 10 = extremely anxious.

Conclusions: The results indicate that desensitization eliminated our patient's claustrophobic reaction to nasal CPAP. It is noteworthy that we achieved results relatively quickly without homework assignments (which are typical of behavioral interventions). Our results also suggest that desensitization may be useful for patients with limited cognitive abilities and for veterans suffering from claustrophobic reactions to nasal CPAP related to combat experiences.

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1462.K1

Self-reported Changes in Functional Health Patterns During 18 Month Followup in a Nurse-Managed Weight and LIfestyle Program for Obese Adults with Obstructive Sleep Apnea

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Introduction: Weight management is a major problem for the majority of adults with obstructive sleep apnea (OSA). Sustaining weight loss is an even a greater problem. With CPAP treatment most patients report improvement in daytime functioning . However we found in a previous study that weight, exercise and sexuality were the 3 functional health patterns out of 18 that showed least improvement. In a subsequent study we did a randomized clinical trial to evaluate the effectiveness of a nurse-managed weight and lifestyle program. A sample of 100 consecutive patients with body mass index (BMI) >27 were randomly assigned to the experimental group (weight and lifestyle program plus standard medical care) or control group (standard medical care). Results at six months (phase 1) showed a mean weight loss of 2.18 kg (p=0.001, CI 0.99 to 3.34) and increase in minutes per week spent in exercise (mean difference 88.04 minutes, p=0.008, CI 15.51 to 150.57). All subjects were then given the option of enrolling in a 12 month followup study under the experimental condition which is reported here. We were particularly interested in the patterns of association between baseline and change in self-report scores on 18 functional health patterns and success in weight loss.

Methods: Twenty-nine subjects from phase 1 (12 experimental and 17

control) agreed to participate in a 12 month followup under the experimental condition of participation in the nurse-managed weight and lifestyle program. The intervention consisted of an individualized contracting approach to assist patients in making positive lifestyle changes built on their own resources and operationalized through regular meetings with a nurse. The 18 item Functional Health Patterns Contour Plot (FHPCP), which consists of 9 concentric circles across which subjects are instructed to mark x for how they feel about that category at the present time. The inner circle, scored as 9, represents a major strength or positive aspect. The outermost circle, scored as 1, represents a major concern or problem. The middle circle, scored as 5, represents a neutral point, neither positive nor negative. The FHPCP was administered at baseline, the end of the initial 6 month trial and end of the 12 month followup. Weight and time spent exercising in the past week were recorded at each visit.

Results: Three patterns of weight loss were identified. Group 1 (n=16, 7 of whom were control in the first six months) lost weight (mean 5.3 kg, range 1.2-23.6kg) over the entire 18 months. Group 2 (n=9, all control) lost weight (mean 3 kg, range 1.3-18.3 kg) in the last 12 months (experimental condition) but not the first 6 months (control condition). Group 3 (n=4, 3 control and 1 experimental during the first 6 months) gained weight (mean 11 kg) over the total 18 months. For all groups weight and activity level were seen as the most major problem areas initially. Group 1 (consistent weight loss) also showed consistent improvement (>2 points on the 9 point scale) in exercise pattern (mean 4.06 to 6.17), appearance (4.00 to 6.17), and weight (3.13 to 5.17). Nine other patterns showed improvement >1 point. Group 2 (weight loss in last 12 months) had the lowest scores for sleep (mean 2.56 compared to 4.19 and 4.33 for groups 1 and 3) and the greatest improvement (4.89 at 6 months and 6.13 at 18 months). They dropped on some scores during the 6 months in the control condition, particularly nutrition (5.44 to 3.75) and activity level (5.67 to 2.88). Both groups 2 and 3 started with higher scores on self-confidence (6.14 and 7.33 compared to 4.81 in Group 1). Group 3 (weight gain) rated weight lowest (2.67) and dropped on activity level (5.33 to 2.75).

Conclusions: Those individuals who were most successful with weight loss also rated most health patterns as improved. Those individuals who were least successful in weight loss showed deteriorating ratings in activity level and consistently low ratings on weight and nutrition. This group of four who did not respond to the intervention began with a higher BMI (mean 38.0) compared to group 1 and 2 (means of 33.7 and 33.1). While the sample size was too small to draw definitive conclusions this comprehensive longterm followup suggests that a nurse-managed weight and lifestyle program using an individualized contracting approach can be effective in assisting some patients to achieve sustained weight loss. It also suggests that weight management is closely linked with perceptions about strengths and concerns across functional health patterns. The results of this study also underline the multidimensionality of weight management and the importance of using a tool such as the FHPCP in clinical and research applications.

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1464.K1

Prevalence of OSAS in 3500 men in Hungary :The real need for CPAP.

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Introduction: During the last couple of years we have developed a multilevel complex protocol for the diagnosis and treatment of OSAS, based on both the recommendations of the ESRS and the construction of the Hungarian health care system. This protocol had been accepted by the professional executive committee's, by the board of the Hungarian Sleep Society and by the Hungarian Ministry of Health. Keeping precisely the rules of this protocol, a large survey was designed to establish the expectable need for CPAP treatment in OSAS patients .Our main purpose was to provide arguments for the negotiations with the Hungarian Health Insurance Office on the extent of official financial support for CPAP users.

Methods: -Features of the survey.Including criteria: snoring and/ or daytime sleepinessNumber, sex and age of patients involved in the survey: 3 500 men, aged between 40 and 60.Steps of protocol:1. Questionnaires, examinations of specialists, pulseoxymetry.2. a. Examination with 8 *channel PG b. Examination with full PSG with nasal flow measurement 3. Determination of the main components of therapy; selection of additional elements of combined therapy;4. Monitoring patients regularly in subjective (diaries) and objective (control PSG) ways. *(SaO2, effort/thorax and abdomen movements/, nasal flow, ECG, pulse, body position, breathing sound,)

Results: As a result of the first step of the protocol, the suspition of OSAS had been proved in 1 356 patients, who were ranked in four clinical severity groups with polysomnography as follows: A1 801 A2 414, A3 113, and A4 28.In-groups A1 and A2 full recovery could be reached with non- specific (behavioral, pharmacological, nasal split) treatment, with fitting oral appliances and with thoroughly selected forms of surgery (LAUP, LMG, etc.), using and combining them individually. These kinds of treatment proved to be successful in 23 patients belonging to group A3, who needed less than 6 wcm therapeutical CPAP pressure to entirely cease the pathological obstructive breathing episodes (OBEs). In 75% of group A3 and in the whole group A4, CPAP (BPAP) treatment was the only effective way of the cure of OSAS.The prevalence of moderate to severe OSAS in 3 500 males aged between 40 and 60 proved to be 4.02 % (N= 141). Keeping consequently both the protocol and the ranking criteria, we found that 103 patients (84 of group A3, 19 of group A4), that is 2.94 % of the whole group involved into the survey, 7.59 % of patients with confirmed suspition of OSAS (N= 1 356) and 73.04 % of patients with moderate to severe OSAS (N= 113) required CPAP therapy.(In addition BPAP were applied in 6 patients of the group A4)

Conclusions: This management system offers many advantages both from professional and cost- beneficial aspects:1. It offers the only possible way to ensure both the access to the officially supported CPAP devices for patients with severe OSAS and the professional control of CPAP users.2. We are able to provide individually selected and combined treatment for each patient.3. In the majority of patients diagnosed as preclinical, mild and mild to moderate OSAS further progression can be prevented with combined treatment including non- specific forms of therapy, oral appliances, and selected surgeries, as well.

1474.K1

Post-therapy Recall of Severity of Daytime Sleepiness in Patients with Obstructive Sleep Apnea.

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Introduction: Excessive day time somnolence(EDS)is a common disabling complication of obstructive sleep apnea(OSA). The response to treatment is often judged clinically by asking the patients to compare their pre- and post-treatment symptoms. It is not known if the patients recall of severity of initial EDS is accurate. The purpose of the present study was to assess the validity of patients'recall of their initial symptoms after continuous positive airway pressure(CPAP) or uvulopalatopharyngoplasty(UPPP).

Methods: We reviewed records of fifty patients diagnosed to have OSA. Each patient had a minimum of thirty apneas on polysomnogram. Thirty six(72%) patients were treated with CPAP and fourteen(28%)underwent surgical therapy. At the time of initial polysomnogram,patients completed a questionnaire which evaluated EDS based on Epworth Sleepiness Score(ESS),a frequently used objective measure of daytime sleepiness. ESS is based on eight questions involving everyday situations with the patient rating their degree of sleepiness on a scale of 0-3. Patients returned to the sleep center after a minimum of three months of therapy and were asked to recall their initial ESS. We compared the initial and recalled ESS in these patients. We also analyzed the eight components of ESS to determine the recall reliability of each.

Results: Fourteen(28%) patients recalled their ESS accurately,while there was a difference in score in remaining 36(72%) patients. The recalled ESS were higher in 23(46%)and lower in 13(26%)patients compared with their original scores. The answers to the questionnaire differed by one answer in 9(18%),by two to five in 20(40%),and by more than five in 7(14%)patients. Only three(21%) patients treated surgically and 11(30%) treated with CPAP could recall their ESS accurately. Among the eight questions,"Lying down to rest in the afternoon when circumstances permit" was answered correctly in 40(80%) questionnaires while "Sitting inactive in a public place " was recalled accurately in only 24(48%) questionnaires.

Conclusions: Based on our results,patients'recall of severity of daytime sleepiness is often unreliable. Symptoms are commonly recalled as being more severe compared to the original assessment. This may have significant impact in patients' perception of clinical response to therapy.

1653.K1

Correlates of Hemostatic Activity in Sleep Apnea

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Introduction: There is growing evidence that obstructive sleep apnea (OSA) is associated with increased prevalence of myocardial infarction, stroke and systemic hypertension. In addition, it has been demonstrated that increased hemostatic activity in terms of hypercoagulability is related to both atherosclerosis and thrombotic events. Also, coagulation is altered in patients with established cardiovascular risk factors such as hypertension, smoking, body mass index (BMI), age and gender. There is also evidence that coagulation is altered by diverse mood states.Several studies have suggested a prethrombotic state in OSA by showing elevation of platelet activity, fibrinogen plasma levels, clotting activity of blood coagulation factor VII and impaired fibrinolysis. The aim of this study was to investigate physiological and psychosocial correlates of hemostatic activity in OSA.

Methods: 37 apneics (22 white, 10 Hispanic, 5 black), who were free of other major illnesses, were studied for two nights with polysomnography to confirm OSA diagnosis. OSA was defined as a respiratory disturbance index ≥ 20 (mean ± SD 49 ± 25). Demographic information was collected including age (47 ± 9 years) and BMI (30 ± 5 kg/m2). 12 individuals were classified as having systemic hypertension (screening blood pressures >140/90 mmHg on two different days). Antihypertensive medication was tapered at least 3 weeks before hemostatic studies. Venous blood was drawn into EDTA containing tubes. After centrifugation, plasma samples were immediately frozen at -80° C until further processing. Fibrin D-Dimer (D-Dimer) and von Willebrand factor antigen (vWF:Ag) were measured with ELISA. Subjects completed the following psychosocial questionnaires: Spielberger State Anxiety, Cook-Medley, Profile of Mood States (POMS).

Results: D-Dimer and vWF:Ag were positively correlated (r=.46, p<.01). vWF:Ag was significantly higher in hypertensive than normotensive apneics (132 ± 66% vs. 90 ± 43%, p<.03) and in blacks than whites (156 ± 81% vs. 91 ± 46%, p<.03). D-Dimer did not differ between hypertensive apneics and normotensive apneics (333 ± 216 ng/ml vs. 272 ± 192 ng/ml, p=.40). There were positive correlations between Spielberger State Anxiety and vWF:Ag (r=.44, p<.01) and between Spielberger State Anxiety and D-Dimer (r=.35, p<.04). Apneics with hypertension showed positive correlations of vWF:Ag with Cook-Medley hostility (r=.75, p<.01), paranoia (r=.70, p<.02), and cynicism (r=.72, p<.01), which remained significant after controlling for age, BMI, and smoking. In hypertensive apneics, D-Dimer was also positively correlated with POMS depression (r=.58, p=.05), confusion (r=.66, p<.03), and anger (r=.66, p<.02), which remained significant after controlling for smoking. Confusion (p<.03) and anger (p<.03) remained significant after controlling for age, BMI and gender; however, depression (p<.12) was no longer significant.

Conclusions: In OSA, demographic factors (ethnicity), comorbidity (hypertension), personality traits (hostility, anger), and dysphoric mood states (depression, anxiety) may contribute to changes in the hemostatic profile and a prethrombotic state. Hemostatic factors such as vWF:Ag and D-Dimer may be markers of biological and psychosocial pathways linking OSA with cardiovascular disorders.

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1839.K1

Physiological Parameters within the Sleep Onset Period Discriminate among Subtypes of Sleep Apnea

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Introduction: Although polysomnographic data on the sleep onset period (SOP) are available during the numerous nocturnal studies of people with sleep apnea, attempts to study this transitional period are seldom undertaken. This investigation sought to explore the possible clinical significance of latencies to physiological parameters within the SOP of patients with sleep apnea. Other studies pointed out differences in the SOP in normal and pathological sleep (Chilcott et al., 1999, Alloway et al., 1999, Lamarche & Ogilvie, 1994) and it was therefore predicted that there would also be unique sleep onset "signatures" which characterize clinical subgroups of sleep apnea. Unique patterns of physiological activity in the SOP would have theoretical and practical clinical significance.

Methods: Polysomnographic data of 55 patients from the Paris Sleep Clinic (mean age 52 ys. (SD= 14.09)) were analyzed retrospectively. Patients were clustered into the following subgoups: mild obstructive sleep apnea (OSA) (n= 10), moderate OSA (n= 10), severe OSA (n= 12) and central sleep apnea (CSA) (n= 11). A group of clinically non- significant sleepers (n= 12) was used as a reference group. All diagnoses were based on the International Classification of Sleep Disorders (ICSD), diagnosed by a sleep specialist. Measures of severity of OSA were established by means of the AHI: mild OSA: AHI 5- 20 (mean=14.60, SD=3.31); moderate OSA: AHI 20- 40 (mean=29.79, SD=7.02); severe OSA: AHI >40 (mean=72.42, SD=15.81). Sleep stages and the occurrence of physiological parameters were scored manually according to standard criteria (Rechtschaffen & Kales, 1968). Latency measures were scored for the following parameters: vertex sharp wave, vertex wave train, k- complex and sleep spindle. Apneas

were classified as central, obstructive or mixed according to standard criteria.

Results: As expected, the microstructure of the SOP in subtypes of sleep apnea does differ significantly. Independent measures t- tests and ANOVAs revealed significant differences between groups for the latency to the first k- complex ($F(4, 48)= 3.43$, $p<.05$), the first sleep spindle ($F(4, 47)=4.37$, $p<.01$) as well as the first apnea ($F(4, 40)=3.81$, $p<.01$) and hypopnea ($F(4, 43)=2.83$, $p<.05$). Latencies to both the first k- complex and the first sleep spindle were longest for the severe OSA group, followed by the CSA group, mild and moderate OSA. Mean latency to the first apnea was highest for the clinically non- significant group, followed by the mild, moderate and severe OSA. CSA patients show the shortest mean latency to the first apnea. Of greater interest were the latencies among sleep onset indices: These were established by calculating the elapsed time period between each parameter combination. Significant group differences were found for a number of relationships, such as first vertex wave to first sleep spindle ($F(4,51)=4.52$, $p=.004$), and first vertex train to first k- complex ($F(3,72)=4.53$, $p=.010$).

Conclusions: The sleep onset period seems to be extremely sensitive to the influence of pathological conditions, now including sleep apnea The SOP of this group- especially the later phase- was shown to be disrupted by apneic events significantly earlier in severe OSA than in the other subgroups. Latencies to physiological parameters are most likely to be longer depending on the timing, frequency and severity of apneic events that interrupt the natural progression from wakefulness to sleep. Induced microarousals or arousals may let the patient return cyclically to an earlier point or the very beginning of the SOP. Clinical subgroups of sleep apnea can be identified by characteristic changes manifested in the SOP. The study of the W/S transition can provide theoretical and diagnostic information which can usefully augment that provided by studying the course of an entire night's sleep – at very little additional cost.

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1505.K1

Physiologic Determinants of Severity in Obstructive Sleep Apnea

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Introduction: The most commonly cited measure of severity in obstructive sleep apnea (OSA) is the respiratory disturbance index (RDI). Studies focusing on the RDI have shown that this index correlates with neuropsychological deficits (Kim et al 1997). However, these respiratory disturbances do not correlate with the severity of physiologic abnormalities like oxygen desaturation. The importance of hypoxemia in OSA severity is suggested by its relationship with cognitive impairments (Findley et al 1986) and pulmonary hemodynamics. Thus, we hypothesize that both RDI and oxygen desaturation contribute to severity in OSA.

Methods: Adult patients who were diagnosed with OSA by polysomnography (PSG) and who completed an SF36 health survey were included in the analysis (n= 63). The SF36 was obtained using a scripted phone interview prior to treatment. A computer program was devised to extract oximetry data from the PSG and to calculate the oxygen desaturation index (number of desaturations/hour of sleep, ODI) using a desaturation criteria ranging from 2%-7%. The program excluded artifactual data. Stepwise multiple linear regression (SAS Version 6.1) was performed using the SF36 subcategories for Mental (MCS) and Physical (PCS) Health (dependent variables) and the best combination of RDI, ODI, and other measures of oxygenation (independent variables).

Table 1. R values correlating MCS and PCS scores to RDI and ODI (p<0.05)**

	ODI 2%	ODI 3%	ODI 4%	ODI 5%	ODI 6%	ODI 7%	RDI
MCS	0.22	0.25	0.27	0.26	0.27	0.27	0.18
PCS	0.34**	0.31**	0.28**	0.28**	0.27**	0.24	0.2

Results: The patient population included 40 men and 23 women with an average age of 52.46±10.52. The racial distribution paralleled the surrounding community. There was a significant correlation between RDI and ODI at all ranges of desaturation 2%-7% ($r >0.8$, $p<0.0001$). Despite this strong correlation, RDI did not prove a significant indicator of disease severity as defined by the SF36. Oxygen desaturation as represented by ODI 2% is significantly and most strongly correlated with the PCS ($r=0.34$, $p=0.006$). These are independent of race, sex and BMI. ODI 6% was the strongest indicator of severity with the MCS ($r=0.27$, $p=0.029$). Lowest saturation and percent of time spent less than 90% were not well correlated with either the MCS or PCS subscores.

Conclusions: Although the RDI is commonly used for assessment of OSA severity, other factors not directly related to the RDI, such as oxygen desaturation, have added physiologic consequences. The observations in this study suggest that the ODI is a more robust indicator of severity than the RDI as measured by the SF36. Despite these findings, the RDI has been shown to be a good indicator of neuropsychological deficits. Because both RDI and ODI correlate with different measures of impact, severity in OSA should be assessed as a composite of RDI and oxygen desaturation. This has direct implications for the initiation of treatment and determinants of outcome in OSA.

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1510.K1

Polycystic Ovary Syndrome is Associated with Obstructive Sleep Apnea and Sleepiness

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Introduction: Polycystic Ovary Syndrome (PCOS) is the most common endocrine disorder of premenopausal women, characterized by hyperandrogenic anovulation and insulin resistance.[1] Obstructive sleep apnea

(OSA) is more common in middle-aged obese men and recent evidence suggests that it is strongly associated with hypercytokinemia and insulin resistance independently of obesity.[2] The goal of this study was to examine whether women with PCOS are at risk for OSA and sleepiness.

Methods: Fifty-three women with PCOS (hyperandrogenemia and oligomenorrhea) and 452 control premenopausal women (age range 20-42) from a general randomized sample for the assessment of OSA in women were included in our study. Both groups were evaluated in the sleep laboratory for one night and completed a comprehensive history and physical examination, including a detailed standardized sleep questionnaire. In addition, women with PCOS were tested for free testosterone, total testosterone, and fasting blood glucose and insulin. The two groups were similar in terms of age while PCOS women compared to controls were heavier (P=0.01).

Results: Nine of the PCOS women (17.0%) were recommended treatment for OSA in contrast to only 3 (0.6%) of the control group (P<0.001). In this unselected population, PCOS women compared to controls were 30 times more likely to suffer from OSA [OR=30.6, 95% CI (7.2, 139.4)] Even when we controlled for body mass index (BMI), the difference between the two groups remained significant. Also, women with PCOS compared to controls demonstrated a significantly higher sleep latency (P=0.05) controlling for BMI. In addition, PCOS women reported more frequently daytime sleepiness compared to controls (76.9% vs 27.0%, respectively, P<0.001). Furthermore, PCOS women who were recommended treatment for OSA compared to those without sleep apnea showed significantly higher fasting insulin levels ($42.7_{+}7.3$ vs $25.3_{+}2.6$ μU/ml, P<0.02) and lower glucose to insulin ratio ($3.0_{+}0.7$ vs $5.1_{+}.4$, P=0.06). The difference remained significant when adjusted for BMI. Free testosterone, total testosterone, and fasting blood glucose were not different between the two groups of PCOS women.

Conclusions: Our data indicate that OSA and sleepiness are markedly and significantly more frequent in PCOS women compared to premenopausal controls. Also, there is a strong association independent of obesity between severity of insulin resistance and sleep apnea in PCOS women. These data support our proposal that sleep apnea is a manifestation of an endocrine/metabolic abnormality in which insulin resistance plays a principal role.

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1512.K1

Effect of nCPAP on Co-existing Medical Problems

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Introduction: Nasal Continuous Positive Airway Pressure (nCPAP) has been shown to effectively treat Obstructive Sleep Apnea Syndrome (OSAS). Patient compliance with nCPAP has been an issue in sleep medicine for many years, with compliance based on many factors. In the course of surfing some sleep apnea forums on the Internet, we were amazed at the number of people posting comments concerning problems with nCPAP. We decided to attempt a novel way to look at nCPAP compliance in an unselected group of patients by utilizing the Internet to perform a survey.

Methods: A multi question form was developed and loaded as the front end on one of our webservers. Invitations to participate in the Internet survey were posted at various sites on the World Wide Web. Some of these sites included the SleepNet Sleep Disorders Forum, the Usenet group alt.support.sleep.disorders, as well as links on Dr. Dement's webpage, the National Sleep Foundation webpage, and the American Sleep Apnea Association webpage. Participants followed URL links to the survey site, selected their responses to the questions, and posted the results to our server.

Results: 257 forms were accepted with all required fields. A total of 114 questions were asked in the survey. The initial seven questions were baseline demographic in nature. The remainder of the questions dealt with their medical history, how they used their nCPAP systems and factors that may or may not influence compliance. The sex ratio of the respondents was 74% male, 26% female. Mean age was 46.93 for males and 47.12 for females. The respondents were very well educated with 91.05% reporting at least some college, and 49.42% reporting a Bachelors degree or higher. The mean and median incomes were in the $60,000 to $69,000 dollar ranges with 20.62% of the respondents reporting their income as more than $100,000. We determined that compliance, in our survey would be using nCPAP 6 or more hours per night, 7 nights per week. According to this standard, 62.56% of respondents were compliant. Analyzing our data with the less strict criteria from Kaplan, Bingisser, et al, (4hrs/night, 5 nights/week) showed a compliance rate of 75.84% in our group, similar to their results. The most striking feature we noticed as soon as results were posted was the response to how nCPAP had affected pre-existing medical conditions. Table 1 summarizes the answers to the question, "Before you were diagnosed with sleep apnea, did you have: (any of the following)". Table 2 summarizes the responses to the follow-up question, "If you had any of the above conditions, before being treated, how did being put on CPAP… affect the condition:".

Table 1

Before dx did you have:	Yes	No	Don't Know	U.S. % for all adults[1]
Hypertension	39.69%	50.97%	9.34%	~33%
Headaches	56.03%	40.47%	3.50%	~25%
Depression	47.86%	42.02%	10.12%	~5-10%
EGRD	41.25%	43.58%	15.18%	~25-30%
Anxiety	43.97%	48.64%	7.39%	~2.5-6.4%
Insomnia	37.74%	57.59%	4.67%	~10%

Table 2

nCPAP Affect	Better	Worse	No Change	N/A	n=
Hypertension	38.24%	0.0%	45.10%	16.67%	102
Headaches	61.11%	2.78%	19.44%	16.67%	144
Depression	41.46%	4.07%	43.90%	10.57%	123
EGRD	48.11%	1.89%	31.13%	18.87%	106
Anxiety	45.13%	3.54%	31.86%	19.47%	113
Insomnia	52.58%	10.31%	20.62%	16.49%	97

Conclusions: The results show that OSAS sufferers generally have a higher prevalence of hypertension, headaches, depression, EGRD, anxiety, and insomnia than the general public. However, the results also show that nCPAP has a positive effect on treating these concomitant disorders.

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1530.K1

Sleep Apnea in Acute Stroke: Diagnosis, Treatment, and Evolution

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Introduction: Sleep apnea was found in a previous polysomnographic (PSG) study in 63% of patients (pts) with acute stroke (Bassetti et al 1999). Risk factors for sleep apnea, diagnostic and therapeutic accuracy of "intelligent" CPAP in this clinical setting, and evolution of sleep apnea after recovery from the acute cerebrovascular event are unknown.

Methods: We prospectively studied 130 new pts (43 women and 87 men; mean±SD age of 55±13, range: 18-80) with acute MRI-proven ischemic stroke. Cerebrovascular risk factors; sleep history (including the Epworth Sleepiness Score=ESS) preceding the acute event; stroke severity (NIHSS), topography, etiology, estimated time of onset and short-term outcome were assessed. Breathing during sleep was prospectively assessed using an "intelligent" CPAP machine (ResMed AutoSet 3.03, diagnostic mode) within a mean±SD of 3±2 day (range: 0-9) from onset of stroke. Sleep apnea syndrome (SAS) was defined as AHI15 or AHI10+hypersomnia. In 31 consecutive pts we compared the AHI derived from PSG with the AHI derived from the AutoSet device. After the diagnostic night CPAP titration was tried in all pts with SAS. Long-term treatment with conventional CPAP was started at a fixed-pressure determined from the results of an automatic CPAP titration (AutoSet, therapeutic mode). Sleep breathing was reassessed in 30 pts with AHI>10 in the subacute stage of stroke.

Results: Diagnosis: The mean±SD AHI was 17±15 (range 0-78). According to our definition 54 (42%) of 130 pts had SAS. In the 31 selected pts the mean±SD AHI was 18±17 when assessed by PSG and 20±16 when assessed by the AutoSet device. The correlation coefficient between AHI-PSG and AHI-AutoSet was 0.746 ($p<0.05$). The sensitivity and specificity of the AutoSet device in detecting pts with AHI15 during PSG was 92% and 89% respectively. Risk factors: Age, gender, BMI, alcohol consumption, and history of diabetes, hypertension, cardiac disease, habitual snoring and witnessed apneas were strongly ($p<0.01$) associated with SAS. History of hypersomnia (ESS), stroke etiology, topography, severity (NIHSS) and short-term outcome did not differ in pts with or without SAS. A linear multiple regression analysis identified age, gender, diabetes, and time of onset of stroke as independent predictors of AHI (R2=0.41). Treatment: CPAP-titration was effectively completed in 34 (67%) out of 51 pts (3 pts were not available for titration) with SAS and 30 out of these 34 pts were discharged from hospital with CPAP. Evolution: after a mean±SD interval of 6 months (range: 3-14) the mean AHI was 16±11 (vs 27±15 in the acute stage, $p<0.001$). The AHI had normalized or greatly improved in 18 (60%) of 30 pts.

Conclusions: In pts with acute ischemic stroke sleep apnea 1) is frequent, 2) should be particularly suspected in elderly male pts with diabetes and nighttime onset of stroke, and 3) can be reliably diagnosed and treated with an "intelligent" CPAP machine. 4) In a significant subgroup of pts breathing abnormalities during sleep improve or even normalize in the subacute stage of stroke.

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1542.K1

Therapy of Sleep Apnea with CPAP: Empiric Choice of Pressure

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Introduction: Continuous positive airway pressure (CPAP)is the main treatment for obstructive sleep apnea (OSA). The pressure needed to control apneas varies between 5-20cmH2O. A patient's optimal CPAP level is determined either during the second half of a diagnostic polysomnogram or during a titration trial done the next night. There are many problems with this approach: inadequate titration time, REM rebound, unavailability of information concerning compliance, and difficulty in scheduling. We wanted to know if a CPAP level could be chosen empirically to address some of these problems. This study evaluates the efficacy of this approach by comparing the chosen CPAP level of 8cmH2O to the final levels determined after a two to six month trial of therapy.

Methods: Ninety-seven patients diagnosed to have OSA by overnight polysomnogram (apnea index >5) underwent a CPAP titration trial after two to six months. Each patient was prescribed 8cmH2O of CPAP during the interim. The sleep technicians were blinded to the CPAP level during the titration trials. The standard paired T-test was used to determine statistical significance.

Results: Our population included 77 males and 20 females, with a mean age of 48.6 years (±11.1). The mean body mass index was 38.6kg/m(±7.9), with a mean neck circumference of 18.3in (±1.67). The mean apnea index during the diagnostic polysomnogram was 37.6 (±25.0). The tolerance to CPAP was good. The mean level of CPAP that was required to eliminate apneas in these patients during their titration trials was 8.1cmH2O (±1.97). There were only nine patients who required more than 10cmH2O and only two who required more than 12cmH2O of CPAP.

Conclusions: The majority of our sleep apnea patients that underwent CPAP titration trials required 8cmH2O of CPAP for effective treatment of their illness. Other sleep laboratories with similar demands and limited resources may consider using 8cmH2O of CPAP as empiric therapy for their patients awaiting CPAP titration trials. This was both effective and tolerable for our patient population.

1564.K1

Cardiovascular and Autonomic Consequences of Snoring During NREM Sleep

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Introduction: It has not been determined whether snoring alone elicits

nocturnal alterations in autonomic and cardiovascular function. A few studies have suggested that snoring does not impact on nocturnal cardiovascular function because similar decreases in blood pressure were observed in snoring and non-snoring individuals. Although this finding is possible, different physiological mechanisms could be responsible for the observed response. Nocturnal decreases in blood pressure in healthy humans are likely the consequence of removal of facilitatory inputs originating from the reticular activating system, while decreases observed in snoring individuals might be due to alterations in intrathoracic pressure associated with increases in airway resistance. This latter suggestion is supported by studies completed on awake healthy humans inspiring against an increased resistive load[1] which demonstrated that a mechanically induced decrease in blood pressure could be induced. This decrease was accompanied by a reduction in sympathetic nerve activity, which might be mediated by increases in afferent feedback from pulmonary stretch receptors. Given these findings, it is possible that increases in airway resistance associated with snoring may elicit similar alterations in cardiovascular and autonomic function during NREM sleep. Thus, the purpose of this study was to explore this possibility.

Methods: Three young non-apneic snoring individuals (1 female and 2 males) that were otherwise healthy completed one nocturnal polysomnography examination following a familiarization night in the sleep laboratory. The following measures were recorded during each stage of sleep: snoring sounds, oxygen saturation, systolic and diastolic blood pressure, electroencephalograms, electrooculograms, electrocardiogram, oronasal airflow and abdominal movements. After data collection, stage II and slow wave sleep was divided into three minute segments. Snoring and breathing frequency, systolic and diastolic blood pressure and R-R intervals (RRI) were obtained from those segments devoid of arousals and apneas/hypopneas. Subsequently, variability of the RRI in the frequency domain was determined. The power content of the low frequency (LF) domain (0.04 - 0.15 Hz) represents sympathetic and parasympathetic activity at the sinus node, whereas the power content in the high frequency (HF) range (0.15 - 0.40) represents parasympathetic activity and sympathovagal balance is defined by the LF/HF ratio.

Results: The results demonstrated that systolic blood pressure recorded from mild (defined as between 5-10 s/min) and severe snoring segments greater than 10 s/min was less compared to non-snoring segments (less than 5 s/min) (non-snoring - 114.3 ±. 6.28; mild snoring - 111.0 ± 4.0; severe snoring - 107.9 ± 5.8 mmHg). This decline was accompanied by a reduction in LF/HF (non-snoring - 1.0 ±. 0.4; mild snoring - 0.7 ±. 0.2; severe snoring - 0.5 ±. 0.2), HF (non-snoring - 3368.3 ±. 820.9; mild snoring - 3042.7 ±. 1257.99; severe snoring - 2118 ± 865 ms2/Hz) and RRI (non-snoring - 1066.1 ±. 16.2; mild snoring - 1023.5 ±. 21.4; severe snoring - 1002.6 ±. 35.5 ms). To examine these relationships further, correlations between snoring frequency and either blood pressure, LF/HF, HF or RRI were performed for NREM cycles recorded during sleep which displayed a gradual progression from non-snoring to snoring. The results showed that a strong inverse correlation between snoring frequency and the cardiovascular and autonomic variables measured was observed for each subject (range of r values 0.67-0.96)

Conclusions: We conclude that decreases in blood pressure in non-apneic snoring individuals are primarily mechanically induced. Furthermore, based on previous results performed on awake humans, we speculate that the decrease in RRI, LF/HF and HF that accompanied the decline in blood pressure might be caused by increases in inhibitory afferent feedback originating from pulmonary stretch receptors.

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1565.K1

Spectral Analysis of Stage Two Sleep in Patients with Obstructive Sleep Apnea: The Effects of Hypoxia and Treatment

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Introduction: Obstructive sleep apnea (OSA) is characterized by respiratory disturbances, arterial desaturation, sleep fragmentation, snoring, daytime sleepiness, and cognitive impairment. Previous analysis of the EEG in OSA patients revealed a relative increase in lower frequencies (Morrison et al, 1998), and suggested this effect was due to hypoxemia. However, respiratory disturbances and hypoxemia were not individually evaluated. We hypothesized that nocturnal hypoxemia would be associated with a shift in the power spectra, from high-to-low frequencies, and that correction of hypoxia would result in normalization of the EEG power frequency spectra.

Methods: To test this hypothesis we reviewed nocturnal polysomnographic tracings of patients with confirmed OSA (i.e. respiratory disturbance index >15/hour of sleep and symptoms) during a split-night protocol that required the identification of >30 respiratory disturbances during the baseline and at least four hours of CPAP titration. Subjects were included if they: were between 18 and 70 years old, were optimally titrated with CPAP, and had completed the SF36 quality of life questionnaire prior to treatment. All patients who had no desaturations less than 90% during the polysomnogram were identified from this group (n=13). These were then age, weight, and gender matched with subjects who demonstrated desaturations to less than 88%. Four epochs of stage two sleep (Rechtschaffen and Kales, 1969) pre- and post-treatment were identified and a 12 second sample of uninterrupted sleep was analyzed using power spectral analysis. Post-treatment samples were taken at CPAP settings identified by the sleep specialist as being optimal. The ratio of low (<8.0 Hz) to high (8-20.5 Hz) frequencies (L/HR) were analyzed in the vertex (C3 and C4) and occipital (O1) leads. Statistical comparisons were made between hypoxic and non-hypoxic patients, and pre and post-treatment groups.

Results: The average ages in the hypoxic and non-hypoxic groups were not different (50.9± 1.8 and 50.4±11.0, respectively, p>0.05). There were 8 males and 5 females in each group. Weights in the two groups were similar (nonhypoxic 222.6±46.4, hypoxic 230.6±41.6, p>0.05). There was a trend toward a higher RDI in the hypoxic group (61.66±40.1 v. 52.7±34.8, p>0.05). The mean low saturation in the hypoxic group was 76.7 ± 11.8, and in the non-hypoxic group 91.4±0.5 (p=0.0003). At baseline, there was no difference in the power frequency spectra between the groups, and there was no change with treatment (figure 1).

Table 1. The L/H Ratio during stage 2 sleep in hypoxemic and normoxic patients with OSA before and after treatment with CPAP.

	Lead C3	Lead C4	Lead O1
Hyoxic	1.38 +/- 0.45	1.23 +/- 0.36	1.21 +/- 0.51
Normoxic	1.31 +/- 0.41	1.27 +/- 0.31	1.12 +/- 0.38
Pre-treatment	1.36 +/- 0.50	1.25 +/- 0.35	1.15 +/- 0.40
Post-treatment	1.34 +/- 0.35	1.24 +/- 0.32	1.18 +/- 0.49

Conclusions: There was no significant difference between the L/HR in EEG tracings of stage 2 sleep in hypoxic and normoxic patients with

OSA. Furthermore, there was no acute response to treatment in any of the leads studied. Further investigations, focusing on the long-term effects of optimal treatment on the power frequency spectra, are needed. Similar analysis looking at other sleep stages, leads and clinical impact data, such as with an SF36, may be illuminating.

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1725.K1

Non-Attended Nasal CPAP Titration in the Home Using Autoset Portable II

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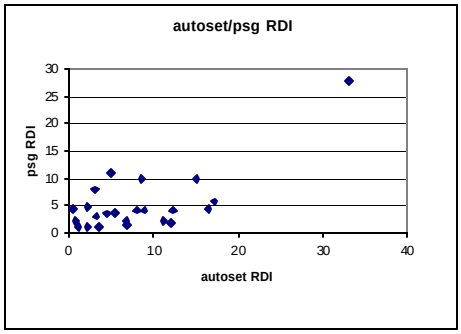
Introduction: A common method of determining nasal continuous positive airway pressures (CPAP) for treatment of obstructive sleep apnea (OSA) is a polysomnography that is titrated by technicians who manually adjust the airway pressures. An alternative is to use self adjusting devices such as Autoset (Resmed) to determine the CPAP pressures. These devices use algorithms that detect airflow limitation and other parameters within individual breaths to identify and then to treat airway obstructions. Although treatment results of these devices have been validated in an attended setting, there is a lack of evidence in an unattended environment for which they were intended. The current study compares respiratory disturbance index (RDI) of Autoset Portable II (Resmed San Diego, CA) to a 16-channel level 2 Digitrace polysomnography (PSG) at a home setting. It also reports on the outcome of automated CPAP titration.

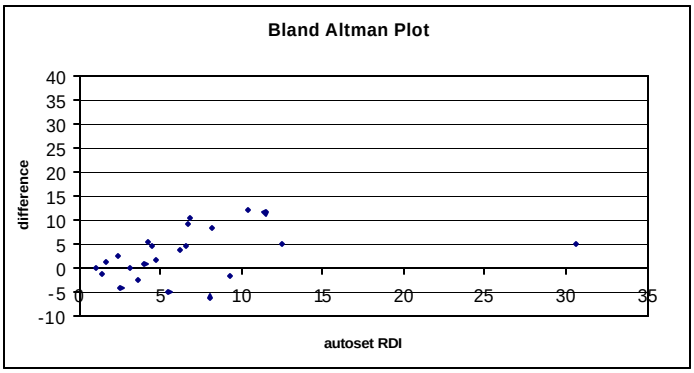
Methods: Twenty-four patients were retrospectively reviewed who underwent pretreatment PSG, in-home 16 Digitrace channel PSG (4 channel electroencephalogram, 2 channel electro-oculography, 4 channel electromyogram, nasal oral airflow, 2 channel respiratory effort, oxygenation saturation, electrocardiogram, and body position) and a nonattended Autoset CPAP titration at home. The pretreatment RDI, lowest oxygen desaturation, and periodic leg movements from the diagnostic PSG were reviewed. Also the post-CPAP RDI were compared between the in-house PSG and the Autoset.

Table 1



Results: Data from 23 of the 24 patients were reviewed. The patients consisted of 19 males and 4 females with the mean age of 48.7 years. The range of the pretreatment RDI was 7.3 to 87.8 events/hour, with the average being 41.3 events/hour. The avaerage pretreatment desaturation was 74.6% with the lowest being thirty percent. There was an average of 38.4 leg movements prior to CPAP and 76.3 movements during the CPAP polysomnography. The average post treatment RDI for the 16 channel PSG was 6.6 events/hour. The Autoset reported an average RDI of 8.2 events/hour. Respiratory distress index was highly correlated between the in-home PSG and Autoset with R=0.77 and p<0.0001. The Bland Altman plot demonstrates that the Autoset study slightly overestimates the RDI compared to the PSG by an average of 2.8 events/hour. Although statistically significant differences were present, these differences were not clinically significant. One patient persisted with an RDI of greater than ten. This patient initially had 47 central apnea which increased to 192 apneas during the CPAP polysomnography.

Table 2



Conclusions: Autoset used in the CPAP titration mode in the home demonstrates significant agreement with the full 16 channel polysomnography performed in the same unattended home environment.

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1630.K1

The Effects of Weight Loss in Obese Men with Sleep Apnea

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Introduction: Although weight loss is a common recommendation for obese patients with obstructive sleep apnea (OSA), few studies have systematically evaluated the changes in sleep architecture following weight loss.

Methods: Polysomnography was used to evaluate the effects of weight loss on sleep architecture in 18 obese males with documented OSA (Respiratory Disturbance Index, RDI > 15). Paired t-tests were used to assess changes in weight and sleep architecture.

Results: There was a strong (r = .63, p = 0.01) bivariate correlation between weight loss and change in total RDI.

Conclusions: These results suggest that a 10% weight loss, the amount recommended by the Institute of Medicine and the NHLBI, is sufficient to produce improvements in sleep apnea among obese men. However, post-treatment RDIs still require treatment with CPAP or other treat-

ments in addition to weight loss. Finally, our data suggest that larger weight losses are likely to produce greater improvements in sleep apnea.

Table 1

Variable	Before Weight Loss	After Weight Loss
Weight (kg)	112.4 ± 15.7	100.5 ± 14.4**
BMI (kg/m^2)	35.6 ± 4.9	32.1 ± 4.7**
Sleep Efficiency (%)	85.4 ± 8.1	85.8 ± 28.7
Latency (min)		
Stage 1	9.0 ± 6.7	9.8 ± 16.7
REM	143.5 ± 108.5	84.0 ± 28.7ψ
Percentage Time (%)		
Stage 1	12.4 ± 6.3	13.3 ± 7.3
Stage 2	69.5 ± 9.2	62.2 ± 5.7**
Stage 3-4	1.2 ± 2.0	1.9 ± 3.6
REM	16.9 ± 8.5	22.5 ± 5.9
Nadir Oxyhemoglobin Saturation (%)		
REM	77.1 ± 17.2	83.4 ± 13.1
Non-REM	81.0 ± 6.9	84.4 ± 6.2*
RDI (events/hour)		
Total	55.5 ± 32.5	39.9 ± 26.1*
REM	30.0 ± 33.5	32.3 ± 27.8
Supine	61.7 ± 30.7	49.1 ± 32.3
Lateral	41.2 ± 40.6	29.9 ± 25.6
Arousals (per hour)		
Total	54.5 ± 31.5	43.9 ± 23.9

*p < .05, **p < .01, ψ = .08

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1634.K1

Sleep Onset REM Periods in Obstructive Sleep Apnea Patients: Results of Treatment.

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Introduction: The object of this abstract is to determine the effect of CPAP (continuous positive airway pressure) treatment on SOREMPs (sleep onset REM periods) in patients with obstructive sleep apnea (OSA). The high incidence of SOREMPs during MSLT (multiple sleep latency tests) in OSA patients is unexplained. Possibilities include coexisting narcolepsy or long-standing sleep disruption, with or without a conceivable secondary effect of the presence or absence of HLA DQB1-0602. This is the first study to determine whether SOREMPs remain in this population after treatment.

Methods: In our laboratory, approximately 150 OSA patients have had SOREMPs on their baseline polysomnogram(PSG)and/or MSLT(4 naps), mostly the latter. As part of their follow-up, 12 of these patients who had SOREMPs returned for repeat MSLT after a variable period of CPAP treatment after ascertaining compliance and a normal sleep routine on the night prior to the MLST. Baseline polysomnograms (PSG) and MSLTs and CPAP titration studies had been performed on each patient. None of the patients had clinical evidence of narcolepsy, depression, or antidepressant use.

Results: Baseline MSLT 1 revealed one SOREMP for each subject (except for two and four SOREMPs in one patient each).During post-treatment MSLT 2, SOREMPs remained in four patients (three with one SOREMP on baseline, two of whom increased to three SOREMPs, while the fourth patient had two SOREMPs and remained at two SOREMPs post-treatment). SOREMPs disappeared in eight of the patients post-treatment. The patient with four SOREMPs had none on MSLT repeat. Apnea-hypopnea index (AHI) was lower in group 1 (retained SOREMP group) (55.3± 9.6 SEM vs 77.6± 7.5). However, group 1 did not differ from group 2 (nonretained SOREMP) in age or body mass index (BMI). Sleep latency on MSLT 1 was higher in group 1 than in group 2 (9.1± 1.9 minutes vs. 5.4± 1.0). The MSLT 2 latency decreased for group 1 while increasing for group 2, resulting in a significant difference between the groups in latency change (-3.5± 1.7 vs. +3.5± 1.4; Spearman rank order correlation: 0.67; $p < .02$). Sleep parameters on the baseline PSG did not differ between the groups but there was a significantly longer time for oxygen saturation under 90% for group 1 (Spearman; 0.64; $p <. 05$), despite the latter group's lower AHI.

Conclusions: One third of these OSA patients with one or more SOREMPs pre-treatment still showed SOREMPs on repeat post-treatment MSLT. This surprising finding must be seen in light of the increase in sleepiness in group 1 post-treatment while group 2 actually improved. This might suggest the presence of subclinical narcolepsy in group 1 and prompts consideration of the use of stimulants in these patients. The number of patients needs to be expanded to confirm these results as well as to evaluate the significance of the differences in AHI and oxygen saturation.

1773.K1

Evaluation of Nasal CPAP Masks within Subjects

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Introduction: The nasal interface is assumed to govern NCPAP compliance. However, there are few objective comparisons of NCPAP masks with regard to compliance. In the absence of objective data, mask selection for patient use is dictated by subjective factors, which may compromise patient compliance. In order to make valid inference from studies of patient compliance and ratings of NCPAP masks, the power of a within-subjects experimental design is called for. The purpose of this study is to compare three masks, the Respironics Profile Lite (P), the Respironics Simplicity (S), and the patients' own (O) mask using subjective ratings and measures of compliance in a within-subjects design.

Methods: Ten male volunteers were recruited from the Sequoia Health Services Sleep Disorders Center AWAKE group. All subjects had been diagnosed with either obstructive sleep apnea or hypopnea by polysomnography. Each subject had a current presciption for NCPAP originally written from 24 to 180 months ago, with pressures ranging from 5 to 16 cm H2O. Identical Respironics Aria LX nasal CPAP blowers recorded compliance in minutes per night. Over a three week period, subjects used nasal masks (or pillows) O, P and S, for one week each. A Latin square design served to balance mask sequences across randomly assigned subjects. At the end of each week subjects completed a series of eleven 10-point Likert scales rating mask and headgear qualities such as fit, stability, comfort and overall satisfaction. Compliance and ratings data were analyzed with repeated measures ANOVA; alpha = .05 for all comparisons.

Results: A composite rating of all 11 scales showed mask P superior to mask O, which was superior to mask S. On individual scales, mask P rated better than mask O for fit and stability. Mask O rated superior to mask S in comfort and overall satisfaction. Mask P was superior to mask S on all but three of the eleven individual ratings. The compliance data demonstrated masks P and O were superior to mask S, averaging about one hour more use per night. Mask P was marginally better than mask O (about 10 minutes); the difference failed to reach significance.

Conclusions: Subjects consistently rated masks P and O superior to mask S. Key ratings were mask P and mask O both significantly higher in overall satisfaction than mask S. Also, mask P rated significantly better for fit and stability than both O and S. The compliance data reflected the subjects' ratings of the masks, with the highly rated Profile Lite showing clear superiority to the Simplicity, and stacking up well against several veteran patients' Own mask. Likewise, the Simplicity mask had poor ratings and equally poor compliance, all of which supports the assumption that the nasal interface governs NCPAP compliance.

Research supported by a grant from Respironics Inc.

1776.K1

Nasal CPAP Use Among Active Duty U.S. Navy Members with Obstructive Sleep Apnea

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Introduction: Obstructive sleep apnea syndrome (OSAS) is not uncommon among young, active duty military personnel. This is somewhat surprising, given the known association between OSA and obesity, and the presumption of high standards of physical fitness in the military. Nasal CPAP is currently the treatment of choice for most of our patients with significant OSA, although surgery and oral appliances are also available. To better define the experience of our military population we conducted a written survey of all patients prescribed nasal CPAP in the past two years. We were especially interested in the experience of sailors who have used nasal CPAP in a shipboard environment.

Methods: Demographic data on 131 consecutive active duty military members diagnosed with obstructive sleep apnea and prescribed nasal CPAP in the past two years at Naval Medical Center San Diego were reviewed. Patients were mailed an anonymous questionnaire that focused on nasal CPAP use aboard ship as well as current use.

Results: The baseline demographic data of our patients is given in the table below. 14.7% of patients had a BMI <26 kg/m2, 41% 26-30 kg/m2, and 44% >30 kg/m2. There was no association between the Epworth Sleepiness Scale score and RDI (p-value = 0.685). To date, 34/131 (26%) of the surveys have been returned and the data analyzed. Of the 34 patients, 29 (85%) were still using nasal CPAP. They reported using nasal CPAP on average 5.7 nights/week (range 2-7 nights) and 6.9 hours/night (range 2-10 hours). 25/29 (86%) used a cold humidifier and 1/29 (3%) used a heated humidifier on a regular basis. 8/32 (25%) reported having used nasal CPAP aboard ship. Of the 24 patients who had not used nasal CPAP aboard ship, 4/24 (17%) were told that it was "not allowed" and 18/24 (75%) had not been stationed aboard ship since treatment began. The most common complaints regarding nasal CPAP use in a shipboard environment were (1) inadequate space, and (2) lack of an accessible electrical outlet. Several patients also complained about the cold air temperature that was exacerbated by cold water humidification. 19/24 (79%) of patients were of the opinion that navy ships should allow nasal CPAP use.

Table 1

N	% Male	Age (years)	BMI (kg/m^2)	RDI	MinO_2 Sat	ESS	CPAP Pressure (cm H_2O)
131	96.9	38.3±7.3	29.4±3.5	39.8±27.3	75.6±11.5	14.6±3.5	9.3±2.2

Conclusions: Active duty military members diagnosed with obstructive sleep apnea at our medical center are often treated with nasal CPAP. Self-reported compliance is high, but needs to be confirmed with objective measurements. Although the overall experience is limited, it is clear that nasal CPAP can be successfully used aboard ship. Interestingly, a number of patients were told that nasal CPAP use was not allowed aboard ship although no such official policy exists. Barriers to treatment such as space limitations, lack of access to electrical outlets, and availability of spare parts are issues that need to be addressed with each individual prior to assignment aboard ship.

1791.K1

CPAP Compliance in Sleep Apnea Syndrome: Should Objective Compliance Data Guide Management Decisions?

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Introduction: Compliance with CPAP for sleep apnea syndrome is a major concern. Appropriate prescription of pressure, mask type, and other equipment is paramount to ensure a high level of compliance. Nearly 40% of patients reject CPAP in the first few months. A search for correctable problems such as the type of mask, headgear, and humidifier should be done prior to discontinuing CPAP therapy or considering other diagnoses to explain persistent symptoms. Sleep physicians often depend upon subjective reports from patients to determine compliance with treatment. Repeat sleep studies may be necessary but this leads to great expense and an overload of limited resources. Objective assessment of compliance by downloading the patient's CPAP unit is recommended for those patients who remain symptomatic despite what appears to be adequate treatment with CPAP.

Methods: We therefore attempted to correlate these compliance data with patients' self reports in a group of 30 patients with OSA treated at the Winthrop Sleep Disorder Center from the period of December 1997 through October of 1999 who were serviced by the same DME (Durable Medical Equipment) company. We selected for study only those patients who reported being fully compliant with their CPAP prescription.

Results: Objective data were as follows:8 patients (27%) were 100% compliant with use of CPAP over average of 17 weeks (range 6-29). They consistently used their CPAP for at least 4 hours per night. Additional 9 patients (30%) had difficulty adjusting to the use of CPAP, but after 2-4 weeks were fully compliant with use.7 patients (23%) were non-compliant and used their CPAP intermittently for less than 3 hours per night or did not use it at all. 6 patients (20%) used the device intermittently from 0-4 hours on occasional nights, but on average used more nights per week than the non-compliant group. No significant differences in compliance were found between the group of patients who had a split-night study versus a full night CPAP titration.

Conclusions: We conclude that subjective reporting of compliance with CPAP is inaccurate in a significant percent of patients (43% in our study). We recommend that objective data be obtained in all patients who continue to have symptoms of excessive daytime somnolence despite what appears to be adequate treatment of OSA.

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1664.K1

Sleep-Disordered Breathing Among Postmenopausal Women: Relationships with Actigraphic Measures

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Introduction: Sleep-disordered breathing (SDB), which may be observed in the absence of daytime sleepiness or snoring, is estimated to affect as much as 25-50% of the US adult population. This study sought to determine the prevalence of SDB among community-dwelling postmenopausal women, without selection for sleep disorders or suspected sleep-apnea syndrome. We also explored whether actigraphic measures could be used as predictors of SDB.

Methods: Volunteers (Median age = 69; Median BMI = 26.2) were recruited from postmenopausal women participating in the Women's Health Initiative study. Although not strictly representative of the San Diego population, a diverse sample (Non-Hispanic White = 72%, Hispanic = 14%, Black = 9%, Other = 5%) was studied from 1995 to 1999. Home sleep and illumination patterns of women were continuously recorded for 7 days (Ambulatory Monitoring, Inc., Ardsley, NY). Additionally, pulse oximetry was monitored for up to 3 nights (VX4, Vitalog Monitoring, Inc., Redwood City, CA). Volunteers maintained usual daily routines including work, intimacy, exercise, and bedtimes. In-bed actigraphic sleep variables (TST, SEI, SOL, WASO) and out-of-bed sleep (OOBS) were derived with a validated ACTION3 scoring algorithm aided by volunteers' reported bedtime and 'light-off, light-on'(METHODS) information inferred from illumination data. Nocturnal activity index (NAI, % epochs with >0 activity), mean activity level (AL), longest wake episode (LWE), longest sleep episode (LSE), mean duration of wake episode (DWE), and mean duration of sleep episode (DSE) were derived with ActionW. A VX4 algorithm processed oximetric data, providing estimates of oxyhemoglobin desaturation >= 4% per hour of sleep (ODI4). ODI4 scores for each volunteer were averaged for all available nights [internight reliability: ICC = .81]. Technically adequate actigraphic and oximetric data were obtained from 360 volunteers.

Results: A median ODI4 of 5.76 characterized women in the sample. As much as 9.2% showed ODI4>= 20. Women (48%) above 69 years old experienced greater ODI4 than those ages 50 to 59 (19%) [adjusted logODI4 mean = .88 and .66, respectively; $F(2,262) = 9.05$, $p < .001$], and non-Hispanic White women had lower ODI4 relative to their minority counterparts [adjusted logODI4 mean = .74 and .87, respectively; $[F(2,263) = 6.14$, $p < .01]$. ANCOVA showed no significant interaction between ethnicity and age or between ethnicity and BMI, but age effects were influenced by BMI $[F(2,260) = 4.90$, $p < .01]$. Partial correlations between actigraphic measures and logODI4 are shown in the table, with age and ethnicity adjusted. Further adjustment for BMI yielded significant correlations only for AL, WASO, SEI, and LWE.

Table 1

Descriptive Actigraphic Measures° by SDB Severity Criteria

ODI4	AL	OOBS	TST	SEI	WASO	NAI	LWE	LSE	DSE	DWE
<5 (41%)	24.8	18.6	369.6	83.8	77.2	40.7	19.7	15.9	17.7	4.6
5-19 (50%)	26.8	22.3	361.9	82.8	84.1	56.7	22.0	15.7	18.0	5.1
³20 (9%)	32.4	29.8	350.9	79.4	108.2	53.4	28.0	15.2	15.2	6.2
Total (n=360)	25.9	20.7	364.4	82.9	82.4	48.9	21.3	15.7	17.8	4.9
rp	.21*	.11*	-.13*	-.20*	.18*	.13*	.17*	-.04	-.12*	.10

Values are minutes expressed in medians; SEI and NAI are expressed in % and AL as activity count
**Correlations were significant at alpha = 0.05*

Conclusions: These results are consistent with previous surveys of sleep-disordered breathing, demonstrating high rates among postmenopausal women without prior suspicion of sleep disorders related to SDB. The associations between ODI4 and actigraphic measures point to the sleep-disturbing effects of SDB-associated CNS arousals, which invariably follow episodes of obstructed respiration. Moreover, they suggest that elevated nocturnal activity may be a consequence of nocturnal arousals, but activity level or activity index accounted for only small percentage of the SDB variance.

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1670.K1

Assessment of a Clinical Prediction Model in the Evaluation of Sleep Apnea

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Introduction: Obstructive sleep apnea (OSA) has been estimated to effect 2 to 4% of the population. With the known associated risk for hypertension, cardiovascular and cerbrovascular diseases, and impaired daily function due to sleepiness, a reliable tool for primary care providers is needed to identify the population at risk. Symptom based questionnaires can be cumbersome, time-consuming, and have limited reliability. Likewise, morphometric indicators alone have had limited application in assessing risk. However, if variables that are independently related to the presence of OSA are grouped together, a clinical prediction model can be formed that should accurately predict the risk for OSA.

Methods: Previously published studies assessing questionnaires and clinical features used to detect the risk of OSA were reviewed (Flemons et al 1994; Kump et al 1994; Viner et al 1991). Variables that were easily obtained and independently related to the severity of OSA were chosen. These included male sex, body mass index greater than 30 kg/m2, age >50 years old, and a history of snoring, witnessed apneas, excessive daytime sleepiness, and hypertension. Four hundred patient charts were reviewed for the presence or absence of the variables. All patients underwent polysomnography and the results were considered positive if the apnea-hypopnea index (AHI) was >20. The univariate association of each variable with the AHI was evaluated by the logistic regression likelihood ratio chi-squared test. The final prediction model was determined by relating the independently significant variables to the AHI by means of logistic regression analysis.

Results: The prevalence of an AHI greater than 20 in our population was 34%. Male sex, BMI, history of EDS, witnessed apneas, and hypertension were found to be predictors of significant sleep apnea. These five univariate variables maintained significance in the logistic regression model. The odds ratio between a patient with all five factors compared to a patient with no factors was 30.

Conclusions: In patients suspected of having obstructive sleep apnea, a strong clinical suspicion in conjunction with these features can serve as a reliable screening test. The ease and reproducibility of obtaining this information can be applied in the outpatient setting during a routine office visit. The results can help primary care providers direct the care of patients in whom they suspect of having sleep apnea.

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POSTER PRESENTATIONS

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1870.K1

Effect of CPAP on HTN

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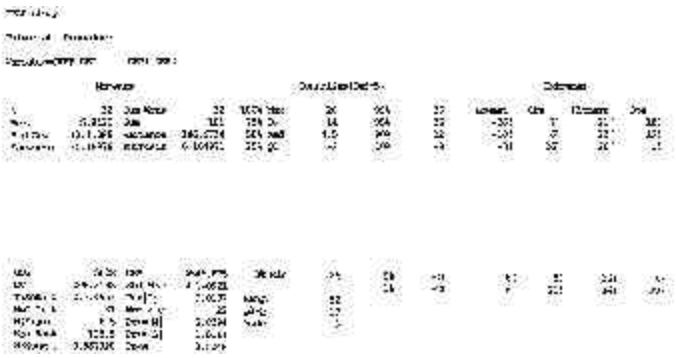
Introduction: A significant body of literature documents the relationship between sleep apnea and hypertension. It is generally agreed upon that obstructive sleep apnea (OSA) is associated with hypertension (HTN) regardless of other patient variables such as age, weight and sex. Our study assesses the effect of Continuous Positive Airway Pressure (CPAP) in regulating hypertension (HTN) and helps in maintaining dose of anti-hypertensive agents.

Methods: To assess the effect of nasal CPAP on HTN in patients with OSA we did a retrospective study of patients seen in the Sleep Clinic who were diagnosed with OSA in our Sleep Center. We studied a total of 3 2 patients (24 men & 8 women) in the age group of 30 - 70. Blood Pressure was measured during baseline evaluations including history and physical examinations in the initial clinic visit prior to the sleep study and after use of CPAP for 2-3 months. All the patients underwent two nights polysonmographic sleep evaluation in which the first night was baseline and the second night was done using CPAP. A list of anti-hypertensive medications that were used was noted and after use of CPAP, they were interviewed in the clinic about change in their anti-hypertensive medication.

Table 1

Results: Of the 32 patients, 19 (59%) had decrease in their systolic blood pressure (SBP); 22 (69%) had decrease in diastolic blood pressure (DBP). 15 (47%) had decrease in both systolic and diastolic blood pressure. Only 5 (16%) had increase in SBP & DBP. And only these people had to increase their anti-hypertensive doses or add new medications. The rest of these patients need no further change in their medications.Two variables were defined to give the difference in blood pressure between the two times. Specifically (Change in systolic blood pressure) $\delta SBP = SBP1$(Systolic blood pressure prior to CPAP) - SBP2 (Systolic pressure after CPAP) and (Change in diastolic Blood Pressure) $\delta DBP = DBP1$ (Diastolic Blood pressure prior to CPAP) - DBP2(Diastolic pressure after CPAP). A positive difference indicates the amount of decrease from time 1 (Baseline Blood Pressure) to time 2 (Blood pressure after use of CPAP). The question is whether there is a significant change in blood pressure. Based on the Wilcoxon signed rank test using a two- sided alternative, we found a statistically significant difference in both cases. For SBP, the mean, median and standard deviation are 9.1, 13 and 20.6 respectively. This change is statistically significant with p-value of 0.008. For DBP, the mean, median and standard deviation of the change are 5.8, 4.5 and 12.1 respectively. For DBP this change is statistically significant with p-value of 0.0 11.

Table 2



Conclusions: Even though this was a limited retrospective study involving a small population this study has shown that the use of CPAP in this group helped control HTN in conjunction with anti-hypertensive medications. The results of which are shown above and they are statistically significant.This set of patients is still being monitored in the clinic regarding changes in CPAP, medications and weight loss.

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1753.K1

CPAP Adherence is Associated with the Decisional Balance Index

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Introduction: Previous studies examining the determinants of adherence to CPAP have limited the variables studied to patient (or sociodemographic), disease status (e.g., apnea-hypopnea index [AHI], oxygen desaturations, sleepiness level, etc.) and treatment variables (e.g., CPAP pressure), with no reliable predictors found. The present study sought to examine the relationship between CPAP adherence and a cognitive variable derived from the Transtheoretical Model, the Decisional Balance Index (DBI). DBI has been shown to be an important variable in predicting behavior change (Prochaska et al, 1997).

Methods: Fifty-one consecutively presenting patients to the Pulmonary Clinic at the Veterans Affairs San Diego Healthcare System participated. All participants were diagnosed with sleep apnea and were prescribed the Respironics Aria LX CPAP machine (Respironics, Inc., Pittsburgh, PA) which came outfitted with an internal clock counter that recorded usage information.. All participants were first-time users of CPAP and none had previous surgical treatment for sleep apnea. Forty-nine men and two women were studied. Measures included in the present study included the Epworth Sleepiness Scale (ESS) (Johns, 1991), the Functional Outcomes of Sleep Questionnaire (FOSQ) (Weaver, 1997), and the Decisional Balance Index. The DBI is a measure of the pros, or benefits, of using CPAP minus the cons, or costs, of using CPAP. Measures were taken at CPAP fitting and one month post-CPAP fitting. Change scores were calculated by subtracting time 1 from time 2. A hier-

archical regression analysis was performed between number of hours of CPAP usage per night (dependent variable) and ESS, FOSQ, and DBI (independent variables) while controlling for CPAP pressure. CPAP pressure was chosen as the covariate because it has been shown that CPAP pressure is in large part a function of body mass index (BMI) and AHI

Results: The mean age of the sample was 54.1 ± 12.3 years (range 30-76). The mean AHI of the sample was 40.1 ± 25.3 (range 2.1-120). Several subjects had an AHI score less than 15 and were included because of a clinical history strongly suggestive of sleep apnea. The mean initial CPAP pressure was 9.1 ± 2.0 cm H2O (range 6-15). The mean BMI was 36.4 ± 9.0 (range 21-61). Mean nightly usage for the sample was 3.4 ± 2.5 (range 0-10.8) hours per night. The mean CPAP usage period for the entire group was 31.7 days (SD=8.0, range 20-67). The results of the regression analyses are shown in the table below. At step 1: R2 = .046, adjusted R2 = .026, p = .138. At step 2: R2 = .264, adjusted R2 = .197, p = .008. change in R2 = .218, p = .009. With a semi-partial correlation of .41, change in DBI alone accounted for 17% of the variance in CPAP usage.

Table 1. Summary of Hierarchical Regression Analysis

Variable	B	SE B	β	T	p-value
Step 1					
CPAP Pressure	0.28	0.18	0.22	1.51	0.138
Step 2					
CPAP Pressure	0.50	0.19	0.39	2.67	0.011
Change in ESS	-0.10	0.08	-0.18	-1.20	0.236
Change in FOSQ	-6.3E-02	0.18	-0.07	-0.46	0.646
Change in DBI	0.14	0.05	0.45	3.01	0.004

Conclusions: The results of the present study suggest a strong positive relationship between CPAP adherence and change in DBI. Restated, CPAP adherence increases as the pros, or benefits, of using CPAP outweigh the cons, or costs, of using CPAP over a one-month period of time. This relationship exists even when CPAP pressure (a function of BMI and AHI), change in sleepiness level, and change in functional outcomes of sleep apnea are taken into account. Future research should investigate whether interventions that focus on efforts to increase pros and reduce cons have an additional effect on CPAP adherence.

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1754.K1

Sleep Apnea Symptomatology: Gender Differences in Initial Symptoms Presentation May Obscure Diagnosis and Lead to a Lower Index of Suspicion for Obstructive Sleep Apnea in Women

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Introduction: Epidemiologic studies consistently demonstrate that women as a group have lower incidence of obstructive sleep apnea, relative to men. However, a recent literature review has indicated that obstructive sleep apnea is much more prevalent in women than previously recognized and is underdiagnosed.[1] The underdiagnosis of sleep apnea in women occurs despite the fact that it has been demonstrated that the diagnostic criteria and clinical indications for apnea have been shown to be similar for women and men in a large community cohort sample.[2] The present study was conducted to evaluate the incidence of classic apneic symptoms in a clinical sample and to determine if women present sleep complaints and non-sleep features which may influence diagnosis.

Methods: Participants were 278 consecutive adult patients who presented to a hospital-based sleep disorders center for evaluation and treatment. Mean age was 46 years (s.d. 13.7), and 71%were male. Patients underwent clinical interview with history and physical, nocturnal full-montage traditional polysomnography (PSG), and completed self-report questionnaires. Patient were grouped according to apnea severity determined by PSG: non-apneic (Apnea/Hypopnea Index < 5), mild (AHI = 5 to 15), moderate (AHI = 16 to 30), or severe (AHI > 30).

Results: Results reveal that the classical signs and symptoms of obstructive sleep apnea were exhibited by both female and male apneics. The symptom of habitual snoring exhibited moderate to high sensitivity and low specificity for women (50% and 24% respectively), and men (88% and 12%). Excessive daytime sleepiness was moderately sensitive and specific for women (41% and 43% respectively), and men (28% and 66%). Observed apnea was moderately sensitive and specific for women (43% and 64% respectively), and men (50% and 69%). The symptom of AM headache achieved lower levels of sensitivity and specificity for sleep apnea in women (36% and 38% respectively), and men (30% and 67%). Women and men were compared on various other sleep and non-sleep related complaints. Results revealed that women reported more concerns over non-restorative sleep, daytime fatigue, restless legs and nightmares than did men ($p < .05$ in all cases). Furthermore, women were more likely to report depression than were men ($p < .01$).

Conclusions: Results support earlier literature which found no statistically significant difference in classic apneic symptoms in women and men diagnosed with sleep apnea. However, these women were more likely than men to report depression and additional sleep complaints not traditionally associated with sleep apnea. In some cases, these gender differences in presenting symptoms may function to obscure the diagnosis of sleep apnea in women.

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1239.K1

Successful Treatment of OSA Using CPAP on Young Adults with Mild MRDD

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Introduction: Young adults classified as mild mental retardation developementally delayed (MRDD) can successfully be treated with continuous positive airway pressure (CPAP) therapy. It has been suggested that intervention during the first month of CPAP treatment can greatly increase compliance.[1] This abstract suggests that in spite of MRDD classification, these young adults can benefit from CPAP therapy.

Methods: Young adults (M=36.6 ± 9.5) (7 female, 4 male) categorized as mild MRDD during the initial consultation were ordered on CPAP therapy. The patients in our group have been using CPAP therapy for M=17.9 months ± 15.35. Intervention and techniques used to improve success include multiple demonstrations and repeated trials of equipment in the clinical setting, emperical usage of CPAP at home prior to CPAP trial study, monthly office visits after set up, weekly phone followups and thorough instruction of the family or caregiver.

Results: Of the 11 patients set up, 9 have been successful in using CPAP. Success was defined as one or more of the following: decrease in Epworth Sleepiness Scale (ESS), subjective statements by family or patient as to "improvement of sleep quality", and compliance downloads from CPAP units(min. of 4 hours per night for 90% of the nights ordered). The patients who used CPAP for slightly less than four hours were included as successful if they also had a decrease in ESS or reported an improvement of sleep quality. Two adults have not used CPAP regularly. Both were potentially related to inability to obtain transportation to the sleep lab (one has a wife with multiple health problems and the other has an unreliable caseworker). Both have expressed desire to use CPAP but needed reinstruction and were unable to obtain transportation to the sleep lab for intervention.

Conclusions: This data suggests that with multiple interventions, mild MRDD adults can be successfully treated with CPAP therapy.

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1243.K1

Sleep Disorders Questionnaire and its Polysomnographic Correlation in Sleep Apnea Patients

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Introduction: The sleep Disorders Questionnaire (SDQ) has shown some evidence of being a reliable instrument for supporting a diagnosis in patients suspected of having sleep apnea, narcolepsy, psychiatric disorders, or PLM disorders.[1] To the extent that data suggest some validity for this instrument in a Hispanic culture, we determined the correlation between items from SDQ and polysomnographic (PSG) variables in a homogeneous sample of morbidly obese patients suspected for sleep apnea.

Methods: Patients. Fifty-two morbidly obese middle-aged outpatients (women n=39, men n=13) from the Obesity Clinic of the National Institute of Nutrition Salvador Zubirán (INNSZ), age mean=40±12 years old, and Body Mass Index (BMI>40 kg/m2), with complaints of snoring or excessive daytime sleepiness underwent two nights of polysomnography under standard laboratory techniques. The study was approved by the local ethics committee and all patients gave informed consent. The diagnosis of obstructive sleep apnea-hypopnea syndrome was defined by a mean Respiratory Disturbance Index (RDI=Apnea+hypopnea / hour of sleep) >5. The patients completed the SDQ two hours before the first night of PSG. The items of SDQ were correlated with PSG variables using the Spearman correlation test.

Results: A wide range of sleep-disordered breathing, ranging from RDI of 2.5 to 128.9 was found, mean=44.5±32.8. Ninety-eight percent of the sample had a RDI>5 (mean=51±37) and 65% of the sample had at least one oxygen desaturation below 65%. Spearman correlations between SDQ complaints and PSG measures are shown in Table 1.

Table 1. Spearman correlations and p values, between SDQ items and PSG variables

SDQ Items	RDI	%SaO2<65 Index
20. I snore in my sleep	0.33 0.002	0.47 0.0001
21. I am told I snore loudly and bother others	0.46 0.0001	0.39 0.0001
56. In the past 6 months, I have fallen asleep accidentally in some of these situations: eating a meal, talking on the phone, talking to someone, riding in a bus or car, watching TV, at a theater, reading a book, at a lecture	0.39 0.008	0.50 0.0003

Conclusions: SDQ items that correlated with objective measurement of sleep apnea (RDI, %SaO2) corresponded to the symptoms that have been recognized as cardinal in the sleep apnea syndrome: snoring and sleepiness, and according to these preliminary data they remain invariable across cultures. It is interesting that in a previous report Maislin et al.[2] found that the sleep apnea symptoms were useful in discriminating patients with and without sleep apnea only if the patient was not extremely obese (i.e. <40 BMI). In individuals with a BMI>40 who had a high risk for sleep apnea, sleep apnea symptoms were not predictive of who did or did not have sleep apnea. By contrast we reported that the complaints of snoring and sleepiness are associated with the level of sleep-related breathing disorder in morbidly obese patients.

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1803.K1

Vital Exhaustion in REM-related Obstructive Sleep Apnea and Primary Snoring Disorder

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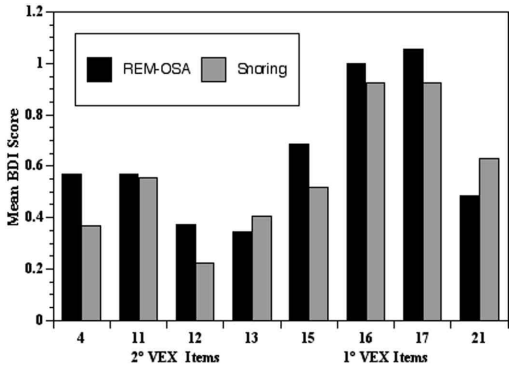
Introduction: The concept of Vital Exhaustion (VEX) is based on research concerning predictors of cardiac illness in a large cohort study (Van Diest et al, 1991). VEX consists of two subscales of the Beck Depression Inventory (BDI)., Primary and Secondary VEX scales. Primary VEX includes work inhibition(#15), sleep disturbance (#16), fatigability (#17), and decreased libido (#21); secondary VEX includes general dissatisfaction (#4), irritability (#11), loss of social interest (#12), and problems making decisions (#13). The concept of VEX has been explored in patient groups with several different sleep disorders, including Obstructive Sleep Apnea (OSA), Upper Airway resistance Syndrome (UARS), narcolepsy, and Periodic Limb Movement Disorder (PLMD) (Gokcebay et al, 1997, 1999). These studies revealed that patients with sleep-disordered breathing (OSA & UARS showed highly similar VEX profiles despite varying levels of disease severity. Patients with narcolepsy and PLMD differed in their VEX profiles from the groups with OSA & UARS. Primary Snoring Disorder (PSD) by definition is a benign condition without sleep-related problems such as daytime sleepiness, non-refreshing sleep or fatigue. In this study, the VEX profiles of patients with PSD are compared to those of sunjects with REM- related OSA (REM-OSA).

Methods: Sixty two (62) subjects were evaluated with Epworth Sleepiness Scale (ESS) and BDI followed by standard nocturnal polysomnography (NPSG) in the Sleep Disorders Center. Of these, 35 (21 M, 14 F, age 47 ± 13 [SD] years) were diagnosed with REM-related obstructive sleep apnea (REM-OSA) with ≥ 10 apneas+hypopneas/hour of REM sleep but ≤ 10 apneas+hypopneas/hour of total sleep. The remaining 27 subjects (15 M, 12 F, age 42.1 ± 13 years) had primary snoring disorder (PSD) with no daytime sleepiness and no pathology on NPSG except snoring. Age, ESS, total sleep time (TST), total arousal index (TAI), BDI and VEX were tabulated and analyzed statistically with paired t-tests.

Figure 1. Vital Exhaustion Profiles in REM-OSA and Primary Snoring



Results: The mean ages for the two groups were not significantly different (p = 0.11). Total sleep times (TST) were comparable for the two groups (p = 0.64). Subjects with REM-OSA had significantly more arousals (13.56 ± 4.63 [SD] arousals/hour than the patients with PSD (5.98 ± 2.38 arousals/hour), p < 0.001. The REM-OSA patients had a significantly higher mean ESS score 10.3 ± 6.15) than the PSD patients (4.76 ± 2.13) , p < 0.001. The Primary and Secondary VEX indices did not show any statistically significant difference between the two groups. However, when individual Primary and Secondary VEX items are plotted for each group, the profiles appeared different, (Fig.1).

Conclusions: In these two groups with significantly different levels of sleepiness, primary and secondary VEX scores were not statistically different. This study further strengthens the hypothesis that VEX is not a just a covariant of sleepiness and is possibly a distinct clinical concept.

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1810.K1

Modulations of Respiratory Effort by Sleep Stages in Normal Controls and Upper Airway Resistance Syndrome (UARS) Patients

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Introduction: Investigation of the role of sleep states on the respiratory effort of controls and subjects with upper airway resistance syndrome (UARS).

Methods: Nine men with UARS and six control men matched for age and body mass index (BMI). One night's monitoring of sleep and breathing, including the determination of respiratory effort with esophageal manometry. Analysis of the data, breath-by-breath, using visual inspection and a computerized program.

Results: A modulation of respiratory effort by sleep state and stages is seen in all subjects. The lowest amount of effort is noted during REM sleep and the most important is associated with Slow Wave Sleep. There is a significant difference between the amount of effort noted in normal controls versus UARS patients when total nocturnal breaths are investigated. Two specific breathing patterns are seen primarily in UARS patients. These patterns are NREM sleep stage dependent. Crescendos are seen mostly during stages 1-2 NREM sleep while segments consisting of regular and continuous, breath-after-breath, high respiratory efforts are associated with Slow Wave Sleep. A visually scored arousal response is seen with a different amount of effort depending on the sleep stage.

Conclusions: There is a modulation of respiratory effort by sleep stage and state. This modulation is different in UARS patients than in controls. As indicated by the visual sleep scoring, the repetitive arousals may lead to more or less severe sleep fragmentation.

1815.K1

The Morning Peak and Disturbance of Circadian Rhythm of Blood Pressure in Patients with Arterial Hypertension and Sleep Apnoea/Hypopnoea Syndrome

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Introduction: It's known, that prevalence of cardiovascular events are higher in the patients (pts) with abnormal nocturnal fall of blood pressure (BP) and predominantly observed during morning peak of BP (MPBP). The purpose of this study to investigate the relationship between the presence of sleep apnoea/hypopnoea syndrome (SAHS) with the MPBP and alteration of circadian rhythm.

Methods: We investigated 61 hospitalized pts (44m,17f) with mild to moderate arterial hypertension, aged between 23 and 72 (52±2y). Noninvasive 24-hour BP recordings (TM-2425, A&D, Japan) was performed with intervals of 15 min in day- and 30 min nighttime. A normal circadian rhythm of BP was defined when nocturnal fall of systolic BP was >10% and <20%. The MPBP we assess, using new index: normalized speed of increase of systolic BP [NSC SBP]=[maximal speed of changes of SBP from 4AM to 12AM]/[(mean awake SBP)-(mean asleep SBP)]. The pts during sleep underwent continuos monitoring of arterial oxygen saturation (NONIN-8500 M, USA). The presence of SAHS was confirmed when desaturation index (DI-number of 4% desaturations from the baseline value), was >15 per hour. Pts with SAHS was assigned the gr.A (n=19) and the remaining pts were assigned to gr.B (n=42). We compared the groups regarding BP profile parameters. Differences were tested by Fisher's exact and Student t tests.

Results: Prevalence of abnormal dipping was significantly ($p<0,05$) higher in the gr. A (84%, including-1 «night-peaker», 14 «non-dippers», 3 «dippers» and 1 «over-dipper»), comparatively with Gr.B (57%, including - 5 «night-peakers», 17 «non-dippers», 18 «dippers» and 2 «over-dippers»). NSC SBP was significantly higher in the gr.A too (3,2±1,1 vs 1,3±0,4h-1, $p<0,05$).

Conclusions: Our results suggest, that sleep apnea/hypopnoe syndrome might contribute to altered circadian rhythm of blood pressure and increase morning peak of BP, and might play worse prognostic role in patients with arteral hypertension.

1568.K2

Safety Profile of 400-mg Doses of PROVIGIL® (Modafinil): A Comparison of Two Dose-Escalation Methods

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Introduction: Two large-scale, 9-week, double-blind, placebo-controlled, clinical trials (18-center and 21-center) conducted in the United States demonstrated that 200-mg and 400-mg daily doses of modafinil are effective and generally well tolerated for the treatment of excessive daytime sleepiness associated with narcolepsy. The two trials used different dose-escalation protocols in both the 200-mg and 400-mg treatment arms. Overall, the incidence of adverse events (AEs) was somewhat higher in patients receiving 400-mg doses of modafinil than in patients receiving 200-mg doses. The analysis presented here focuses on the first few weeks' experience in the 400-mg treatment arms to determine if there was a difference between the two dose-escalation protocols in the rates of treatment discontinuation and the incidence rates and severity of the most common AEs.

Methods: Patients in the 200-mg treatment arm of the 18-center study (N = 96) received once-daily 200-mg doses on all study days. Patients in the 200-mg treatment arm of the 21-center study (N = 89) received once-daily 100-mg doses of modafinil for the first week of the trial followed by once-daily 200-mg doses for the remainder of the trial. In the 18-center study, 95 patients were randomized to treatment with 400-mg doses of modafinil and received a dose of 200-mg of modafinil on the first day of the study followed by 400-mg doses of modafinil for the remainder of the 9-week trial. In the 21-center study, 89 patients were randomized to treatment with 400-mg doses of modafinil. In this trial, a more gradual dose-escalation protocol was used: patients received 100-mg daily doses of modafinil during the first week of the trial, a single dose of 200 mg on day 8, and then 400-mg daily doses for the remainder of the trial. AEs were recorded throughout the trial, including notations about the type of AE, day of onset, severity of the AE, relationship to study drug, and whether the AE led to discontinuation from treatment.

Table 1

Treatment Discontinuations From the 400-mg Treatment Arm of the 18-Center Study

Pt. #	Reason for Discontinuation	Pt. #	Reason for Discontinuation
1	chest pain	7	nausea†; palpitation†; dyspnea
2	headache; depression; flu	8	headache†; insomnia
3	cataplexy*	9	nervousness
4	headache; nausea	10	tachycardia†
5	depression	11	headache; dizziness; dry mouth; hypertonia; confusion; others
6	cataplexy*		

* Considered to be unrelated to study drug.
† Rated as severe; all others were rated as mild or moderate.

Table 2

Common AEs Occurring in Patients in the 400-mg Treatment Arms of Two Trials

	No. of Reports							
	Weeks 1 & 2				Weeks 3-9			
	18-Site		21-Site		18-Site		21-Site	
AE	T*	M†	T*	M†	T*	M†	T*	M†
Headache	37	14	31	8	11	4	17	9
Nausea	11	2	5	1	1	—	6	3
Nervous	9	3	2	—	—	—	2	—
Insomnia	7	3	1	0	—	—	—	—
Diarrhea	6	—	—	—	1	—	9	4
Depression	4	1	1	0	2	1	1	0
Dry mouth	4	1	4	—	—	—	3	—
Anorexia	3	1	2	—	—	—	4	1
Rash	2	—	—	—	5	1	—	—
Dizziness	2	1	2	—	—	—	4	1
Anxiety	2	1	3	2	—	—	3	1
Dyspepsia	2	—	4	—	—	—	4	1

* Total; † Moderate to severe.

Results: Of the patients receiving 200-mg daily doses of modafinil, only 1 patient (in the 21-center study) discontinued treatment because of an AE (severe hypoventilation) considered by the investigator to be possibly related to treatment. In the 18-center study, 11 patients in the 400-mg treatment arm discontinued treatment due to AEs compared with none in the 21-center study ($P < 0.005$ by Fisher's exact test). For 9 of the 11 patients, the AEs leading to treatment discontinuation were considered to

be related to study drug (Table 1). Most of the AEs were considered to be mild to moderate in nature, but 3 patients experienced severe AEs. Eight of the 11 patients discontinued treatment within the first 10 days of treatment, with 1 patient each discontinuing at days 17, 18, and 19. The 3 patients with severe AEs discontinued treatment on days 2 or 3 of the study. The most common AE in the 400-mg treatment groups was headache, which occurred most frequently during the first 2 weeks of the trial (Table 2). In the 18-center study, 14 of 37 cases (38%) of headache occurring during the first 2 weeks of treatment were considered moderate to severe in nature compared with 8 of 31 cases (26%) in the 21-center study. There were 37 reports of nausea, nervousness, insomnia, diarrhea, and depression reported during the first 2 weeks of the 18-center study (16% rated moderate to severe) in the 400-mg treatment arm compared with only 9 reports of the same AEs in the 400-mg treatment arm of the 21-center study (11% rated moderate to severe). Few cases of these AEs were reported during weeks 3 through 9 in either study (except for nausea and diarrhea in the 21-center study) among patients receiving 400-mg doses of modafinil.

Conclusions: A significantly smaller number of patients who were gradually escalated to doses of 400 mg of modafinil over a 9-day period discontinued treatment compared with the number of patients who discontinued treatment after escalation to 400-mg doses over a 2-day period. With the exception of headache, the incidence of the 5 most common AEs during the first 2 weeks of treatment also was lower in patients gradually escalated to 400-mg doses. Although 400-mg daily doses of modafinil are effective and well tolerated, physicians may wish to consider starting patients with narcolepsy on daily doses of 100 mg or 200 mg of modafinil for 1 week to improve tolerability to treatment before increasing the daily dose to 400 mg.

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1584.K2

Treatment of Excessive Daytime Sleepiness Associated With Narcolepsy: A Post-hoc Analysis of Clinical Response to 200-mg and 400-mg Doses of PROVIGIL (modafinil)

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Introduction: Two large-scale, randomized, double-blind, placebo-controlled, 9-week clinical trials conducted in the United States have demonstrated that 200-mg and 400-mg daily doses of modafinil are effective and generally well tolerated for the treatment of excessive daytime sleepiness (EDS) associated with narcolepsy. Anecdotal reports from investigators in each of these trials suggested that many patients experienced greater therapeutic benefit with 400-mg doses than with 200-mg doses of modafinil. However, when mean scores from each of the four efficacy measures used in the trials were analyzed for the study population as a whole, there was no consistent statistical evidence in either trial of additional therapeutic benefit for doses above 200 mg. This post-hoc analysis of combined data from the two trials examined the agreement between 2 or more efficacy parameters in the trials and was conducted to determine whether there was a difference in overall objective and subjective EDS-related clinical response rates between patients receiving 200-mg and 400-mg doses of modafinil.

Methods: Efficacy measures in the two studies included the Clinical Global Impression of Change (CGI-C), the Epworth Sleepiness Scale (ESS), the Maintenance of Wakefulness Test (MWT), and the Multiple Sleep Latency Test (MSLT). Patients were included in this post-hoc analysis if they had evaluable efficacy data at baseline and Week 9, but were excluded if they had ESS scores ≤ 12 *and* mean MWT sleep latency times ≥ 12 minutes at baseline. These absolute cutoff criteria for the ESS and MWT are consistent with "normal" actuarial data reported in the literature.[1,2] Using data obtained at Week 9 and the EDS response criteria defined in Table 1, patients were assigned to 1 of 3 EDS response categories (see Table 2). The change-from-baseline criteria for the ESS and MWT listed in Table 1 were considered to be sufficiently large to demonstrate clinically significant improvements in EDS in severe cases of narcolepsy where normalization of scores may not be clinically feasible. Changes in mean MSLT sleep latency times (ie, improvement at Week 9 to >10 minutes or a change from baseline of ≥ 5 minutes) also were examined for correlation with the 3 EDS response categories. Additionally, data from patients who met 2 or more EDS response criteria ("responders") were analyzed to determine what proportion of these patients were considered to be clinically improved by an independent clinical investigator *and* had ESS scores ≤ 12 *and* mean MWT sleep latency times ≥ 12 minutes (ie, within the range found in the normal population). All statistical comparisons were made by chi-square analysis.

Table 1

Criteria	Parameter	EDS Response Criteria
1	MWT	mean sleep latency >=12 min AND/OR increase in mean sleep latency time of >=5 min
2	ESS	total score <=12 AND/OR decrease in total score of >=6
3	CGI-C	score of 1, 2, or 3 (ie, any improvement)

Table 2

		EDS Response Categories		
		>=2 Criteria (Responders)	1 Criteria	0 Criteria
	N	N (%)	N (%)	N (%)
Placebo	167	30 (18.0)	57 (34.1)	80 (47.9)
200 mg	161	71 (44.1)	54 (33.5)	36 (22.4)
400 mg	160	97 (60.6)	32 (20.0)	31 (19.4)

Results: Of the 530 patients enrolled in the two studies, 508 patients (96%) had evaluable data at baseline and Week 9. At baseline, 91% of these patients had ESS scores >12 and 86% had mean MWT sleep latency times <12 minutes; only 20 patients (4%) had ESS scores ≤ 12 *and* mean MWT sleep latency times ≥ 12 minutes at baseline and were excluded from the analysis. Results of the analysis are presented in Table 2. The percentage of patients who met 2 or more EDS response criteria ("responders") at Week 9 was significantly greater ($P < 0.01$) in the 400-mg treatment group (61%) than in the 200-mg treatment group (44%). Nearly half of the patients (48%) in the placebo-treatment group met none of the EDS response criteria compared with about one in five patients (19% to 22%) in either of the modafinil treatment groups. The percentages of patients with improvements in mean MSLT sleep latency times at Week 9 were significantly correlated ($P < 0.05$) with EDS response categories in patients receiving either dose of modafinil, but were not significantly correlated with EDS response categories in patients receiving placebo. At Week 9, ESS scores *and* mean MWT sleep latency times were normal or near normal in 22 of 161 patients (14%) in the 200-mg modafinil treatment group and 30 of 160 patients (19%) in the 400-mg modafinil treatment group as compared with only 4 of 167 patients (2%) in the placebo treatment group ($P < 0.001$ for overall treatment effect; $P \geq 0.05$ for comparison between 200-mg and 400-mg doses of modafinil).

Conclusions: The EDS associated with narcolepsy was improved in a significantly greater proportion of patients receiving 400-mg doses of modafinil than patients receiving 200-mg doses of modafinil. For many patients with narcolepsy, 400-mg doses of modafinil may offer greater therapeutic benefit than 200-mg doses.

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1889.K2

The Efficacy of Gamma-Hydroxybutyrate (GHB) in Narcoleptics: 9 Years

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Introduction: Over the last 14 years, narcolepsy patients have participated in an ongoing efficacy study of gamma-hydroxybutyrate (GHB) in treating narcolepsy. The first 5 years of summary data has already been reported.[1] The following summarizes the efficacy of the last 9 years.

Methods: Since late 1990, there have been 53 patients added to the original 12 patients in this study, bringing the total participants to 65 (men: 40, women: 65). The age range of the participants was from 13 to 83. GHB doses of 25 mg/kg hs, repeated 3-4 hours later was the starting dose for all patients. Titration to two higher doses was also available if the patient required it. These two doses were 32.5 mg/kg hs, repeated 3-4 hours later and 40 mg/kg hs and repeated 3-4 hours later. Concomittent stimulants, hormone replacement and blood pressure medications were allowed. At the end of this study, 36 patients were still enrolled. Patients have been followed by daily sleep-wake-sleepiness-cataplexy logs, annual (semi-annual, last 2 years) side effects questionnaire and most recently a survey of symptom status. This report will summarize the side effect questionnaire that was a fixed set of possible side effects (surveying the systems of the body & write-ins) and a survey of symptoms status. Questionnaires were sent to all participants, their responses were tabulated and summarized with descriptive statistics. Drop outs and reasons for dropping out from this study are also summarized, to glean the overall success rate of GHB in this sample. Therapeutic success rate was 77% for the 65 patients.

Results: Since 1990, there have been a total of 29 (45%) patients who dropped out for various reasons: 2 patients claimed being cured after taking GHB for several years, 3 cases of serious adverse events after about 3 years GHB use (seizure during sleep, mild heart attack and oversedation resulting from combination with another sedative hs); 1 case of plan to have a baby; 9 who felt cataplexy was too mild to require it (1 case got a less stressful job); 3 cases of other problems developed (2 cases of depression); 4 cases of insufficient therapeutic effect; 2 for financial reasons; 5 loss of patient contact.Patient reported side effects from a fixed side effect questionnaire, collected annually then semi-annually, over the last 2 years, will be presented at the meeting in a table with means and range values.The most common side effects reported by patients (mean per year) from the side effect questionnaire were under: 'excess gas': 5.1 (most of these patients also described having lactose intolerance). 'eye pain or discomfort': 3.1 'stuffy nose': 2.7 'decreased libido': 2.4 'urinary urgency upon awakening' and 'mentally slow': 2.3 'swelling in extremities' and 'loose stools' or 'diarrhea': 2.2 per year. Other noteworthy side effects include: 'euphoria': 2; 'dizziness': 1.7; increased 'nausea' & 'libido': 1.3; 'ambulation difficulty': 1; 'sleep walking' and 'bedwetting': 1.4 per year.The survey of the 36 patients on GHB revealed the following results on patient impact: 83% or 29 patients: GHB had life-altering positive impact14% or 5 patients: GHB had moderate positive impact 1% or 1 patient: GHB had slight positive impactCataplexy severity was improved to: slight to hardly noticeable in 97% of the respondersSleep attacks and excessive sleepiness severity was improved to: mild to hardly noticeable in 86%Sleep paralysis severity was improved (n: 23, 13 were symptom-less): slight to hardly noticeable in 91%Hypnagogic Hallucinations was improved (n: 27, 9 were symptom-less): slight to hardly noticeable in 91%

Conclusions: GHB is safe and effective for most narcolepsy patients, to control cataplexy, sleep paralysis, hypnagogic hallucinations & reduce excessive sleepiness,[2] with predominately only mild side effects. GHB is not to be used in seizure patients and GHB must not be combined with other CNS depressants.

References:
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(2) Scrima L, Shander D. Letter to Editor. New England Journal of Medicine, 1-24-91, 324(4): 270-271.

1610.K2

Hypocretin Mutation Screening in Narcoleptic Dogs

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Introduction: We have recently shown that exon-splicing mutations in the hypocretin (orexin) receptor 2 (Hcrtr2) gene cause autosomal recessive narcolepsy in two breeds of dogs. In Dobermans, exon 3 of the Hcrtr2 is spliced directly to exon 5. A SINE insertion upstream of the 3´splice site of the fourth exon generates abnormal splicing, probably by interrupting a branchpoint consensus sequence. In Labradors, exon 5 is spliced directly to exon 7 as the result of a mutation in the 5' exon-intron boundary consensus sequence. These mutations produce a truncated transcript that likely result in a loss of function for Hcrtr2. Genetic alterations in the preprohypocretin gene (Hcrt), have also been shown to induce narcolepsy in mice. In this study, the Hcrtr2 and Hcrt genes were characterized in additional narcoleptic dogs to examine if other hypocretin mutations induce narcolepsy.

Methods: 12 novel unrelated narcoleptic animals were explored in this study. These included 4 Dachshunds, 7 Poodles, 1 Labrador. Two cases were probands of multiplex families. One case was a family of Dachshund with 3 affected and 2 unaffected offsprings; this family was previously used to map canarc-1 but the causal mutation was not yet identified. The second multiplex family was a litter of 10 Poodles with 2 affected dogs. 10 healthy and 4 SINE positive colony Dobermans, 10 healthy and 4 exon-6 altered Labradors and 10 healthy Poodles were used as controls. All seven exons of the Hcrt2 loci plus at least 30bp of the flanking intronic regions were sequenced from genomic DNA using an ABI 377 Sequencer and aligned using Sequencher 3.11. Characterization of the canine Hcrt locus and sequencing of the two exons of this gene is ongoing.

Results: An G to A change at position 160 of exon 1 causing a Glutamic Acid to Lysine substitution in the N-terminal portion of the Hcrtr2 protein was identified in familial Dachshund narcolepsy. This G to A transition was not observed in control dogs. The study of other polymorphisms in the Hcrtr2 locus indicated that the unaffected recombinant

animal of this litter (Fritz) used to map canarc-1 in a previous study has a cross over within the Hcrtr2 locus. No other Hcrtr2 and Hcrt mutation has been identified to date but data analysis and complete sequences results are presented.

Conclusions: The disrupted splicing of the hypocretin 2 receptor mRNAs in Dobermans and Labradors is predicted to lead to truncated receptor proteins, with consequent loss of function. The novel Hcrtr2 mutation observed in Dachshunds is a milder alteration that will be interesting to further study at the functional level. The transition leads to a Glutamic Acid to Lysine substitution immediately prior to the first transmembrane region and may affect conformation for the receptor or ligand binding. Absence of other mutations in investigated dogs would indicate etiological heterogeneity in canine narcolepsy, paralleling recent results obtained in humans.[1]

References:
(1) Faraco J. et al.: Mutation screening of hypocretin system genes in human narcoleptics (Abstract presented at the 14th Annual Meeting of the Associated Professional Sleep Societies, June 17-22, 2000)

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POSTER PRESENTATIONS

1633.K2

Effect of Different Symptom Profiles on the Efficacy of Modafinil for the Treatment of Excessive Daytime Sleepiness in Patients With Narcolepsy

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Introduction: Narcolepsy is a disorder of unknown etiology characterized by excessive sleepiness. In addition to excessive sleepiness, cataplexy, sleep paralysis, and hypnagogic-hypnopompic hallucinations constitute narcolepsy's classic symptom tetrad. However, most patients do not have all of these symptoms. Modafinil is a novel wake-promoting agent found effective for improving wakefulness in patients with narcolepsy. In the U.S. pivotal trials, all participants were physiologically sleepy and had REM sleep occurrences on multiple sleep latency testing. The purpose of the present study was to determine whether particular symptom profiles were associated with differences in treatment efficacy.

Methods: A post-hoc analysis was performed using data from 2 large-scale, 9-week, double-blind, placebo-controlled, parallel-group, multicenter trials designed to evaluate the efficacy and safety of modafinil in patients with excessive daytime sleepiness associated with narcolepsy. Patients were randomly assigned to once-daily administration of placebo, modafinil 200 mg, or modafinil 400 mg. We assessed manifest sleepiness with the maintenance of wakefulness test (MWT) and subjective sleepiness with the Epworth Sleepiness Scale (ESS). Patients were evaluated at baseline and at the end of weeks 1, 3, 6, and 9. In this analysis, data from baseline and week 9 were analyzed and compared using standard analysis of variance (ANOVA) methods. ANOVA interaction effects for TREATMENT GROUP X SYMPTOM PRESENCE were tested at the $p<0.05$ level for mean MWT sleep latency times and ESS scores.

Results: A positive history of cataplexy was found in 81%, sleep paralysis in 60%, and hypnagogic-hypnopompic hallucinations in 65%. MWT data at baseline and week 9 were available for 476 patients and ESS data were available for 517 patients. The table shows changes from baseline for mean MWT sleep latency times and ESS scores for patients with and without cataplexy (CAT), sleep paralysis (SP), and hypnagogic-hypnopompic hallucinations (HH). Patients with and without cataplexy had equivalent MWT response to modafinil at all doses. By contrast, ESS improved more in patients without cataplexy taking 400 mg of modafinil compared with those with cataplexy taking 400 mg doses. Similarly, patients with and without sleep paralysis had equivalent MWT response to modafinil at all doses. However, patients without sleep paralysis taking 200 mg had greater improvement on ESS than patients with a history of sleep paralysis. Finally, no difference was found for either MWT or ESS between patients with or without a history of hypnagogic hallucinations in terms of modafinil-related improvement at any dose.

Table 1

Measure	Treatment Group	Without CAT	With CAT	Without SP	With SP	Without HH	With HH
MWT	Placebo	-1.23	-0.18	0.29	0.76	0.50	-0.73
	Modafinil, 200 mg	4.10	2.41	3.04	2.51	3.23	2.43
	Modafinil, 400 mg	2.99	3.35	3.57	3.05	3.51	3.15
	Modafinil, combined	3.54	2.86	3.30	2.77	3.36	2.78
ESS	Placebo	-1.70	-1.57	-1.62	-1.58	-1.94	-1.43
	Modafinil, 200 mg	-4.74	-3.78	-5.03 *	-3.19	-3.74	-4.11
	Modafinil, 400 mg	-6.89 *	-4.62	-5.33	-4.92	-6.05	-4.57
	Modafinil, combined	-5.83	-4.19	-5.18	-4.05	-4.81	-4.35

* $p<0.05$ for comparison of patients with and without the symptom.

Conclusions: Recent discovery of hcrt2 receptor gene defects in narcolepsy animal models opens the possibility that differential response to pharmacotherapy may reflect true variations in phenotype. Furthermore, such phenotypic variations may ultimately be linked to different genetic defects. Nonetheless, modafinil is equally effective for improving wakefulness, as objectively measured using the MWT, in patients with narcolepsy regardless of the presence or absence of a history of cataplexy, sleep paralysis, or hypnagogic-hypnopompic hallucinations. Although some variation was found in subjective assessments of EDS according to dose and symptom history for cataplexy and sleep paralysis, no consistent pattern emerged.

This research was supported by the Cephalon, Inc.

1325.K2

Long-term Efficacy and Safety of PROVIGIL® (Modafinil) for the Treatment of Excessive Daytime Sleepiness Associated with Narcolepsy in Patients with and without Cataplexy

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Introduction: Two large-scale, 9-week, randomized, fixed-dose, double-blind, placebo-controlled, clinical trials conducted in the United States demonstrated that PROVIGIL®; (modafinil) is effective and generally well tolerated for the treatment of the excessive daytime sleepiness (EDS) associated with narcolepsy. For safety reasons, patients in the two studies were required to discontinue treatment with anticataplectic agents. Although modafinil does not have an effect on the symptoms of cataplexy, it was of interest to determine whether there was a difference in EDS after treatment with modafinil between patients with and without cataplexy. A post-hoc analysis of the 9-week data from the two trials demonstrated that modafinil was equally effective for improving wakefulness in patients with and without a history of cataplexy. In two 40-week, open-label, extension trials conducted after the 9-week studies, patients were permitted to reinitiate treatment with anticataplectic agents. The purpose of the post-hoc analysis reported here was to compare the long-term efficacy and safety profiles of modafinil in patients with and without cataplexy in the two open-label, extension trials.

Methods: Patients could enroll in the two open-label extension trials if

they had completed either 9-week study or had discontinued either trial for reasons other than intolerable adverse events (AEs). All patients entering the open-label trials underwent a 2-week washout period, during which mean Epworth Sleepiness Scale (ESS) scores returned to the baseline levels observed in the double-blind trials. Patients from the first 9-week trial (N = 238) were then assigned to receive flexible doses of modafinil (ie, 200 mg, 300 mg, or 400 mg daily). Patients from the second 9-week trial (N = 240) received 200-mg doses of modafinil daily for 1 week, followed by 400-mg doses the following week. Investigators and patients then determined the most appropriate dose, and patients maintained treatment with that dose throughout the the trial if possible. Efficacy was assessed using the physician-rated Clinical Global Impression of Change (CGI-C) and the patient-rated ESS at Weeks 2, 8, 24, and 40. Quality of life (QoL) was assessed at Weeks 4, 8, 24, and 40 using the 36-item short form health survey (SF-36). Data from the two trials were combined and all statistical comparisons were made against open-label baseline using a last-observation-carried-forward algorithm. Safety was monitored by recording AEs throughout the 40-week period.

Figure 1

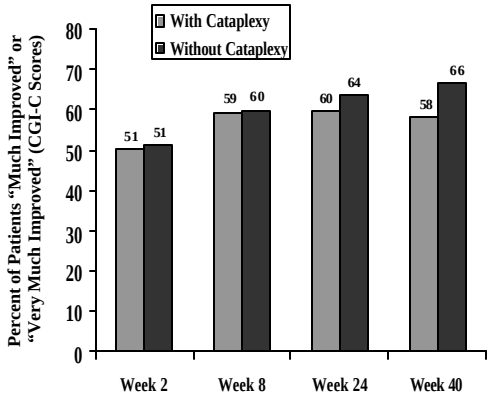
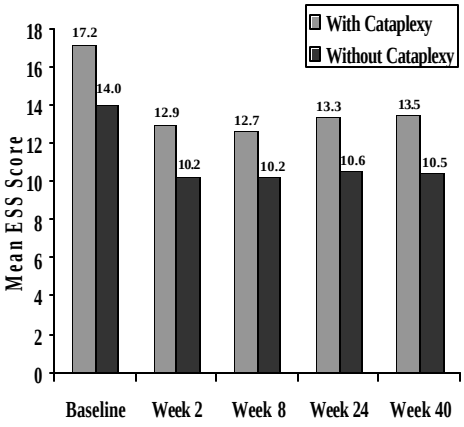


Figure 2



Results: The mean age of the patients was 42 years, and 75% of patients were considered to be moderately to markedly ill at baseline. Virtually all patients (99%) reported narcolepsy-associated EDS, and 384 patients (80%) had a history of cataplexy. Overall, 60% to 95% of patients reported the presence of other symptoms typically associated with narcolepsy. 341 of 478 patients (71%) completed the open-label trials. At Week 2, 51% of patients with cataplexy and 51% of patients without cataplexy were rated as "much improved" or "very much improved" according to CGI-C scores (Figure 1). At the end of the 40-week period, the corresponding percentages were 58% and 66% (P >=0.05). As shown in Figure 2, the mean ESS scores at open-label baseline were significantly higher (P <0.001) for patients with cataplexy (17.2) than for patients without cataplexy (14.0). During treatment with modafinil, ESS scores improved significantly in both groups of patients, but the mean changes in scores from baseline were not significantly different between patients with and without cataplexy. Throughout the study, overall mean scores were significantly improved (P <0.01) in 6 of the 8 SF-36 domains: mental health, physical functioning, role emotional, role physical, social functioning, and vitality. Overall, there were no significant changes from baseline in scores for general health and overall bodily pain. Except for social functioning at Week 4, there were no significant differences in mean change-from-baseline scores between patients with and without cataplexy for any of the SF-36 domains. The most common treatment-related AEs in patients with and without cataplexy were headache (12% vs 14%, respectively), anxiety (3% vs 10%), nervousness (7% vs 9%), nausea (5% vs 5%), and somnolence (2% vs 5%). 35 patients with cataplexy (9%) discontinued treatment due to AEs compared with 7 patients without cataplexy (8%). 47 patients with cataplexy (12%) discontinued treatment due to insufficient efficacy compared with 8 patients without cataplexy (9%).

Conclusions: Long-term treatment with modafinil is effective and well tolerated in patients with narcolepsy with and without a history of cataplexy. Although baseline ESS scores were significantly higher in patients with cataplexy than in patients without cataplexy, the efficacy and safety profiles of modafinil were similar between the two groups of patients.

Research supported by Cephalon, Inc., West Chester, PA

1330.K2

Effect of PROVIGIL® (Modafinil) on Nighttime Sleep in Patients with Narcolepsy

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Introduction: Modafinil (200 and 400 mg/day), a novel wake-promoting agent, is effective and generally well tolerated in the treatment of excessive daytime sleepiness (EDS) in patients with narcolepsy. The 15-hour half-life of oral modafinil supports the recommended once-daily dosing in the morning. In two 9-week, randomized, double-blind, placebo-controlled, multicenter trials of the efficacy and safety of modafinil, nocturnal polysomnography (NPSG) data were collected to determine the effect of modafinil on nighttime sleep parameters in patients with narcolepsy.

Methods: Patients with a diagnosis of narcolepsy, according to criteria established by the International Classification of Sleep Disorders, were recruited for two 9-week, randomized, double-blind, placebo-controlled, clinical trials. Exclusion criteria included other disorders that could cause EDS (eg, sleep apnea, restless legs syndrome, sleep deprivation), any clinically significant disease (eg, gastrointestinal, cardiovascular, hepatic, renal, neoplastic), and use of drugs or substances with psychotropic effects, including central nervous system stimulants, within 14 days of the baseline visit (week 0). Eligible patients were randomized to receive modafinil 200 mg/day, modafinil 400 mg/day, or matching placebo approximately 30 to 45 minutes after a morning meal. NPSG data, collected during overnight clinic visits at week 0 and week 9, included sleep duration, sleep efficiency (ie, sleep duration as a percentage of time in bed), percentage of time in sleep stages 1-4 and rapid eye movement (REM) sleep, number of arousals, number of awakenings (total number and number lasting >2 minutes), and time awake after sleep onset. Adverse events (AEs) were recorded throughout the study.

Results: A total of 554 patients (mean age: 42 years; female/male ratio:

1.2/1; mean time since narcolepsy diagnosis: 8.1 years) received treatment with placebo (N=185), modafinil 200 mg (N=185), or modafinil 400 mg (N=184) in the two trials. Demographics at baseline were comparable among the treatment groups. Of these patients, 521 had at least one post-baseline NPSG assessment and were included in the analysis of nighttime sleep parameters. After 9 weeks of treatment, sleep duration, sleep efficacy, the percentage of time in REM and non-REM stages of sleep, and the number of arousals and awakenings were similar to those at baseline (week 0) for all three treatment groups (Table 1). The time awake after sleep onset at week 9 was comparable to that at baseline for placebo and modafinil 400 mg, whereas treatment with modafinil 200 mg resulted in a small but significant decrease compared with the time awake after sleep onset at baseline. The most frequently reported AEs with incidence rates that were greater for the modafinil groups than for the placebo group were headache (40% placebo, 47% modafinil 200 mg, 52% modafinil 400 mg), nausea (4% placebo, 13% modafinil 200 mg, 13% modafinil 400 mg), and rhinitis (8% placebo, 11% modafinil 200 mg, and 12% modafinil 400 mg). Only 19 patients (5%) receiving modafinil discontinued because of an AE compared with 3 patients (2%) receiving placebo.

Table 1

Parameter	Placebo		Modafinil 200 mg		Modafinil 400 mg	
	Wk 0	Wk 9	Wk 0	Wk 9	Wk 0	Wk 9
Sleep duration, min	395	393	402	399	397	394
Sleep efficacy	85%	87%	87%	88%	88%	88%
% of sleep time						
Stages 1-4	77%	78%	77%	76%	77%	77%
REM stage	23%	22%	24%	23%	23%	23%
No. arousals	83	82	77	73	80	75
No. awakenings						
Total	24	24	24	24	24	23
>2 min	6	6	5	5	5	5

Conclusions: Treatment with modafinil 200 mg/day or 400 mg/day had no effect on the quantity, quality, or architecture of nighttime sleep in patients with narcolepsy. Modafinil was generally well tolerated, with a low rate of discontinuation of treatment because of AEs.

Research supported by Cephalon, Inc., West Chester, PA

1346.K2

Preservation of Hypocretin Neurons in Genetically Narcoleptic Dogs

Thannickal TC, Nienhuis R, Ramanathan L, Gulyani S, Turner K, Chestnut B, Siegel JM

Introduction: Lin et al[1] recently reported that a mutation in the gene encoding the hypocretin 2 receptor in narcoleptic Dobermans pinschers and Labrador retrievers. We have previously reported[2] degenerative changes in basal forebrain, septal and amygdala regions of narcoleptic Dobermans. The areas of degeneration are within the projection fields of the hypocretin cell groups. One plausible hypothesis uniting Lin et al's finding and our degeneration finding is that the hypocretin neurons themselves are degenerating. To test this hypothesis, we have counted and mapped the hypocretin neuronal population in four narcoleptic and four control Doberman pinschers.

Methods: Sections were incubated in the primary antisera [rabbit polyclonal Orexin A and rabbit polyclonal Orexin B; 1mg/2ml, (Oncogene Research products, Orexin A (Ab-1) and Orexin B (Ab-1)] for 68 hr at 4°C. After this sections were incubated in the secondary antibody followed by avidin-biotin peroxidase. The tissue-bound peroxidase was visualized by the diaminobenzidine reaction.

Results: Cells were counted "blind" on a Neurolucida computerized microscope interface. In the process of staining, we noted two types of hypocretin morphology. The first type comprised cells resembling those reported in prior studies in the rat, having smooth membrane structure moderately dense staining and relatively large size (31.36±7.85 m). The second had a more darkly stained cytoplasm, irregular membrane outline and was on average relatively smaller (19.72±3.31 m). Although the two types of cells were intermixed, the first type was generally found more dorsolaterally and the second ventromedially. We found no difference in the number of hypocretin cells of either type in narcoleptics vs. controls. We see no significant correlation between age or sex and total cell number or with the number of type one vs. type two cells.

Conclusions: We see no abnormality in the number or distribution of hypocretin cells in narcoleptic dogs. This indicates that : 1. The receptor mutation does not cause significant degeneration of hypocretin cells. 2. Degeneration of hypocretin cells is not the source of the axonal fragments that we have seen in the amygdala and basal forebrain of narcoleptic dogs at the time of symptom onset.

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1709.K2

Polysomnographic Characterization of Orexin-2 Receptor Knockout Mice

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Introduction: Neurons containing the neuropeptide orexin (hypocretin) are located exclusively in the lateral hypothalamus and send axons to numerous regions throughout the central nervous system. We have recently reported that *orexin* knockout mice exhibit a marked disruption of sleep-wakefulness regulation remarkably similar to human narcolepsy.[1] Further, a mutation in the *orexin-2 receptor* gene was recently reported to be responsible for canine narcolepsy.[2] Here we report the polysomnographic characterization of *orexin-2 receptor (OX2R)* knockout mice.

Methods: *OX2R* knockout mice were produced by homologous recombination in embryonic stem cells using standard methods. Six homozygous and 6 wildtype littermates, 18 to 22 weeks of age, were prepared for chronic monitoring of EEG/EMG signals using the technique we have previously described[1]. All mice recovered from surgery and habituated to the recording conditions for a minimum of 14 days before recording began. Each mouse was recorded for 3 consecutive 24 hr periods, beginning at 07:00. EEG/EMG records were visually scored into 20 sec epochs of Awake, REM and non-REM sleep according to standard criteria of rodent sleep.

Results: Sleep state parameters and hypnograms for the 12 hr light phase were almost indistinguishable between the *OX2R* knockout and wildtype mice. However, marked disruption of sleep-wakefulness regulation was evident in the hypnograms (Figure 1) and vigilance parameters (Table 1) of the knockout mice during their active dark phase. *OX2R*

knockout mice exhibit increased non-REM sleep and a decrease in awake time. The mean duration of these states is also reduced, associated with an increase in episode frequency, illustrating the marked overall fragmentation of their sleep-wake cycles. REM latency is reduced, but only a small difference in other REM parameters was observed.

Figure 1. Representative 6 hr dark period hypnogram for a wild-type and homozygous knockout mouse.

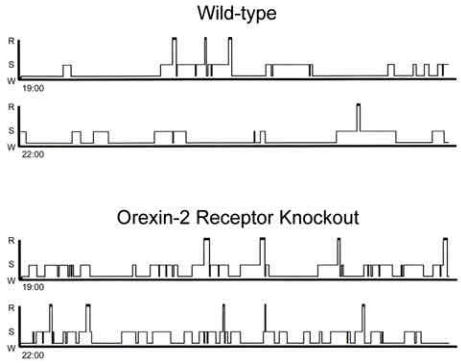

Table 1. Vigilance state parameters recorded from orexin-2 receptor knockout mice and wild-type controls (mean ± SEM)

	-/-	+/+
REM Sleep		
Total Time (min)	30.4 ± 2.5	25.6 ± 3.6
Duration (sec)	81.6 ± 5.5	84.6 ± 2.7
Frequency (hr)	1.61 ± 0.3	1.35 ± 0.4
REM latency (min)	6.1 ± 0.5	8.5 ± 0.8
REM interval (min)	29.3 ± 2.4	35.8 ± 4.4
Non-REM Sleep		
Total Time (min)	319.2 ± 20.1	270.0 ± 32.6
Duration (sec)	218.8 ± 29.2	279.1 ± 10.4
Frequency (hr)	5.46 ± 0.9	3.48 ± 0.7
Awake		
Total Time (min)	369.1 ± 22.2	423.1 ± 33.9
Duration (sec)	252.6 ± 23.9	489.0 ± 93.8
Frequency (hr)	4.97 ± 1.0	2.74 ± 0.5

Conclusions: Sleep-wakefulness in *orexin-2 receptor* knockout mice is characterized by increased non-REM sleep and decreased awake time with rapid state cycling during the dark period. This pattern is very similar to that observed in the *orexin* knockout mice. However, while shortened REM latency is similar between the ligand and receptor knockouts, ligand knockout mice have more severe REM sleep disturbance with an increased REM sleep time, REM duration, and a more shortened REM interval. This suggests a possible role for the orexin-1 receptor in regulating sleep-wakefulness.

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1381.K2

Cataplexy After the Electrical Stimulation of the Pontine Inhibitory Area in the Narcoleptic Dog.

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Introduction: Narcolepsy is a debilitating sleep disorder with excessive sleepiness and abnormalities of motor control. Cataplexy is a symptom of narcolepsy characterized by an abrupt loss of muscle tone during sudden strong emotions. The pontine inhibitory area (PIA) has been implicated in the coordination of locus coeruleus and medullary mechanisms mediating muscle tone suppression. We have investigated whether stimulation of the PIA could elicit muscle atonia and cataplexy in the freely moving narcoleptic dog. We also studied whether a cholinergic antagonist or alpha-1 agonist that blocked food-induced cataplexy could block the behavioral effect of stimulation.

Methods: This study was carried out on three genetically narcoleptic Doberman pinschers. Under isoflurane anesthesia, concentric bipolar stimulating electrodes were implanted bilaterally into the PIA (A 5, H 7, L 4). As a control, stimulating electrodes were implanted into locus coeruleus (LC) and parabrachial area (PB). Electrodes for recording electroencephalogram (EEG) electrooculogram (EOG) electromyogram (EMG) and hippocampal activity were also implanted (Siegel et al., 1991). Electrical stimulation of the PIA was done (100 μA-400 μA, 0.2 msec, 100 Hz, 300 ms duration trains every 2 sec) bilaterally. The effect of the stimulation was also studied after pretreatment with muscarinic antagonist atropine sulfate (100-120 μg/kg, i.v.) or alpha-1 agonist methoxamine (400 μg/kg, i.m.).

Results: Bilateral electrical stimulation of the PIA produced cataplexy in freely moving narcoleptic dogs. At 200-400 μA, the dog became alert, and during the last phase of the 30-120 sec stimulation period it went into a cataplexy state as defined by electrophysiological and behavioral criteria. Stimulation-induced cataplexy continued for 2-10 minutes after the end of stimulation. This cataplexy state was similar to food-induced cataplexy, during which the animal was able to respond to sensory stimulation with orientation or arousal. However, the stimulation-induced cataplexy was consistently longer duration with greater muscle relaxation than food- or play-induced cataplexy seen in the same animals. Power spectral analysis of the hippocampal EEG showed a similar spectrum, with predominance of theta activity, during food and electrical stimulation-induced cataplexy. The power spectrum during cataplexy differs significantly from the spectrum of quite waking. The dog did not show a behavioral response to electrical stimulation of PIA during either elicited or spontaneous cataplectic states. However, stimulation during non-REM and REM sleep produced arousal. Pretreatment with the same dose of atropine that blocked food induced cataplexy did not prevent, but significantly ($P<0.01$) reduced the duration of the post-stimulus cataplexy state (from 216.77 ± 34.9 to 76.7 ± 18.7 sec). Methoxamine blocked both the stimulation-induced increase in theta activity and cataplexy. Unilateral stimulation of the PIA did not produce cataplexy. In the control studies, stimulation of LC and PB produced arousal and increased muscle tone but did not induce cataplexy.

Conclusions: Our finding shows that activation of the PIA induced cataplexy in the behaving narcoleptic dog. We hypothesize that activation of cholinoceptive glutamatergic neurons in the PIA that project to the nucleus magnocellularis of medulla may be responsible for the PIA stim-

ulation-induced cataplexy. Our study suggests that activation of LC cells may block the effect of the PIA stimulation. Stimulation elicited cataplexy may be a useful tool for the analysis of the neural substrates of muscle atonia and cataplexy induction in canine narcolepsy.

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1724.K2

Clinical and Genetic Aspects of Narcolepsy and Cataplexy Across Ethnic Groups

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Introduction: Narcolepsy is associated with HLA-DR2 and DQB1*0602 across ethnic groups, suggesting a common etiology for the disorder that transcends cultural boundaries. The core symptoms of narcolepsy occur in all cultures but their clinical expression, frequency and severity have never been compared across ethnic groups and in relation to HLA status. Investigators in Japan, North America and Europe have long stressed that cataplexy is the only pathognomonic symptom of the narcolepsy syndrome. HLA positivity is high (e.g. 90-100%) in patients with definite cataplexy and decreases dramatically in subjects with no cataplexy (40%), suggesting etiological heterogeneity in narcoleptic subjects without cataplexy. Even in cataplectic patients however, substantial differences in HLA association have been reported (70-100%). This has lead investigators to believe that cataplexy may be overdiagnosed in some cases. A possible explanation for this problem may be the imprecise definition of cataplexy currently listed in international classifications. Recent studies have shown that up to 30% of the non-narcoleptic population reports "muscle weakness episodes triggered by emotions", the current ICSD 10 definition for cataplexy. To address the problem of a less subjective definition for cataplexy, we recently validated a questionnaire focusing on cataplexy and found that cataplexy was best defined when triggered by a particular pattern of emotions. In this study, we used well-characterized Stanford narcolepsy database patients to compare the clinical features of narcolepsy and cataplexy across ethnic groups. A second aim of the study was to correlate HLA typing data with our previously validated questionnaire-based definition of cataplexy in a large number of subjects.

Methods: Four hundred fourteen unrelated subjects (183 males and 231 females) with narcolepsy and cataplexy were studied. These subjects were randomly recruited at the Stanford University Center for Narcolepsy Research. Subjects included 314 Caucasian, 60 Black and 40 patients of other ethnicities. All subjects had completed the Stanford Sleep Inventory and provided a blood sample for HLA typing. Epworth sleepiness scale scores and MSLT data were used to assess daytime sleepiness. The presence and frequency of sleep paralysis and hypnagogic hallucinations were assessed from the questionnaire. The decision tree proposed by Anic-Labat et al, (1999) was used to categorize cataplexy (category 1: episodes not triggered by either laughing or joking; category 2: episodes triggered by joking but not by anger or episodes triggered by laughing alone; category 3: episodes triggered by joking and anger). Self reported ages of onset for these symptoms were also compiled. All parameters were then compared between sex and ethnic groups.

Results: None of the parameters examined differed between sex and ethnic groups. The distribution of the cataplexy codes was similar across sex and ethnic groups, with approximately 45% of the subjects reporting category 3 cataplexy, triggered by joking and anger. This distribution is similar to that initially reported in 63 narcoleptic subjects during the cataplexy validation study of 983 subjects (Anic-Labat et al, 1999). Cataplexy severity and age of onset (19.1 years) were also similar between groups. Sleepiness as assessed by the Epworth Sleepiness Scale or MSLT data did not differ across groups. Sleep paralysis occurred in 66-78% of subjects, with a mean age of onset of 20.8 years. Hypnagogic hallucinations occurred in 67-75% of subjects, with a mean age of onset of 18.9 years. The percentage of subjects who tested positive for HLA-DQB1*0602 was 77% (309) in Caucasians, 86% (60) in Blacks and 80% (40) in "others". The most striking result was the observation that HLA positivity strongly correlated with the cataplexy code as defined by Anic-Labat et al. (1999). Whereas the DQB1*0602 percentage did not differ between ethnic groups, only 47% of category 1 cataplexy were HLA positive when compared to 78% in category 2 and 93.4% in category 3. These differences were highly significant ($X2 = 65.0$, $p = 0.00001$).

Conclusions: The clinical characteristics of narcolepsy-cataplexy were compared across sex and ethnic groups and found to be literally identical across groups. We also used this large sample of subjects to correlate HLA typing data and cataplexy categories as defined by questionnaire analysis of self-reported emotional triggers. Our results indicate that almost all (93.4%) subjects with cataplexy triggered by joking and anger (45% of all narcoleptic subjects, category 3) were HLA positive. In contrast, most subjects reporting the least specific cataplexy-like episodes of muscle weakness (not triggered by laughter or anger, 16% of all narcoleptic patients, category 1) were HLA negative (53%). The HLA typing data correlated tightly with the Anic-Labat decision tree, suggesting that an increasing number of subjects with physiological episodes of muscle weakness are included in the less specific cataplexy categories. We believe classifying cataplexy into these three categories may facilitate further clinical and genetic research.

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1730.K2

Effects of Thalidomide Analogs on Cataplexy and Sleep in Canine Narcolepsy

Nishino S, Riehl J, Hong J, Mignot E

Introduction: We recently found that thalidomide (a-N-phthalimidoglutarimide) dramatically exacerbates cataplexy in narcoleptic dogs.[1] Since thalidomide never induces cataplexy-like behavior in normal dogs, it is likely that the mode of action of thalidomide on cataplexy is specifically involved in the pathophysiology of narcolepsy. It is known that thalidomide has sedative-hypnotic and anti-inflammatory (tumor necrosis factor alpha [TNF-alpha] inhibition or PDE4 inhibition) properties,[2] and some of these properties could be specifically involved in the cataplexy-enhancing effect of thalidomide. Several thalidomide analogs lacking some of these properties are now available for experimental use.[2] The effects of various thalidomide analogs on cataplexy and sleep were therefore tested in narcoleptic dogs to determine the pharmacological property most likely to be involved in the cataplexy- and sleep-enhancing effects of thalidomide.

Methods: Five thalidomide analogs (CC-1069, CC-1088, CC-4047, EM-12 and CC 6022; 0.5 to 4.0 mg/kg i.v.) and 3 non-thalidomide reference compounds (pentoxifylline, TNF-alpha inhibitor, 0.5 to 4.0

mg/kg i.v.; glutethimide, a sedative-hypnotic structurally similar to thalidomide, but without a phthalimide ring, 0.5 to 4.0 mg/kg i.v.; and rolipram, a phosphodiesterase-4 (PDE4) inhibitor, 0.4 to 25 µg/kg i.v.) were administered to 6 narcoleptic Dobermans, and effects of compounds on cataplexy were evaluated using the Food Elicited Cataplexy Test. Effects of EM-12, CC1088, glutethimide and pentoxifylline on 6 hour daytime sleep in 3-5 implanted narcoleptic Dobermans were also evaluated.

Results: CC-1088, which is 5 times more active in inhibiting TNF-alpha than thalidomide, dose-dependently aggravates cataplexy. CC-1069, another potent TNF-alpha inhibitor, (up to 4 mg/kg) was tested in 2 animals. An increase in cataplexy was observed in one animal (at 4mg/kg i.v), but this dose induced convulsions in another animal. Pentoxifylline, CC-4047 and CC-6020 inhibit TNF-alpha production, but did not modify cataplexy. EM-12, an analog with immunomodulatory properties and sedative effects, and glutethimide were inactive. Rolipram also had no effect on cataplexy. EM-12 and glutethimide dose-dependently increased sleep in narcoleptic dogs, while CC-1088 had little effect on sleep. Pentoxifylline had no sleep-altering effect.

Conclusions: TNF-alpha inhibition is believed to be one of the key pharmacological properties mediating the anti-inflammatory effects of thalidomide, and this property could also be involved in the cataplexy- and sleep-enhancing effects of thalidomide. However, pentoxifylline, CC-4047 and CC-6020 inhibit TNF-alpha production, but did not modify cataplexy. Some thalidomide analogs have PDE4 inhibitory properties, and PDE4 inhibition is known to decrease TNF-alpha production. However, Roliprom, a PDE4 inhibitor, did not aggravate cataplexy. Thus, neither TNF-alpha nor PDE4 inhibition is likely to be involved in the cataplexy-aggravating effect of thalidomide. EM-12 and glutethimide (structurally similar to thalidomide, but lacking a phthalimide ring) dose-dependently increased sleep, while CC-1088 had little effect on sleep. Pentoxifylline also had no effect on sleep. These data suggest that the sleep-inducing effects of thalidomide may be independent from immunomodulatory effects, and may rather be related to the glutamide ring. Although the effects on cataplexy can be differentiated from the sleep-inducing effect of thalidomide analogs, the cataplexy aggravating mechanisms of thalidomide are still unknown. The results of this study, however, are informative in the development of hypnotics that lack immune-modulating properties, as well as in the development of immunomodulatory thalidomide analogs that have no sedative effects.

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1741.K2

Hypocretin Neurons in Narcoleptic and Control Dobermans

Okura M, Ripley B, Fujiki N, Mignot E, Nishino S

Introduction: We discovered that mutations in the hypocretin receptor-(Hcrtr 2) 2 gene cause narcolepsy in Dobermans and Labradors.[1] Hypocretins (orexins) are novel neuropeptides and hypocretin –1 and -2 are derived from the same precursor peptide (prepro-hypocretin) by proteolytic processing. They bind and activate two related G-protein-coupled receptors, termed Hcrtr 1 and Hcrtr 2. Hcrtr 1 is selective for hypocretin-1 whereas Hcrtr 2 has equal affinity for both hypocretin-1 and -2. Prepro-hypocretin mRNA and immunoreactive hypocretin-1 and hypocretin-2 neurons are specifically localized within and around the lateral hypothalamic area (LHA) in the adult rat brain.[2] A previous study in narcoleptic Dobermans showed that the mean age of onset of cataplexy is 9.7 weeks and that severity increased up to 1 year, reaching a plateau at 16-24 weeks of age. This suggests that the pathological process slowly establishes itself while the brain is maturing and that it takes several months to fully establish the complete narcolepsy phenotype.[3] In this study, we hypothetized that morphological and quantitative changes in hypocretin neurons and their projections due to the disruption of Hcrtr-2 during the development may be critical in establishing narcolepsy. To test this hypothesis, we immunocytochemically stained hypocretin neurons in narcoleptic and control dogs and compared both quantity and morphology of neurons between the two groups.

Methods: Two narcoleptic Dobermans (32 months, two males) and two control Dobermans (38.5 months, one male and one female) were used. Brains were perfused transcardially (saline with heparin, followed by ice-cooled 4% paraformaldehyde and picric acid in 0.1M phosphate buffer saline). Following perfusion, brains were removed, post-fixed, dissected into blocks, and cryoprotected in 30% sucrose, 0.1 M PGS, 0.1% sodium azide . Selected blocks were frozen and cut on a cryostat into 30 mm sections. Immunohistchemical detection of hypocretin was done by sequential incubations of free-floating sections in either anti-hypocretin 1 antiserum (Phoenix Pharmaceuticals, CA) or mouse/rat hypocretin-2 antibodies (ALPHA DIAGNOSTIC, TX), followed by biotinylated goat anti-rabbit IgG, and finally, by the Vecstain Elite ABC-Peroxidase Kits (Vector Laboratories Inc., CA). Sections were mounted on slides and were observed with an Olympus BH-2 microscope.

Results: Hypocretin-1 and hypocretin-2 immunoactive neurons are specifically localized in neurons in the perifornical nucleus and dorsal and lateral hypothalamic areas in adult control dog brains. In narcoleptic brains, neurons are also positively stained and hypocretin immunoactive neurons similarly localized. Gross microscopic inspection shows no clear difference in morphology, number, or distribution of neurons in narcoleptic and control dog brains. Quantitative analysis using computer imaging is now in progress.

Conclusions: We have demonstrated that hypocretin neurons are normaly distributed no difference in adult narcoleptic and control dogs. This suggests no massive cell death or proliferation in hypocretin neurons in receptor-2 mutated animals. This also corresponds with the finding that hypocretin-1 is detectable consistently in narcoleptic Dobermans at levels similar to those found in control Doberman CSF (Ripley et al, in this issue), and further suggests that hypocretin receptor-1 mediated function is intact in these narcoleptic animals. Distribution of Hcrtr1 and Hcrtr2 mRNA was recently reported and the results clearly demonstrated that the two receptors are differentially localized: Hcrtr-1 mRNA is abundant in the dorsal raphe and locus coeruleus, while Hcrtr-2 mRNA is localized in the nucleus accumbens, mamino thalamic tract, SN and VTA (Lu et al., personal communication). Considering the fact that Hcrtr-2 are enriched in DA nucleus and terminals, Hcrtr-2 mediated neurotransmission on the DA system may be critical for the expression of narcoleptic symptoms. It is thus interesting to study whether there is a change in morphology and quantity of hypocretin neuronal projections to these brain structures in narcoleptic Dobermans

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1413.K2

Narcolepsy and Hypocretin: Searching for Novel Intracellular Partners for Hcrtr2

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Introduction: Recent studies have shown that genetic alterations in the hypocretin (orexin) gene[1] and the hypocretin receptor-2 (Hcrtr2) gene[2] produce a narcolepsy phenotype in mice and dogs, respectively. These data indicate that the Hcrtr2 mediates the most important features of the narcolepsy phenotype. Intracellular signals of Hcrtr2 are likely to be primarily mediated by a G-protein pathway, but studies of other receptor systems suggest other intracellular factors may also be involved. A better understanding of the intracellular signaling of Hcrtr2 could thus lead to novel molecular targets for sleep regulation. A potential tool to isolate novel partners is the yeast two-hybrid system, an in vitro system detecting protein-protein interactions. In this study, we have used the two-hybrid system to isolate potential intracellular partners for this receptor, focussing on the region of Hcrtr2 least homologous to Hcrtr1.

Methods: An intracellular part of mouse Hcrtr2 (Hcrtr2C) was subcloned into a yeast expression vector pGBKT7. A yeast two-hybrid screen was carried out using a GAL4 activation domain fusion library in yeast expression vector pACT2. Interacting proteins were isolated by growth selection on amino-acids dropout plates and by alpha-galactosidase assays. To confirm specificity of the interacting plasmids, the alpha-galactosidase-positive clones were recovered and retransformed into yeast, and then the yeast was mated with another yeast expressing pGBKT7-Hcrtr2C or pGBKT7 alone.

Results: 1.2x10e7 library clones were screened by yeast mating to identify interaction between pGBKT7-Hcrtr2C and library-pACT2. 735 candidate clones were selected form growth on plates lacking tryptophan, leucine, and histidine. 480 clones remained after subsequent selection on plates lacking tryptophan, leucine, histidine and adenin. 73 alpha-galactosidase-positive clones were recovered and retransformed. 20 colonies were verified positive two-hybrid interactions, because they showed interaction not with pGBKT7 but with pGBKT7-Hcrtr2C. Co-immunoprecipitation study and candidate expression studied are underway to examine if these interactions are functional in vivo.

Conclusions: The two-hybrid system is a tool to isolate potentially novel target genes within a pathway of interest. We hope further characterization of the candidate proteins presented above will lead to identify novel intracellular Hcrtr2 pathways of importance in sleep regulation.

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1749.K2

Switching to PROVIGIL (Modafinil) From Methylphenidate in Patients with Narcolepsy: An Open-label Safety Study to Assess the Optimum Strategy

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Introduction: Modafinil, a novel wake-promoting agent, has been shown to be an effective and generally well-tolerated treatment for excessive daytime sleepiness (EDS) in patients with narcolepsy. The traditional psychostimulants used in the management of EDS in narcolepsy, including methylphenidate, dexamphetamine, and pemoline, have been associated with untoward side effects, tolerance, and the potential for abuse. With the availability of modafinil, patients with EDS associated with narcolepsy who are not satisfied with or are unable to tolerate treatment with traditional stimulants may be candidates for a switch to modafinil therapy. This 5-week, randomized, open-label study was designed to evaluate the optimum strategy for switching patients from methylphenidate to modafinil.

Methods: Adult patients with a diagnosis of narcolepsy, according to criteria established by the International Classification of Sleep Disorders, who had been receiving treatment with 10-60 mg/day methylphenidate immediate-release formulation for at least 1 month and who provided written informed consent were eligible for inclusion in a 5-week, randomized, open-label study. Exclusion criteria included active significant gastrointestinal, cardiovascular, hepatic, renal, hemologic, neoplastic, endocrine, or neurologic disease; obstructive respiratory disease; systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg; or a history of alcohol, narcotic, or any other drug abuse. Patients meeting the inclusion and exclusion criteria were randomized to one of the following three treatment groups: 1) No Washout Group (Group A), who received methylphenidate on days 1-14 at the dosage previously prescribed (final dose on day 14 was taken no later than 4 pm), followed by treatment with modafinil 200 mg/day on days 15-21 and modafinil 400 mg/day on days 22-35; 2) Washout Group (Group B), who received methylphenidate on days 1-12 at the dosage previously prescribed (final dose on day 12 was taken no later than 4 pm), followed by a 2-day treatment washout period, treatment with modafinil 200 mg/day on days 15-21, and treatment with modafinil 400 mg on days 22-35; and 3) Taper Group (Group 3), who received methylphenidate on days 1-14 at the dosage previously prescribed, followed by a 20%-40% reduction in the methylphenidate dose on day 15, the same methylphenidate dose plus modafinil 200 mg on day 16, an additional 20%-40% reduction in the methylphenidate dose on day 17 plus modafinil 200 mg, modafininil 200 mg only on days 18-21, and modafinil 400 mg on days 22-35. Adverse events were recorded throughout the study.

Results: A total of 35 patients (mean age: 41 years; 51% female, 49% male) were randomized to treatment (Group A, n=11; Group B, n=12; and Group C, n=12). For days 15-21 of the study, the overall incidence rate of newly reported adverse events and new adverse events that occurred in more than 1 patient for each of the three treatment groups are listed in Table 1. The most commonly reported adverse event in each treatment group was headache (27% of patients in Group A; 36% of patients in Group B; and 25% of patients in Group C). Nervousness and insomnia each occurred in 2 patients (17%) in Group C (tapered treatment). For the three treatment groups, the adverse events were transient and mild (87%) or moderate (13%) in nature. During the washout phase in Group B, 1 patient experienced increased sleepiness and 1 patient experienced insomnia. Only 1 patient (Group B) discontinued treatment

because of an adverse event (moderate headache). No serious adverse events were reported.

Table 1

	Group A (n=11)	Group B (n=12)	Group C (n=12)
No. patients with AEs	4 (36%)	5 (42%)	8 (67%)
Total no. of AEs	11	9	14
AEs*			
Headache	3 (27%)	4 (36%)	3 (25%)
Nervousness	0	0	2 (17%)
Insomnia	0	0	2 (17%)

* Adverse events reported by >1 patient in any group

Conclusions: The results of this study suggest that in patients with narcolepsy the switching of treatment from methylphenidate to modafinil is generally well tolerated by those who are switched without a washout period, those who have a washout period between the two treatments, and those whose methylphenidate dose is gradually tapered during the initiation of modafinil therapy.

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1761.K2

Analysis of Onset Location, Laterality and Propagation of Cataplexy in Canine Narcolepsy

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Introduction: Narcolepsy with cataplexy is a more homogeneous etiological subset of the disorder, and it is argued by several authors that the presence of cataplexy is required to confirm the diagnosis of narcolepsy.[1] A better understanding of the mechanisms for triggering cataplexy is thus critical in understanding the pathophysiology of narcolepsy. However, no systematic studies have focused on varying characteristics of cataplexy in human narcolepsy. This is partially due to the fact that most patients are moderately affected with cataplexy, coupled with the fact that cataplectic attacks are difficult to provoke in a clinical setting. In contrast, narcoleptic Dobermans are greatly affected with cataplexy, and attacks can be easily elicited with emotional stimuli (presenting food or play). In the current study, we analyzed the occurrence and propagation of cataplexy, utilizing both behavioral and electrophysiological analyses, in genetically narcoleptic Dobermans.

Methods: Ten Narcoleptic Doberman pinschers (2 male and 8 female, means of age 3.7 years) were used in this study. Cataplexy attacks were elicited by the Food Elicited Cataplexy Test and Play Elicited Cataplexy Test. One hundred or more observations of cataplectic attacks were collected from each dog and analyzed for 3 parameters: 1) Onset location (classified into 8 patterns: neck while standing, front legs, front left leg, front right leg, rear legs, rear left leg, rear right leg, or complete, namely, attack in all four legs and the neck). 2) Bilaterality. 3) Propagation. Data for each parameter is presented as means of the 10 dogs studied. We also confirmed the typical pattern of occurrence seen by behavioral bioassay with electromyography (EMG) recordings from neck, right and left deltoid, and right and left gluteus muscles with surface electrodes and/or disposable bipolar needle electrodes.

Results: Onset location: 80 % of all attacks began in the rear legs. 8 % and 6 % began in the front legs or the neck while standing, respectively. 6 % were complete attacks. Bilaterality: 98 % of attacks showed bilateral onset. There was no difference between right and left side occurrence in all unilateral attacks (2 % total). Propagation: 49 % of attacks were propagating. The most common propagating attack progressed from rear legs to front legs and, finally, to neck (48 % of all propagating attacks). The second most common pattern was rear legs to front legs (23 %). Of non-propagating attacks, 79% involved the rear legs bilaterally, and 15 % were complete attacks. Additionally, bilateral occurrence was seen 94 % and 99 % in propagating and non-propagating attacks, respectively.

Conclusions: Results suggest that most cataplectic attacks are bilateral and are initiated in the rear regs; this is similar to clinical features noted in humans. As reported in some humans,[1] walk during cataplexy is also seen in dogs, and was a result of incomplete atonia or atonia in the process of being propagated. It is interesting to note that atonia during propagation is most often bilateral. Studies using narcoleptic canines have demonstrated that dopamine autoreceptor stimulation at the level of the midbrain and diencephalone dopominergic nucleus is critically involved in the induction of cataplexy.[2] Thus, emotionally-related, bilaterally-projecting signal pathways to these structures[3] may be important for the induction of cataplexy.

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1111.K2

Sleepy, DR2 Positive Children in North China have Narcolepsy

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Introduction: Narcolepsy is usually recognized after the second decade of life and childhood presentations are uncommon. Normative values for the multiple sleep latency test (MSLT) criteria are problematic in children because maturational factors affect circadian rhythm and sleep wake behavior. This report describes polysomnography (PSG) and human leukocyte antigen (HLA) test results in a group of sleepy, HLADR2 positive children.

Methods: Between September 1998 and September 1999, 26 (20 male, 6 female, 6~16 years) patients in approximately one million outpatient visitors to Beijing Children's Hospital in North China were suspected of having narcolepsy because of a chief complaint of excessive daytime sleepiness and a positive finding for HLADR2. Patients then underwent brain CT scan and MRI test, as well as examination by a pediatric neurologist. After the clinical interview with the patients and their parents, all the children received a MLST test following a routine night's sleep. Three who reported occasional snoring also underwent nocturnal PSG. HLADRB1*15, HLA DRB1*1501 and HLA DQB1*0602 typing were performed on 16/26 using polymerase chain reaction assays (DRB1*15 and DRB1*1501, SSP UNITRAY TM, PEL-FREEZ Clinical Systems, LLC; FASTYPETM - DQB1SSP, BIO-SYNTHESIS).

Results: In all patients there was no reported history of neural disease nor drug use. Brain CT scan and MRI showed no structural abnormalities. Cataplexy was present in 100% of the cases; sleep paralysis in 36%; and hypnagogic hallucinations, in 64%. Psychosocial problems including emotional irritability and social isolation were present in 96% of the patients. Twenty-one of 22 school children (96%) had academic problems; 3 discontinued school by the time of diagnosis. Twenty-four of the

26 patients were normal or below normal for weight; two children had body mass index of 33kg/m2 and 31.1kg/m2. There was no family history of narcolepsy. The MSLT indicated a mean sleep latency of 1.7 minutes. Sleep-onset rapid eye movement (SOREM) occurred during 2/5 naps in all patients and 3/5 in 25/26 patients. The average number and latency of SOREM episodes were 4.5 episodes and 4.3 minutes, respectively. Nocturnal PSG did not disclose sleep apnea hypopnea syndrome in the three snorers. Those 16 who underwent locus testing were 100% HLADRB1*15, HLADRB1*1501 and HLADQB1* 0602 positive, higher than that found in 107 of a random North Chinese population (HLADR2, 19%; HLADRB1*15, 18%; and HLADQB1* 0602, 12%).

Conclusions: There exists a small group of children characterized by sleepiness and HLADR2 positivity that often exhibit cataplexy and ³2 SOREM on MSLT. HLADQB1*0602 positivity is also present to a greater extent than expected in the general population of North China. In these individuals the presentation for narcolepsy is identical to that reported in older age groups.

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POSTER PRESENTATIONS

1142.K2

Change From Conventional Stimulants to Modafanil in Patients with Narcolepsy or Idiopathic Hypersomnia

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Introduction: Modafanil, a novel wake promoting agent approved for the treatment of narcolepsy, appears to have fewer side effects than traditional stimulants. No formal comparison studies have been performed, but there is some evidence that modafanil may have less alerting effect than methylphenidate or amphetamines.[1] The aim of this study was to evaluate the change from traditional stimulants to modafanil in patients with narcolepsy or idiopathic hypersomnia.

Methods: All patients with narcolepsy or idiopathic hypersomnia (ICSD criteria) changed from a traditional stimulant to modafanil by one of 2 board certified sleep specialists) between February and September 1999 were identified. Charts were reviewed and data analyzed. Follow-up information was obtained by telephone.

Results: Eighteen male and 11 female patients were identified. Mean age was 37.0 years. Eighteen had narcolepsy, 11 idiopathic hypersomnia. Twenty patients were using methylphenidate, 5 methamphetamine, and 4 pemoline. Twenty-two patients reported side effects of their current medication, including 13 with mood changes. Reasons for change included side effects or short duration of action of current medications, desire to try a new medication, and new restrictions on the use of pemoline. In 20 patients the current drug was stopped and modafanil substituted, while in 9 patients, the 2 drugs were overlapped or alternated for 12-15 days. Modafanil dose was increased from 200 mg to 400 mg in all but 2 patients over 1 week to 3 months. By the time of analysis, 19 patients had discontinued modafanil (66%) while 10 (34%) continued to use it. Reasons for discontinuing were reduced efficacy compared to previous medication in 7 (37%), side effects in 6 (32%), both reduced efficacy and side effects in 5 (26%), and financial considerations in one (5%). Side effects included headache in 5, insomnia in 3 and an unpleasant urine smell in 3). No relationship was found between discontinuation or continuation of modafanil and the following factors: narcolepsy versus idiopathic hypersomnia, previous type of stimulant used, mean sleep latency on MSLT, Epworth sleepiness scale before change, or whether the original stimulant was suddenly discontinued or overlapped / alternated with modafanil. Of the 20 patients taking methylphenidate previously, all 6 who continued modafanil were on methylphenidate doses ≤60 mg daily while 11 /14 who discontinued modafanil were taking doses of methylphenidate ≥70 mg daily ($p<0.01$) (Chi-squared or Wilcoxin rank tests).

Conclusions: Despite strong motivation for changing to modafanil, 66% of our patients returned to using their original stimulant, mainly because of inadequate alertness and side effects. The only significant factor in predicting continuation or discontinuation of modafanil was the previous dose of methylphenidate. This suggests that the alerting effect of modafanil may be perceived as too weak in patients needing high doses of conventional stimulants. A possible future strategy might be to investigate combining modafanil with lower than previously used doses of traditional stimulants.

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1143.K2

Symptomatic (Secondary) Narcolepsy: Does it Occur?

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Introduction: Narcolepsy secondary to other brain disorders is a controversial entity. Case reports and short series often report diencephalic pathology. However, in many cases the relationship between narcolepsy and the underlying disease is uncertain. To reduce selection bias, we used a computerized record linkage system to identify all patients with narcolepsy and a second disorder of the central nervous system (CNS) seen at our institution.

Methods: The Mayo Clinic computerized record system was used to identify all patients seen between 1975 and 1998 with both a diagnosis of narcolepsy, cataplexy or excessive daytime sleepiness (EDS), and a diagnosis of any disorder of the CNS. Three hundred seventy four patients were identified but chart review revealed that only 18 fulfilled criteria for EDS with either cataplexy or 2 or more sleep onset REM periods on multiple sleep latency testing. These patients' histories were reviewed in detail. All but 2 patients had undergone sleep studies; both of these had clinically definite cataplexy, as did 14/17 of the remainder.

Results: Group One consisted of 9 patients whose onset of sleepiness or cataplexy occurred within 1 year of onset or diagnosis of another CNS disorder. These included 4 patients with hypothalamic-pituitary syndromes (1 sarcoidosis, 1 hypothalamic-pituitary failure of unknown cause, 1 with pituitary adenoma and 1 with a craniopharyngioma), 2 following brain irradiation (1 for a frontal lobe astrocytoma and 1 for prophylaxis in acute lymphoblastic leukemia), 1 at the time of transverse myelitis with subcortical white matter lesions on MRI, 1 within days of a hypoxic-ischemic insult following cholecystectomy, and 1 within 10 days of a closed head injury. Group Two consisted of 9 patients whose onset of sleepiness or cataplexy occurred >1 year before or after the onset or diagnosis of another CNS disorder. These included 2 patients with poliomyelitis (6 and 26 years earlier), 4 with diverse disorders all > 25 years later (Parkinson's disease, CNS lymphoma, glioma, indeterminate pontine lesion) and 3 with pituitary adenomas (1 with radiation 9

years earlier, the others 6 years after and 40 years before onset of sleepiness).

Conclusions: Four of 9 Group 1 patients had pathology in the hypothalamic-pituitary region, while the other 5 had pathology of uncertain localization. Although the time differences make a causative relationship less likely in Group 2 patients, 3 of the 9 also had pituitary adenomas. Thus this study confirms that there is occasionally a relationship between pathology in the hypothalamic-pituitary region and narcolepsy. This is of special interest because hypocretins, synthesized in the hypothalamus, are implicated in the causation of narcolepsy.[1] Our study does not provide evidence for pathology in any other brain area causing narcolepsy. The relationship to head injury remains uncertain; and case-control studies are needed to explore this further.

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1467.K2

PROVIGIL® (Modafinil) in the Treatment of Excessive Daytime Sleepiness in Narcolepsy: Effect of Previous Treatment With Stimulants on Clinical Response and Safety

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Introduction: Modafinil is a novel wake-promoting agent that is indicated for the treatment of excessive daytime sleepiness (EDS) in patients with narcolepsy. Prior to the availability of modafinil, central nervous system stimulants, such as, methylphenidate, pemoline, and amphetamine, were the principal medications for the management of EDS. Unlike stimulants, which demonstrate widespread neuronal activity in the brain in preclinical studies, modafinil acts in selective areas of the brain thought to regulate normal wakefulness. In addition, modafinil promotes wakefulness without increasing locomotor activity. The efficacy and safety of modafinil in the treatment of EDS in patients with narcolepsy have been established in placebo-controlled clinical trials conducted worldwide, including two US trials in which 558 patients were randomized to treatment. To determine the effect of prior treatment with stimulants on the efficacy and safety profiles of modafinil in the treatment of EDS in patients with narcolepsy, a post-hoc subanalysis was conducted using data from two US, 9-week, multicenter, double-blind, placebo-controlled, clinical trials of modafinil.

Methods: Data were retrospectively analyzed for two subgroups of patients (those with no history of treatment with stimulants and those who had received previous treatment with stimulants) enrolled in two US 9-week, multicenter, double-blind, placebo-controlled, clinical trials that evaluated the efficacy and safety of modafinil in the treatment of EDS in narcolepsy. Patients eligible for enrollment in these two studies were aged 18 to 68 years with an established diagnosis of nacolepsy, according to the International Classification of Sleep Disorders, and were free of all medications or substances with psychotropic effects for at least 14 days prior to exposure to modafinil or placebo. Exclusion criteria included other disorders that could cause EDS (eg, sleep apnea, restless legs syndrome, sleep deprivation) and any clinically significant disease (eg, gastrointestinal, cardiovascular, hepatic, renal, neoplastic). Eligible patients were randomized to receive modafinil 200 mg/day, modafinil 400 mg/day, or matching placebo approximately 30 to 45 minutes after a morning meal, for 9 weeks. Efficacy assessments included two objective measures of sleepiness, the Maintenance of Wakefulness Test (MWT) and the Multiple Sleep Latency Test (MSLT), and two subjective measures, the Clinical Global Impression of Change (CGI-C) scale and the Epworth Sleepiness Scale (ESS). For this analysis, efficacy measures were analyzed at baseline (week 0) and at the end of treatment (week 9) for statistical differences between patients with (PS) and those without (NS) previous treatment with stimulants. Adverse events were recorded throughout the study, and statistical differences between the PS and NS patient subgroups were analyzed.

Results: Of the 530 patients with EDS associated with narcolepsy included in the post-hoc subanalysis, 161 (30%) were newly diagnosed and had no history of treatment with stimulants (NS) and 369 (70%) had received previous treatment with stimulants (PS). In the PS subgroup, methylphenidate was the most frequently used stimulant (n = 241), followed by pemoline (n = 179) and amphetamine (n = 100). Baseline demographic characteristics of the PS and NS subgroups were generally similar for those receiving modafinil 200 mg/day, modafinil 400 mg/day, and placebo. At week 9, no significant differences in the response to modafinil treatment were demonstrated between the PS and NS subgroups as measured by the MWT (Figure 1), the MSLT, the CGI-C scale (Figure 2), and the ESS. For patients receiving modafinil (200 or 400 mg/day), the proportion of patients with a normalized mean sleep latency on the MWT (ie, greater than or equal to 12 minutes) was comparable for patients in the PS subgroup (64/244, 26%) and those in the NS subgroup (31/106, 29%). The frequency and nature of adverse events for patients receiving modafinil were similar in the PS and NS subgroups and demonstrated no significant differences.

Figure 1. MWT results at baseline and week 9 for patients with (PS) and without (NS) previous treatment with stimulants.

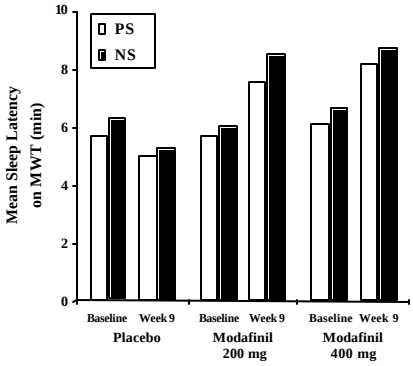
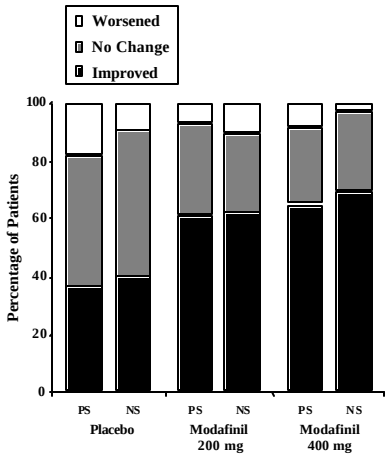


Figure 2. CGI-C results at week 9 for patients with (PS) or without (NS) previous treatment with stimulants.



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Conclusions: Modafinil is equally effective in promoting wakefulness in patients with EDS associated with narcolepsy who had received previous treatment with stimulants and in those who had no previous treatment with stimulants. Treatment with modafinil is well tolerated in patients with and those without previous therapy with stimulants.

Research supported by Cephalon, Inc., West Chester, PA

1499.K2

Long-term Efficacy, Safety, and Dosing Profile of PROVIGIL® (Modafinil) for the Treatment of Excessive Daytime Sleepiness Associated with Narcolepsy

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Introduction: Modafinil is a novel, wake-promoting agent that is chemically and pharmacologically distinct from traditional stimulants, such as methylphenidate and dextroamphetamine, and is believed to act at selective sites in the brain that regulate normal wakefulness. Unlike the traditional stimulants, modafinil does not interfere with nighttime sleep and has a very low potential for substance abuse. Two large-scale, 9-week, randomized, fixed-dose, double-blind, placebo-controlled, clinical trials conducted in the United States demonstrated that PROVIGIL® (modafinil), at doses of 200 mg and 400 mg daily, is effective and generally well tolerated for the treatment of the excessive daytime sleepiness (EDS) associated with narcolepsy. The purpose of the studies reported here was to determine the long-term efficacy and safety of modafinil in two 40-week, open-label, extension trials.

Methods: Patients with narcolepsy were eligible for enrollment in the open-label extension trials if they had completed either 9-week study or had discontinued either trial for reasons other than intolerable adverse events (AEs). Following a 2-week washout period, patients from the first 9-week trial (N = 238) were initially assigned to receive 200-mg doses of modafinil followed by flexible doses of modafinil thereafter (ie, 200 mg, 300 mg, or 400 mg). Patients from the second trial (N = 240) also underwent a 2-week washout period. These patients then received 200-mg doses of modafinil for 1 week, followed by 400-mg doses the following week. Investigators then met with the patients to determine the most appropriate maintenance dose (ie, 200 mg or 400 mg), and patients remained on that dose throughout the rest of the trial if possible. Efficacy was assessed using the physician-rated Clinical Global Impression of Change (CGI-C) and the patient-rated Epworth Sleepiness Scale (ESS) at Weeks 2, 8, 24, and 40. The effect of treatment on quality of life (QoL) was assessed at Weeks 4, 8, 24, and 40 using the Medical Outcomes Study 36-item short form health survey (SF-36). Intention-to-treat data from the two trials were combined. Statistical comparisons of ESS and QoL data were made against data obtained at open-label baseline using the Student paired t test and a last-observation-carried-forward (LOCF) algorithm. LOCF comparisons for CGI-C data were made against data obtained at Week 2 using McNemar's test. The conservative LOCF approach minimizes bias that may be introduced by excluding study dropouts. Safety was monitored by recording AEs throughout the 40-week period.

Results: The mean age of the patients was 42 years and 75% of patients were considered to be moderately to markedly ill at baseline. Virtually all patients reported narcolepsy-associated EDS, and 60% to 95% of patients reported the presence of other symptoms typically associated with narcolepsy. 341 of 478 patients (71%) completed the open-label trials. At Week 2, more than half of the patients (54%) were receiving 400-mg doses of modafinil. At Weeks 8, 24, and 40, nearly three quarters of the patients were receiving 400-mg doses of modafinil (74%, 77%, and 75%, respectively). Forty-nine percent (49%) of patients were rated as "much improved" or "very much improved" at Week 2. The percentages of patients rated as "much improved" or "very much improved" on the CGI-C scale at Weeks 8, 24, and 40 were significantly (P <0.001) greater than at Week 2 (Figure 1). The mean ESS score at baseline was 16.5. Mean ESS scores were significantly decreased from baseline at Weeks 2 through 40 (Figure 2). At Week 4, the mean change from baseline in SF-36 scores indicated highly significant (P <0.001) improvements in the domains of mental health, physical functioning, role emotional, role physical, social functioning, and vitality. Significant (P <0.05) improvement also was observed in general health; there was no significant change in bodily pain. The improvements from baseline in domain scores were maintained throughout the study except for the general health domain. The most common treatment-related AEs were headache (13% of patients), nervousness (8%), and nausea (5%). Forty-three patients (9%) discontinued treatment due to AEs (7 due to nervousness, 5 due to nausea, 4 due to anxiety, 3 due to depression). Four patients experienced serious AEs, none of which was considered to be treatment related. Fifty-five (55) patients (12%) withdrew due to insufficient efficacy.

Figure 1

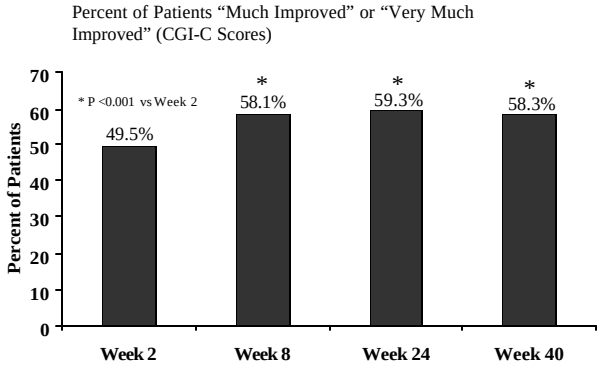
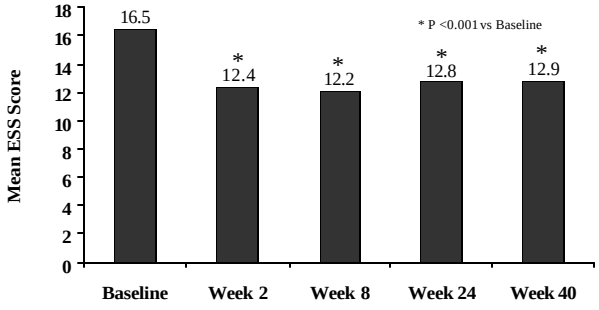


Figure 2



Conclusions: Long-term treatment with modafinil was effective and well tolerated in patients with narcolepsy. The majority of patients were receiving 400-mg maintenance doses of modafinil by Week 2, with no evidence of tolerance developing over the next 38 weeks.

Research supported by Cephalon,Inc., West Chester, PA.

1161.K2

Obstructive Sleep Apnea in Narcolepsy: The Exception or the Rule

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Ohio Sleep Medicine Institute

Introduction: Sleep apnea is thought to be infrequent in narcoleptics, and it has been common practice to exclude patients with obstructive sleep apnea (OSA) in narcolepsy research, since it is assumed that REM episodes in MSLT naps of OSAS patients are due to REM deprivation rather than narcolepsy. We previously documented a high incidence of sleep disordered breathing in narcoleptics with cataplexy.1 The focus of this study was to examine in detail those patients who did not have cataplexy but had chronic hypersomnolence and were diagnosed with narcolepsy based on the appearance of sleep onset REM periods (SOREMP) in 2 or more naps of the MSLT.

Methods: A retrospective study was performed on all narcoleptics (without cataplexy) who underwent a full night diagnostic PSG and next day MSLT at our clinic over a 4-year period. 114 patients were thus identified. 20 of these patients were excluded for the following reasons: use of psychotropic, hypnotic, or antiepileptic medication within one week prior to the PSG (n=16), having a clinical history of depression (n=3), and having a tracheotomy (n=1). The remaining 94 patients (72 men, 22 women) were further examined for a variety of sleep characteristics.

Results: Mean age was 40.4 (±14.1) and mean BMI was 30.9 (±7.4). Stage one and slow wave sleep percentage were inversely correlated ($r = -.59$, $p < .01$), and consistent with sleep fragmentation. 43 patients (45.7%) reported hypnogogic hallucination and/or sleep paralysis. The presence of subjective indicators of sleepiness (paralysis, hallucinations, automatic behaviors and morning sleep drunkenness) were present in 73% of the patients and the presence of these symptoms was positively correlated with NPSG stage REM sleep percentage ($r = .34$, $p < .01$). Objective daytime hypersomnolence was present in all patients with a mean sleep onset latency of 3.8 minutes (+2.3) during their next day MSLT's. 13 patients had their MSLT's following CPAP titration. NPSG stage REM percent (mean 18.2, ±5.4) approaches normal in this sample and is unlikely to support the claim that REM sleep deprivation is the cause of the SOREMP's in the next day MSLT. In our previous study we have found that patients with A+HI<5 and those with an A+HI³5 but <10 are clinically and statistically indistinguishable.2 Based on this categorization, 45 patients (47.9%) had an A+HI³10 (defined as the "OSA group") with the remaining 49 (52.1%) having an A+HI<10 (defined as the "Non-OSA group"). Student t-test revealed that the OSA group was significantly older ($p<.001$), more obese ($p<.001$), had higher stage one ($p<.05$) and stage two ($p<.001$) sleep percentage and had lower slow wave ($p<.001$) and REM ($p<.05$) sleep percentage. There was no significant difference between the OSA and the non-OSA group in mean sleep onset latency in the MSLT. In this entire sample (n=94), 50 patients responded to stimulant medication, 24 to CPAP alone, 15 to a combination of stimulant medication and CPAP. Of the remaining patients, 1 refused intervention and 4 chose other forms of treatment (e.g. surgical approaches).

Conclusions: These results further support our earlier observation that sleep disordered breathing is surprisingly common in patients with narcolepsy.1 Neither in this nor in our previous abstract (narcolepsy with cataplexy) did REM deprivation appear to be present in the nocturnal PSG. The Non-OSA group is similar to the OSA group in regards to sleep fragmentation and in all likelihood have Upper Airway Resistance Syndrome. Scoring of their respiratory related arousals is in progress. If a more traditional cutoff of an A+HI>5 is utilized for the diagnosis of OSA, then two-thirds of our patients with narcolepsy have obstructive sleep apnea syndrome (62 of 94), which is virtually identical to our narcolepsy with cataplexy group. This may explain the well-known nocturnal fragmentation of sleep in narcoleptics and the continuing problems with sleepiness and lack of improvement in MSLT sleep onset latency scores with CNS stimulant treatment alone. The lack of awareness of the very common co-existence of these disorders may lead to inadequate diagnosis and treatment.

References:

(1) Schmidt HS, Berendts BP. Narcolepsy and Sleep Disordered Breathing: Insights into Sleep Fragmentation and Treatment Failures. Sleep 1999, 22 Supplement: S64.
(2) Schmidt HS, Berendts BP, Hinkle RM. Differentiating between UARS and OSAS Based on Sleep and Cephalometric Characteristics in 184 Patients. Sleep 1998, 21(3) Supplement: 60.

1176.K2

Prevalence of Cataplexy, Hypnagogic Hallucinations, and Sleep Paralysis in Patients with Excessive Daytime Somnolence

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Introduction: Narcolepsy is characterized by a set of symptoms including excessive daytime somnolence (EDS), sleep attacks, cataplexy (CP), hypnagogic hallucinations (HH), and sleep paralysis (SP). Cataplexy, the pathognomonic symptom of narcolepsy, is present in 80% of patients at some point in the disease course. Hypnagogic hallucinations and sleep paralysis are present in 25%-50% of narcoleptic patients and in up to 8%-15% of normals. Hypnagogic hallucinations and sleep paralysis would be expected to be more common in patients with obstructive sleep apnea (OSA) and periodic limb movement disorder (PLMD) due to frequent awakenings from rapid eye movement (REM) sleep. The presence of both narcolepsy and OSA is estimated to occur in approximately 6% of patients. To our knowledge, the prevalence of these symptoms in patients with other causes of EDS has not been described.

Methods: We reviewed records of all new patients with EDS who underwent polysomnogram (PSG) at our institution in 1997. Patients were asked about the presence of cataplexy, sleep paralysis, and hypnagogic hallucinations in a questionnaire which described these symptoms. PSG were evaluated for apnea-hypopnea index (AHI), arousal index, snoring, myoclonus, oxygen desaturation, and sleep efficiency. Patients were classified as having OSA based on AHI > 5 and the presence of at least 30 apneas. Upper airway resistance syndrome (UARS) was diagnosed if the AHI was < 5 with an increased arousal index and crescendo snoring prior to arousals. Narcolepsy was defined as reduced sleep latency on multiple sleep latency test (MSLT) and the presence of a minimum of two sleep-onset REM periods.

Table 1. Cumulative symptoms

	0 symptoms	1 symptom	2 symptoms	3 symptoms
OSA	79 (57.2%)	34 (24.6%)	19 (13.8%)	6 (4.3%)
UARS	42 (60.9%)	19 (27.5%)	7 (10.1%)	1 (1.4%)
Narcolepsy/ IH	3 (27.3%)	5 (45.5%)	2 (18.2%)	1 (9.1%)
PLMD	11 (55%)	7 (35%)	2 (10%)	0
Other	19 (70.3%)	5 (18.5%)	3 (9.1%)	0

Results: A total of 298 patients underwent PSG during 1997, of which 265 were included. Excluded were 26 patients whose records were unavailable and 7 who did not complete questionnaires. There were 138 (52.1%) patients with OSA and 69 (26%) patients with UARS. Eleven

POSTER PRESENTATIONS

patients (4.1%) had narcolepsy or idiopathic hypersomnolence (IH), 20 (7.5%) had PLMD, and 27 (10.2%) had other diagnoses (e.g. poor sleep efficiency, non-diagnostic PSG). In patients with OSA/UARS, hypnagogic hallucinations were reported in 14%-21%, sleep paralysis in 25%-27%, and cataplexy in 10%-17%. Among patients with narcolepsy/IH, 36% reported cataplexy and 54.5% hypnagogic hallucinations. Sleep paralysis was present in 40% of patients with PLMD.

Table 2. Prevalence of narcolepsy symptoms

	OSA	UARS	Narc/ IH	PLMD	Other
CP	24 (17.4%)	7 (10.1%)	4 (36.4%)	0	0
HH	30 (21.7%)	10 (14.5%)	6 (54.5%)	3 (15%)	7 (25.9%)
SP	35 (25.4%)	19 (27.5%)	2 (18.2%)	8 (40%)	5 (18.5%)

Conclusions: Classical symptoms of narcolepsy such as sleep paralysis, hypnagogic hallucinations, and cataplexy had a high prevalence in our patients with EDS. Presence of these symptoms should not be considered specific for narcolepsy. The higher prevalence of cataplexy reported in our OSA/UARS patients may represent an increased incidence of narcolepsy in this population; however, it could reflect the difficulty patients may have in differentiating symptoms associated with sudden sleepiness from cataplexy.

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1189.K2

Effect of PROVIGIL® (Modafinil) on Excessive Daytime Sleepiness Associated with Narcolepsy in Patients Who Previously Received Un-atisfactory Treatment with Dextroamphetamine, Methylphenidate or Pemoline

Schwartz JR,[1] Feldman NT,[2] Fry JM[3]
(1) , Integris Southwest and Baptist Medical Centers (2) , Palms of Pasadena Hospital (3) , Center for Sleep Medicine

Introduction: Treatment of excessive daytime sleepiness (EDS) associated with narcolepsy with common CNS stimulants, such as dextroamphetamine (DEX), methylphenidate (MP), and pemoline (PEM), is associated with many adverse experiences (AEs) and other complications (Mitler et al, 1994). The use of DEX and MP are associated with a substantial potential for abuse, tolerance, and rebound upon withdrawal. Additionally, treatment with PEM may lead to serious hepatic dysfunction. Modafinil, a newer agent, has been shown to be an effective wake-promoting agent that is generally well tolerated (US Modafinil in Narcolepsy Multicenter Study Group, 1998) and has a low potential for abuse (Warot et al, 1993). Thus, for patients whose prior therapy has been unsatisfactory, modafinil is a promising treatment option. This study evaluated the efficacy and safety of modafinil in patients who previously received unsatisfactory treatment with either DEX, MP, or PEM for EDS associated with narcolepsy.

Methods: 151 patients with narcolepsy who had been unsatisfactorily treated for EDS with DEX (N=48), MP (N=66), or PEM (N=37) were enrolled in this 6-week, open-label, multicenter study. After a 2-week washout period, patients were assigned to flexible doses of modafinil (200 mg, Week 1; 200 or 400 mg, Weeks 2-6). Efficacy was assessed by the Epworth Sleepiness Scale (ESS) at baseline and Weeks 1, 2, and 6 and the Clinical Global Impression of Change (CGI-C) at Weeks 1, 2, and 6. Safety was evaluated by recording AEs throughout the study.

Results: 123 of the 151 subjects (81%) successfully completed the study. During Weeks 2-6, approximately 77% of the patients were receiving 400-mg daily doses of modafinil. Regardless of the stimulant previously received, the mean ESS scores were significantly improved as early as Week 1 (Figure 1). Overall, 86%, 90%, and 79% of the patients showed some improvement on the CGI-C Scale at Weeks 1, 2, and 6, respectively. At Week 6, 62% of the patients were rated as much or very much improved on the CGI-C Scale (Figure 2). The most common AEs reported by the patients were headache (35%), nausea (10%), and insomnia (9%). Most AEs were mild or moderate in nature. Six of the 151 patients (4%) withdrew due to the following AEs, which were considered possibly or probably related to treatment with modafinil: asthenia, asthma, dizziness, headache, mental distress, or nausea.

Figure 1

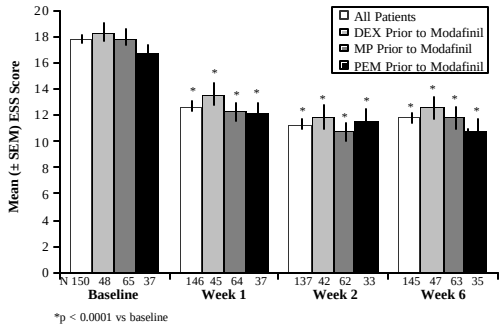
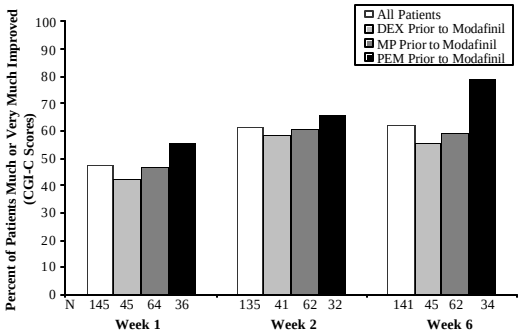


Figure 2



Conclusions: Modafinil was shown to significantly and clinically improve EDS in patients with narcolepsy who previously received unsatisfactory treatment with either DEX, METH, or PEM. Beneficial effects of modafinil were observed as early as the first week of treatment, and therapy with modafinil was generally well tolerated.

References:
(1) Mitler MM, Aldrich MS, Koob GF, Zarcone VP. ASDA Standards of Practice: narcolepsy and its treatment with stimulants. Sleep 1994;17:352-371.
(2) US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. Ann Neurol 1998;43:88-97.
(3) Warot D, Corruble E, Payan C, et al. Subjective effects of modafinil, a new central adrenergic stimulant in healthy volunteers: a comparison with amphetamine, caffeine and placebo. Eur Psychiatry 1993;8:201-208.

Research supported by Cephalon, Inc., West Chester, PA.

1190.K2

Effect of PROVIGIL® (Modafinil) on the Quality of Life and Mood of Patients Who Previously Received Unsatisfactory Treatment With Dextroamphetamine, Methylphenidate, or Pemoline for Excessive Daytime Sleepiness Associated With Narcolepsy

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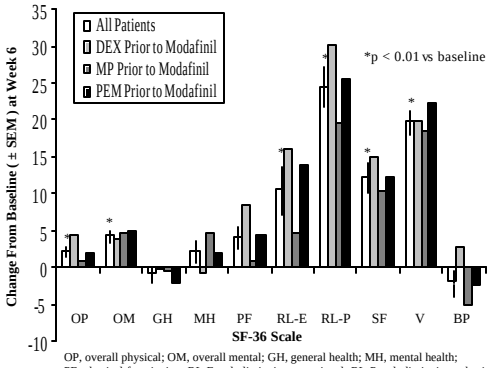
Introduction: Patients who have excessive daytime sleepiness (EDS) associated with narcolepsy have impaired daytime functioning and experience a decline in their quality of life. Common medications for EDS, such as dextroamphetamine (DEX), methylphenidate (MP), and pemoline (PEM), are associated with many adverse experiences (AEs) and other complications (Mitler et al, 1994). The use of DEX and MP are also associated with a substantial potential for abuse, tolerance, and rebound upon withdrawal. Additionally, treatment with PEM may lead to serious hepatic dysfunction. Modafinil, a newer agent, has been shown to be an effective wake-promoting agent that is generally well tolerated (US Modafinil in Narcolepsy Multicenter Study Group, 1998) and has a low potential for abuse (Warot et al, 1993). Thus, for patients whose prior therapy has been unsatisfactory, modafinil is a promising treatment option. This study evaluated the effect of modafinil on the quality of life and mood of patients who previously received unsatisfactory treatment with either DEX, MP, or PEM for EDS associated with narcolepsy.

Methods: 151 patients with narcolepsy who had been unsatisfactorily treated for EDS with DEX (N=48), MP (N=66), or PEM (N=37) were enrolled in this 6-week, open-label, multicenter study. After a 2-week washout period, patients were assigned to flexible doses of modafinil (200 mg, Week 1; 200 or 400 mg, Weeks 2-6). The effect of modafinil on quality of life was assessed with the Short Form Health Survey (SF-36) at baseline and Week 6. The effect of modafinil on mood was assessed using the Profile of Mood States (POMS) questionnaire at baseline and Weeks 1, 2, and 6.

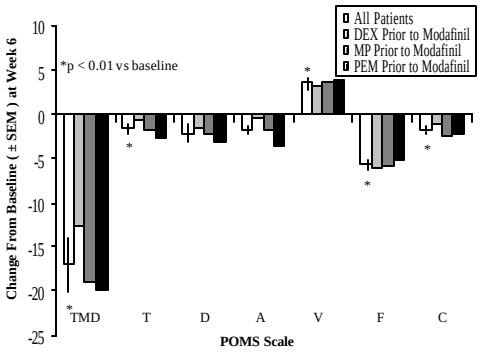
Figure 1



OP, overall physical; OM, overall mental; GH, general health; MH, mental health; PF, physical functioning; RL-E, role limitations-emotional; RL-P, role limitations-physical; SF, social functioning; V, vitality; BP, bodily pain

Results: 123 of the 151 patients (81%) successfully completed the study. During Weeks 2-6, approximately 77% of the patients were receiving 400-mg daily doses of modafinil. At Week 6, patients demonstrated significant ($p<0.01$) improvements from baseline on the global estimates of functionality (ie, the overall physical and mental domains of the SF-36 [Figure 1] and the total mood disturbance domain of the POMS [Figure 2]). Significant improvements were also noted on other domains of each survey.

Figure 2



TMD, total mood disturbance; T, tension-anxiety; D, depression-dejection; A-anger-hostility; V, vigor-activity; F, fatigue-inertia; C, confusion-bewilderment

Conclusions: Treatment with modafinil resulted in significant improvements in the quality of life and mood of patients who had previously received unsatisfactory treatment with the CNS stimulants DEX, MP, and PEM for EDS associated with narcolepsy.

References:
(1) Mitler MM, Aldrich MS, Koob GF, Zarcone VP. ASDA Standards of Practice: narcolepsy and its treatment with stimulants. Sleep 1994;17:352-371.
(2) US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. Ann Neurol 1998;43:88-97.
(3) Warot D, Corruble E, Payan C et al. Subjective effects of modafinil, a new central adrenergic stimulant in healthy volunteers: a comparison with amphetamine, caffeine and placebo. Eur Psychiatry 1993;8:201-208.

Research supported by Cephalon, Inc., West Chester, PA.

1553.K2

Cataplexy in the Elderly

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Introduction: Relatively few reports have described narcolepsy in the elderly. The prevailing opinion is that while narcolepsy is a chronic sleep disorder, cataplectic episodes become less common as patients age. The explanation has been that patients tend to avoid situations that provoke cataplexy or learn coping strategies that permit them to preempt cataplectic episodes. Understanding the phenomenon of cataplexy in the elderly is important because of the risk of fractures and other injuries associated with falls.

Methods: Three cases of narcoleptic patients (> 65 years of age) with persisting cataplexy were identified from the practice of a large sleep disorders center. The patients were interviewed along with a family member to provide collateral history. The patients were all female, age 66, 69, and 90 at the time of their multiple sleep latency test (MSLT). Medical records were available providing information about the course of the patient's disease since diagnosis which in all cases had been made on a clinical basis years before the MSLT.

Results: Excessive daytime sleepiness (EDS) developed at age 49, 28 and 23 respectively. Cataplexy developed after EDS in all cases. None experienced a diminution in frequency or intensity of narcoleptic symptoms including cataplexy. The first patient reported over time more fre-

quent cataplexy (total body weakness occurring several times per week on methylphenidate and imipramine) triggered both by humor and spontaneously. She had three serious falls resulting in pelvic and rib fractures. The second patient, 12 years after her MSLT, at age 73 when she was grieving her husband's death, had more frequent cataplexy (leg and face weakness with dysarthria occurring weekly on methylphenidate). She fell several times but was not injured. The third patient experienced cataplexy (falling with preserved consciousness but inability to move for a minute) several times per year without any specific trigger after her methylphenidate dose was reduced. She was not injured. In all cases patients were treated with more aggressive regimes of psychostimulants and two patients also received sertraline. All three patients had a decrease in cataplexy frequency and no further falls to date.

Conclusions: Cataplexy does not remit with age in all narcoleptic patients and appears to become more frequent in some cases. Two of these three patients developed spontaneous cataplexy in late life. This case series indicates a need for further research into late life narcolepsy and appropriate pharmacologic treatment to prevent cataplexy-related injuries.

Supported by a grant from the Mayo Foundation (Piscopo Fund)

1227.K3

Persistence of Sleep Perceptions in Insomniacs and Normal Sleepers

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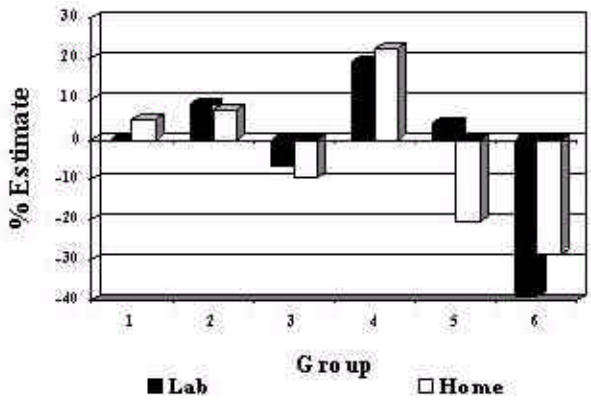
(1) VA Medical Center, Durham, NC (2) John Umstead Hospital, Butner, NC (3) Nova Southeastern University, Fort Lauderdale, FL

Introduction: Previous studies have consistently demonstrated that insomniacs underestimate sleep time when compared to objective sleep measures obtained by polysomnography (PSG). However, some evidence indicates that a subset of insomniacs overestimate sleep time; this finding argues against sleep time underestimation being a generic characteristic of all insomniacs and has led researchers to suggest that sleep time misperceptions are best viewed as on a continuum (Edinger & Fins 1995; Reynolds et al 1991). We explored the stability of subjective sleep estimates in insomniac and normal sleepers across multiple nights and settings (laboratory and home).

Methods: Age and gender-matched samples of middle-aged and older insomniacs (n = 52; 25 male, 27 female) and normal sleepers (n = 49; 27 male, 22 female) served as participants. Insomniacs had a complaint of insomnia for > 6 months and met diagnostic criteria for primary insomnia. Normal sleepers had no history of sleep complaints and failed to meet criteria for any sleep disorder. All participants were screened for the absence of medical and/or psychiatric difficulties that could compromise sleep. Participants underwent 3 consecutive nights of laboratory PSG and 3 consecutive nights of home PSG on separate weeks during a 1-month period, providing subjective estimates of their sleep the morning following each PSG. The first night of sleep recording in each setting (lab and home) was considered an adaptation night and thus not included in analyses. PSG-derived total sleep time (TST) measures were averaged for the second and third recording nights and then compared to subjective estimates of TST. A hierarchical cluster analysis was used to empirically identify subtypes among insomniacs and normal sleepers.

Results: The clustering procedure resulted in the identification of 6 mixed insomnia and normal sleeper subgroups. The figure depicts the percentage that subjective perceptions of TST over- or underestimated objective TST in each setting, with zero representing perfect agreement. Groups 1, 2, and 4 consisted of predominantly normal sleepers who varied on the degree to which they overestimated TST, but were consistent in estimating TST in the lab and home. Groups 3, 5, and 6 consisted of predominantly insomniacs. Group 3 slightly underestimated TST in both settings, whereas group 6 grossly underestimated TST by over 1.5 hrs at home and almost 2.5 hrs in the lab. Group 5 represented a group of insomniacs who slightly overestimated TST in the lab, but significantly underestimated TST at home.

Figure 1



Conclusions: Our findings support the conclusion that the underestimation of sleep time is not a trait common to all insomniacs. Also noteworthy is the finding that some insomniacs (Group 5) were accurate in estimating TST in the lab but grossly misrepresented their home experience, suggesting that setting factors may have a strong influence on subjective perceptions of sleep.

References:
(1) Edinger J, Fins A: The distribution and clinical significance of sleep time misperceptions among insomniacs. Sleep 1995;18:232-239.
(2) Reynolds C, Kupfer D, Buysse D, Coble P, Yeager A: Subtyping DSM-III-R primary insomnia: A literature review by the DSM-IV work group on sleep disorders. Am J Psychiatry 1991;148:432-438.

Research supported by the Department of Veterans Affairs Merit Review Grant #0009 (J. Edinger, Principal Investigator)

1573.K3

Comparison of People with Insomnia and Noncomplaining Poor Sleepers in a Normative Sample

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Introduction: There exists a substantial amount of data comparing self-reported sleep patterns between people with insomnia (PWI) and non-complaining good sleepers (NGS). There exists little data, however, comparing PWI and NGS to noncomplaining poor sleepers (NPS). Previous researchers concluded that NPS have similar sleep patterns as PWI, but differ in daytime functioning, including mood and cognitive-affective evaluation, with NPS resembling NGS on daytime measures (Fichten et al., 1995). The focus of the current paper is to determine if differences exist between these three groups.

Methods: We used random-digit dialing to solicit participation from at least 50 men and 50 women in each decade from 20 to 80 and older in the metropolitan Memphis (TN) area. Volunteers were paid between $15 and $175 for completing a 14-day sleep diary and measures of health, mood, and daytime functioning. In order to qualify as poor sleep, participants must exhibit an insomnia pattern characterized by sleep latency > 30 minutes, or awake time during the night totaling > 30 minutes, at least

three times per week. Poor sleepers who complained of a sleep problem were classified as PWI and poor sleepers who did not were considered NPS. Daytime functioning measures included in the sample were the Insomnia Impact Scale (IIS), the Epworth Sleepiness Scale (ESS), the Stanford Sleepiness Scale (SSS), the Fatigue Severity Scale (FSS), the State-Trait Anxiety Inventory (STAI), and the Beck Depression Inventory (BDI).

Results: We have collected data from 727 people, and have completed analyzing the data of 515 people. There are 136 PWI (26.4%), 262 NGS (50.9%), and 117 NPS (22.7%). We will report analyses on seven sleep measures: SOL, WASO, TST, SE, # awakenings, naps, and sleep quality rating. We will also report analyses on six daytime functioning measures: IIS, ESS, SSS, FSS, STAI, and BDI. For each category of functioning (sleep and daytime measures), a MANOVA was performed to compare PWI, NGS, and NPS. The MANOVA for sleep was significant, Wilks' L = .47, F(16, 1010) = 28.87, p <.001. Follow-up ANOVAs were significant for all measures. On all measures but naps, PWI had significantly worse sleep than the other two groups. On all measures but TST, NPS had significantly poorer sleep than NGS. The MANOVA for daytime functioning was also significant, Wilks' L = .80, F(12, 992) = 9.88, p <.001. Follow-up ANOVAs were significant for all daytime measures. On all measures but the ESS, PWI had significantly worse daytime functioning than the other two groups. On the ESS, PWI were worse than NGS, but not different from NPS. On all measures but the BDI, NPS and NGS were not significantly different. For the BDI, there were significant differences between all three groups in descending order of severity: PWI, NPS, and NGS.

Conclusions: Based upon people's perceptions, these preliminary results indicate that half of this random sample exhibited an insomnia sleep profile. In general, PWI slept worse than NPS, who in turn slept worse than NGS. Daytime functioning discriminated PWI from the other two groups, but these latter two groups differed little.

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1882.K3

No Next-Day Residual Sedation Four Hours After Middle-of-the-Night Treatment with Zaleplon

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Introduction: Zaleplon is a novel pyrazolopyrimidine hypnotic that binds selectively to the type I site on the GABAA/benzodiazepine chloride ion channel complex. Its time to peak plasma concentration and elimination half-life are both approximately I hour. In clinical studies, zaleplon 5 and 10 mg significantly shortened sleep latency in elderly and nonelderly insomnia patients, respectively.[1,2] Zaleplon's pharmacological properties make it ideal for "as needed" use when patients awaken during the night and have difficulty reinitiating sleep. The present study assessed residual sedation and hypnotic efficacy with zaleplon 10 mg, zolpidem 10 mg, or placebo administered after a middle-of-the-night awakening in patients with sleep maintenance insomnia.

Methods: This was a randomized, double-blind, 3-period crossover-design study. Thirty-seven (37) healthy patients with sleep maintenance insomnia (mean age 44 years) were enrolled based on criteria of > 45 minutes wakefulness measured by a sleep log on 4 of the last 7 screening nights and latency to persistent sleep (LPS) ~! 20 minutes after a nocturnal awakening on 2 of 3 polysomnograpky (PSG) screening nights. Patients received zaleplon 10 mg, zolpidein 10 mg, or placebo after an experimental awakening on 2 consecutive nights separated by 5 or 12 washout days. Patients were awakened 4 hours after lights out, received treatment, and were kept awake for 30 minutes before returning to bed for 3 more hours. The primary measure of residual sedation was the sleep latency test (SLT) conducted at 4, 5, 6, and 7 hours after treatment. Also assessed at those times were digit symbol substitution test (DSST), level of alertness, and ability to concentrate. LPS and total sleep time (TST) were recorded by PSG during the entire night. Data for each 2-day treatment period were averaged before analysis using ANOVA. Pairwise comparisons between active treatments and placebo were performed by using Dunnett's test.

Results: Thirty-two (32) patients had data from each of the 3 treatment periods and no major protocol violations. There were no significant differences from placebo with zaleplon 10 mg in measures of daytime sedation assessed by SLT, DSST, or subjective measures. In contrast, SLT at 4 and 5 ($p < 0.001$), and 7 hours ($p < 0.05$) after zolpidein 10 mg was significantly shorter than after placebo. Ability to concentrate measured at 4, 5, and 6 hours and level of alertness at 4 hours after treatment with zolpidein 10 mg were also significantly worse than those subjective measures with placebo ($p < 0.05$). Scores on the DSST were significantly lower with zolpidem 10 mg than with placebo ($p < 0.001$) at 4 and 5 hours after treatment. LPS after middle-of-the-night dose administration with zaleplon 10 mg and zolpidem 10 mg was 27 and 31 minutes, respectively, shorter than LPS with placebo ($p < 0.001$, both comparisons). TST after dose administration with zaleplon 10 mg and zolpidein 10 mg was 22 ($p < 0.001$) and 30 ($p < 0.001$) minutes, respectively, longer than that with placebo.

Conclusions: No residual sedation was detected by objective (SLT, DSST) and subjective (questionnaire) assessments after a middle-of-the-night dose administration with zaleplon 10 mg. The results of this study indicate that both zaleplon 10 mg and zolpidem 10 mg effectively shorten the time to sleep and lengthen sleep duration when taken after a nocturnal awakening. However, patients did not experience significant next-day sedation with zaleplon as little as 4 hours after dose administration, whereas signs of residual sedation were detected with zolpidem 10 mg up to 7 hours after middle-of-the-night treatment.

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1244.K3

Self-Reported Fatigue Before and After Sleep: A Comparison Between Aged Insomniacs and Controls

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Introduction: In addition to reduced sleep quality, insomniacs commonly report increased fatigue (Lichstein et al., 1997). These symptoms are thought to be causally related. However, it remains to be established whether insomnia is associated with increased fatigue.

Methods: Potential subjects were recruited from a media campaign asking for good and poor sleepers aged >55y. After completing a 7-day sleep diary, poor sleepers were recruited if they showed an average sleep efficiency <85%, total sleep time <6.5h, and wake after sleep onset >30min; and good sleepers if they showed average sleep efficiency >90%, total sleep time >7.5h, and wake after sleep onset <30min. Subjects were also carefully screened for medical, psychiatric and occult sleep disorders. From a potential 206 subjects, we recruited 19 male [mean (SD) age = 66.3 (7.4)y]and 26 female [64.6 (6.9)y] insomniacs and 19 male [65.3 (7.4)] and 33 female [63.5 (6.4)y] controls. The data collection involved subjects maintaining an additional 7-day sleep diary together with an 18 item, 10pt scale, fatigue and energy questionnaire (Lee et al., 1992) This was completed before sleep and at least 30min after sleep offset. Group differences were tested by entering the averaged fatigue/energy scores into one within (before and after sleep) and two between [sex and sleep status (insomniac and control)] ANOVA. Student t-tests (within and between) were used to explore significant interaction effects.

Table 1. Mean (SD) Fatigue and Energy scores before and after sleep.

Sleep Status	Gender	Energy		Fatigue	
		Before	After	Before	After
Control	Male (n=19)	4.1(1.8)	6.6 (1.8)	4.8 (2.0)	1.4 (1.0)
	Female (n=33)	4.2 (1.6)	5.6 (1.6)	4.1 (1.8)	1.8 (1.3)
Insomniac	Male (n=19)	4.4 (1.2)	5.9 (2.0)	4.2 (1.4)	2.3 (1.6)
	Female (n=26)	3.7 (1.3)	4.7 (1.3)	4.7 (2.1)	3.3 (1.9)

Table 2. ANOVA F-Value results for self-reported fatigue and energy scores. Nb *p<0.05, ****p<0.001, & *****p<0.0005

Dependent Variable	Before-After Sleep	Sleep Status	Sex	Before-After Sleep x Sleep Status	Before/After Sleep x Sex	Sleep Status x Sex	Before/After Sleep x Sex x Sleep Status
Fatigue	167.5*****	4.1*	1.1	12.3****	5.4*	1.8	0.8
Energy	100.4*****	3.0	6.1*	4.4*	6.9*	0.9	1.0

Results: The Mean (SD) fatigue/energy scores are reported in Table 1 and the ANOVA F-values for the fatigue and energy analyses in Table 2. The Fatigue ANOVA revealed a significant main effect for Before/After Sleep [Before Sleep = 4.4 (1.8) > After Sleep = 2.2 (1.7)] and Sleep Status [Insomniac = 3.7 (1.7)> Control = 3.0 (1.3)], and significant interaction effects (all p<0.0001) between Before/After Sleep and Sleep Status (Insomniac = Control Before Sleep > Insomniac After Sleep > Control After Sleep scores) and, likewise, Before/After Sleep and Sex (Female = Male Before Sleep > Female = Male After Sleep scores). The Energy ANOVA revealed a significant main effect for Before/After Sleep [Before Sleep = 4.1 (1.5) < After Sleep = 5.6 (1.7)] and Sex [Female = 4.9 (1.3) < Male = 5.2 (1.5)], and significant interaction effects (all p<0.05) between Before/After Sleep and Sleep Status (Control After Sleep > Insomniac After Sleep > Insomniac = Control Before Sleep scores) and, likewise, Before/After Sleep and Sex (Male After Sleep > Male Before Sleep = Female Before Sleep = Male After Sleep scores).

Conclusions: Although fatigue/energy scores were comparable at sleep onset, at sleep offset insomniacs compared to controls tended to report higher fatigue and lower energy scores (a trend that was also more evident for female subjects). The present findings suggest that insomnia in the aged is associated with increased fatigue and reduced energy levels. Moreover, they support the assumption that reduced sleep quality may underlie increased fatigue levels.

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1884.K3

Dose Response Effects of Behavioral Insomnia Therapy

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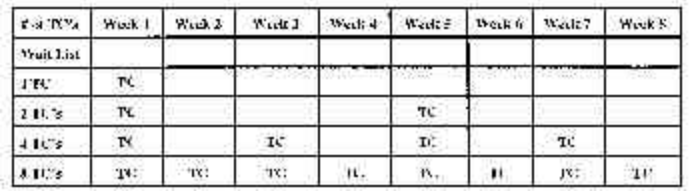
Introduction: Previous studies have shown that Cognitive Behavioral Therapy (CBT) produces both short term and enduring sleep improvements among those with Primary Insomnia. Despite these findings, little is known about the dose-response curve associated with this intervention. Specially, the relationship between insomnia treatment outcomes and such dosing factors as time in treatment and number of therapist contacts remains unexplored. This initial report describes our ongoing study designed to examine these relationships.

Methods: The study design shown below allows for the randomization of study participants across 5 conditions. The timing of scheduled treatment sessions within this protocol allows for separate examination of time in treatment and number therapist contacts (TC's) received. Statistical comparisons conducted while holding time constant test for the effects of varying number of treatment sessions; comparisons conducted while holding number of therapist contacts constant test for the effects of time in treatment. The wait list (WL) controls for time and self-monitoring effects. Prospective study participants are being screened via structured interviews, medical examinations, TSH testing, and ambulatory polysomnography. Consenting individuals between the ages of 40 and 75 who meet DSM-IV criteria for Primary Insomnia and have an average wake time after sleep onset (WASO) ≥ 60 min. are enrolled in the study if they have no other sleep disorder and do not have a co-morbid medical or Axis I psychiatric disorder that might contribute to their sleep difficulty. Study participants complete baseline assessment including sleep logs (2 weeks), actigraphy (one week), and multiple symptom-related questionnaires. They are then randomized to one of the 5 conditions shown above. During the treatment phase, they complete logs, actigraphy, and selected symptom-related questionnaires each week. Subsequent 3 and 6 month follow-up assessments repeat all measures taken at baseline.

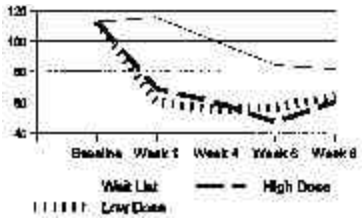
Table 1



POSTER PRESENTATIONS

Results: To date, 22 (12 F, 10 M) have enrolled and been assigned to treatments. Of these, 15 have completed the 8 week protocol whereas the remainder are active in the study but have yet to complete the 8 week treatment phase. Figure 1 shows changes (adjusted for baseline differences) in mean values of WASO for those in the low dose (I or 2 TC's), high dose (4 or 8 TC's), and WL conditions.

Figure 1. Mean changes in WASO



Conclusions: Thus far, low and high dose outcomes appear similar across the 8 weeks suggesting even low dose CBT may be effective if those receiving such treatment are afforded sufficient time to implement treatment recommendations. The study will continue until 90 Primary sleep-maintenance insomnia sufferers are randomized and all in-treatment and follow-up assessments are completed.

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1888.K3

The Effects of Zolpidem and Temazepam Taken at 2 a.m. on Driving Starting at 7:30 a.m. in Subjects with Non-organic Insomnia

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Introduction: Zolpidem is the most commonly used hypnotic in the world. Also temazepam is a commonly used hypnotic. We know that both drugs are often taken after midnight. A question rises about their possible residual effects next morning. In most previous studies hypnotics have been given at least 8-10 hours before driving. The aim of this double blind placebo controlled cross-over study was to test the effect hypnotics on psychomotor skills and driving ability after 5 hours of sleep. To evaluate the functional effect of the elimination half time, two drugs were chosen: temazepam, which has a longer half time (5- 13 hours) and zolpidem with a half-life of approximately 2.4 hours.

Methods: Fifteen (15) women, age 35-60 suffering from chronic non-organic insomnia participate. All subjects drive regularly. A polysomnography is made four times for each subject. The subjects go to bed at 2:00 am and they are awakened at 07:00 the next morning, i.e. after 5 h of sleep. During the first (baseline) night the subjects receive no medication. On the three other nights a pill of placebo or 10mg zolpidem or 20 mg temazepam is given at 2:00 am with 100 ml water. The interval between each night 3-14 days. The following morning, at 07:30, a driving simulator test is driven with a STISIM simulator built in a real personal car. The baseline test is driven after the baseline night. Subjects control the car in a normal matter. The first part of the scenario is a 10 km long drive that is driven with other vehicles appearing in front of the simulator car. The simulator controls the speed. Reaction times (RT) to other vehicles and lane position deviation (LPD) is measured. The second part consists of a 90km long foggy highway drive. The driver controls both speed and gear and RT is measured to divided attention tasks. LPD and deviation of speed are measured. After the drive neuropsychological tests are given (Fepsy, Het Instituut voor Epilepsiebestrijding). The subjects have to recognise different words and shapes shown repeatedly.

Results: Preliminary results of this ongoing study are interesting. We have already seen differences in the driving performances. One subjects has fallen asleep a number of times at two test-drives. On both cases falling asleep at the wheel caused several crashes. One subject reported severe nausea and headache in the morning, due to sleep deprivation, she stated, and she was unable to drive a car.

Conclusions: Because the study is still running we cannot break the code. The hypothesis is, of course, that hypnotics with longer half time are more likely to affect driving if only 5 hours of sleep is allowed. The final results will be given at the congress.

1259.K3

Cognitive-Behavior Therapy for Insomnia Associated with Anxiety or Depression

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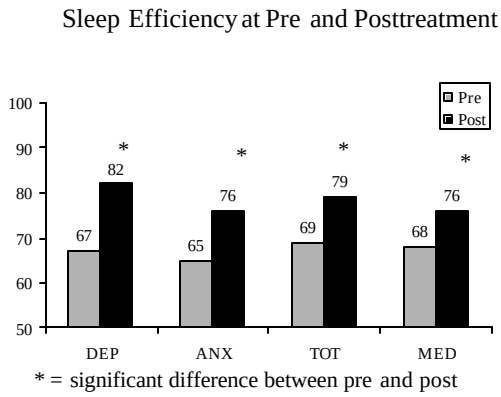
Introduction: Insomnia is a frequent complaint among patients with comorbid anxiety or affective disorders. Although the benefits of cognitive-behavior therapy (CBT) have been well documented for primary insomnia, little information exists on the moderating effect of comorbid psychopathology and medication use on the efficacy of CBT for insomnia. This paper reports on the efficacy of CBT for sleep difficulties in anxious and depressive patients and on whether the use of medication for these disorders influences the outcome of insomnia treatment.

Methods: Participants were 43 adults (M age = 45 years old, SD = 13.2) with chronic insomnia and comorbid anxiety or mood disorders. They were seeking treatment for insomnia at a sleep disorders clinic. There were 23 participants who were taking at least one anxiolytic or antidepressant medication for their psychopathology. Participants received an average of 6.5 CBT sessions for insomnia. Treatment duration (from initial to last visits) lasted an average of 10 weeks. They completed daily sleep diaries and self-report measures of depression [Beck Depression Inventory (BDI)] and anxiety [State Trait Anxiety Inventory (STAI-Trait and STAI-State)] at pre and posttreatment. The main outcome variable from the sleep diary was sleep efficiency. BDI and STAIs scores were also compared for 15 participants who completed those measures at posttreatment. Two groups were created a posteriori: Insomnia with anxiety disorders (IANX; n = 17) and insomnia with mood disorders (IDEP; n = 26).

Results: Analysis of variance (ANOVA) with repeated measures showed that sleep efficiency was significantly improved from pre to posttreatment in both IANX and IDEP groups ($p < .0001$) (see Figure 1). There was no significant difference between groups. ANOVAs also showed that BDI, STAI-T and STAI-S total scores significantly decreased from pre to posttreatment ($ps < .0001$). These results are depicted in Figure 2. Significant posttreatment improvements were obtained for sleep efficiency for participants using either anxiolytic or antidepressant medications ($p < 0.01$). Furthermore, there was no difference between medication users and non-users on measures of sleep efficiency, BDI and STAIs

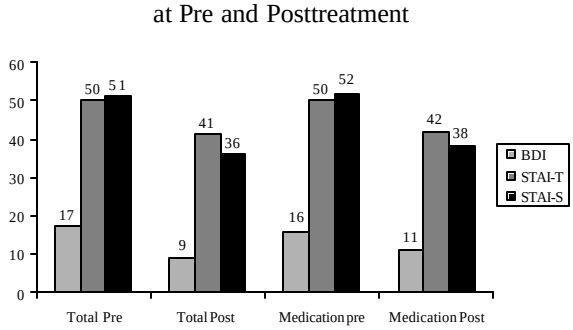
at posttreatment.

Figure 1



* = significant difference between pre and post

Figure 2



Note. Changes are significant between pre and post for both groups

Conclusions: These preliminary findings suggest that CBT is effective for alleviating sleep difficulties among patients with comorbid anxiety or depression disorders. In addition, insomnia treatment reduced depressive and anxiety symptoms. Thus, the presence of anxiety or depressive conditions, and the use of psychotropic medications for those conditions, does not seem to alter the effectiveness of CBT for insomnia.

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1271.K3

A Comparison of Disease Burden Among Sleep Disorder Patients

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Introduction: Unlike hypersomnia, insomnia is often trivialized or ascribed to extrinsic factors rather than specific disease mechanisms (Matheson, 1998). We compared rates of total disease symptoms to test whether disease burden varies systematically among insomnia, hypersomnia, delayed sleep phase syndrome (DSPS) or major depression. Patients were seen in a psychiatry sleep clinic.

Methods: We reviewed clinical records of patients primarily diagnosed with insomnia, hyper-somnia, DSPS or major depression. Data included standardized intake questionnaires that patients com-pleted before they were first seen, intake interview records and laboratory results. After review of 100 conse-cutive charts, extra DSPS charts were randomly retrieved to obtain adequate numbers. Ambiguous records were clarified by two-rater consensus. Patient identifi—ca-tion, age, diagnostic category and each disease symptom in the initial evaluation were tabulated. Symptoms that occurred in at least 10 patients were defined as frequent. Statistics were analyzed by SAS (SAS Institute, Cady, NC). Mean rate of frequent symptoms per patient was calculated for each diagnostic group. Chi-square tests were used to find whether each of 24 frequent symptoms occurred dispro-por-tion-ately in any diagnostic group. Significance level (.05) was not adjusted for multiple comparisons in this exploratory study.

Results: Numbers of frequently-recurring symptoms are presented in the Table. Means were similar across groups. Insomnia patients varied relatively more in number of frequent symptoms. Sleep disorder patients had statistically similar numbers of frequent symptoms, as did depressed patients. The complaint of anxiety was dispro-portionately increased in depressed patients as expected (Chi2 = 9.5; p= .02). Unexpected numbers of DSPS patients had elevated hyperarousal scores (chi2 = 11.2; p = .01), indicating a tendency to overly intense respon-sive-ness (Regestein et al, 1993). Common symptoms such as dry mouth, ear ache and back pain were proportionately distributed within the patient population. Frequent symptoms were related to psychiatric or vigilance problems, diarrhea and palpitations, and tended to be of apparent central or autonomic nervous system origin.

Table 1

Group	Insomnia	Hypersomnia	DSPS	Depression
N	55	23	29	17
Mean	6.6	6.1	5.4	4.5
SD	6,8	2.9	2.6	3.1
C.V	104	48	41	50

Conclusions: Patients who have severe grades of insomnia such as that seen in specialty clinics may carry as much disease burden as that of other sleep disorders.

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1275.K3

Treatment of Comorbid Insomnia and Generalized Anxiety Disorder

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Introduction: Insomnia is a prevalent complaint among patients with generalized anxiety disorder (GAD). Although it is generally assumed that treatment of the predominant condition will decrease or even eliminate the symptoms of the secondary condition, this issue has not been examined empirically. Preliminary findings have shown that sleep difficulties improved following treatment of GAD, although participants did not necessarily meet the diagnostic criteria of chronic insomnia at pretreatment. The objective of this study was to assess the effect of CBT for insomnia on GAD symptoms and vice-versa among patients suffering from comorbid insomnia and GAD.

Methods: Ten women (M aged: 44.5 years, SD:10.09) underwent a multi-focused evaluation of anxiety, depression, and insomnia. Patients also completed daily diaries of insomnia and anxiety symptoms through-

out the study. Five participants were treated for insomnia first and subsequently for GAD and the other five participants began with a GAD treatment, followed by insomnia treatment when necessary. Treatment for insomnia included stimulus control instruction, sleep restriction, cognitive therapy, sleep hygiene education, whereas, treatment for GAD included awareness training, correction of intolerance of uncertainty, problem solving, and cognitive exposure.

Results: Two outcome measures (sleep efficiency, time spent worrying) were collected on a daily diary and the remaining measures were administered at baseline, at the end of each teratment phase, and at a 3-month follow-up. The results showed that both insomnia and anxiety symptoms improved when participants were treated first for GAD. Additional therapeutic gains were made when the insomnia treatment was implemented; those benefits were well-maintained at 3-month follow-up. When treatment targeted insomnia first, improvements on sleep and anxiety were also noted. However, sleep difficulties subsequently increased at the end of GAD treatment but did not reach a clinical status. At follow-up, although not clinically interviewed, both insomnia and anxiety symptoms remained above clinical threshold.

Table 1. Means and SD for each variables among treatment condition

	Patients treated first for insomnia n=5		Patients treated first for GAD n=5	
Insomnia severity (0-8)	M	SD	M	SD
Pre	6.4	0.6	5.4	0.6
Post insomnia / GAD	1.4	1.3	3.2	1.9
Post GAD / insomnia	1.8	1.3	0.0	0.0
Sleep efficiency (0-100)				
Pre	60.4	6.8	73.0	6.5
Post insomnia / GAD	82.4	5.8	80.0	9.8
Post GAD / insomnia	77.5	4.9	84.3	8.6
Fu-3	72.8	0.2	86.0	3.5
Sleep Impairment Index (0-28)				
Pre	22.2	3.7	17.8	3.6
Post insomnia / GAD	11.6	6.1	13.4	7.1
Post GAD / insomnia	13.5	5.6	8.5	3.1
Fu-3	17.0	9.9	8.7	3.8
GAD severity (0-8)				
Pre	6.4	0.9	5.6	0.9
Post insomnia / GAD	4.4	2.5	1.8	1.6
Post GAD / insomnia	3.3	0.5	0.0	0.0
Time spent worrying (0-100)				
Pre	72.6	13.9	81.4	14.7
Post insomnia / GAD	54.6	21.0	39.6	28.9
Post GAD / insomnia	44.0	24.4	30.4	21.0
Fu-3	61.3	20.8	32.5	10.0
Penn State Worry Questionnaire (0-68)				
Pre	62.0	7.9	64.8	3.8
Post insomnia / GAD	54.8	6.2	41.8	2.4
Post GAD / insomnia	50.0	3.6	39.7	4.0
Fu-3	59.3	10.4	42.8	5.4

Conclusions: These data suggest that treatment targeting both sleep and anxiety symptoms produce clinically significant improvements on both types of symptomatology among patient suffering from a comorbid insomnia and generalized anxiety disorder. Therapeutic gains were better maintained when treatment focused first on GAD symptoms. Additional research is needed to replicate these findings and to evaluate other methods (sequential VS concurrent) for implementing multi-focused treatments for insomnia associated with comorbid psychopathology.

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1296.K3

Measurement of Sleep Beliefs in the General Adult Population

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Introduction: Early attempts to measure sleep beliefs in the general population made use of a 58-item Sleep Belief Questionnaire constructed from beliefs voiced during semi-structured interviews (Floyd, 1993). An attempt to classify all 58 items using sleep belief themes originally identified in chronic insomniacs by Morin (1993) was only marginally successful (Floyd & Medler 1999), perhaps because Morin's themes were conceptually, rather than statistically, derived. The purpose of this research was to determine if Morin's themes could be replicated statistically in the general adult population. We also were interested in identifying additional factors unique to the general population.

Methods: Two independent sub-samples were created randomly from our full sample of subjects who had completed the Sleep Belief Questionnaire (N=826). Mean age was similar for sample 1 and sample 2 (57.2, SD=12.7 vs. 56.4, SD=12.7). Sex composition of samples also was similar (44% males vs. 38% males). Exploratory factor analysis was performed on sample 1 using principal component analysis (PCA). Resulting factors that were not conceptually meaningful were not retained. Finally, we ran a confirmatory factor analysis by specifying the factor structure obtained from sample 1 and applying this to sample 2.

Results: A five-factor final solution was accepted. The labeled factors extracted from PCA emerged in the following order: (1) long-term health consequences, (2) immediate consequences, (3) self-medication attributions, (4) circadian regularity, and (5) importance of sufficient sleep. Sixty-two percent of the total variance was explained. When this five-factor solution was applied to sample 2, again 62% of the total variance was explained. All items loaded on the appropriate factor. However, the factors emerged in a different order. For the confirmatory factor analysis, all factor loadings were significant, but the model did not demonstrate overall goodness of fit as evidenced by the following indices: CHISQ(67) = 229.50, RMSEA = .08, GFI = .92, NNFI = .76, CFI = .83.

Conclusions: Two of Morin's themes were replicated statistically in the general adult population: (1) consequences, and (2) attributions. However, the consequences theme contained two factors, one involving long-term consequences and the other involving more immediate consequences. We also identified two factors that seem distinct to the normal adult population: (1) circadian regularity, and (2) importance of sufficient sleep. Further research is needed to substantiate the presence of these factors. The poor model fit reflects, in part, the large error associated with each indicator. Future research using more items per sub-scale may alleviate this problem. Revised sub-scales with additional items have been developed and are currently being tested with a new sample.

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POSTER PRESENTATIONS

1649.K3

Sleep and Daytime Functioning of Different Insomnia Types

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Introduction: It is common practice in the field of insomnia research to consider insomnia a homogeneous disorder. Few investigators examine differences between insomnia subsets. In this research project we investigated how the different insomnia types (i.e., onset, maintenance, mixed, and combined) performed on several commonly used daytime measures.

Methods: We used random-digit dialing to solicit participation from at least 50 men and 50 women in each decade from age 20 to 80 and older. People who agreed to be in the study were then mailed a questionnaire packet, which included a 14-day Sleep Diary, Beck Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI), Fatigue Severity Scale (FSS), Insomnia Impact Scale (IIS), Epworth Sleepiness Scale (ESS), and a Stanford Sleepiness Scale (SSS). We then assigned people to different insomnia groups based on 1) a report of insomnia for at least the past six months; 2) a sleep onset latency of >30 min at least three nights a week (Onset); 3) a time awake after sleep onset totaling >30 min at least three nights a week (Maintenance); 4) did not meet criteria of either 2 or 3 separately, but did have at least three nights a week where they met the criteria of either 2 or 3 (Mixed); or 5) met criteria for both 2 and 3 (Combined). We will be reporting on the differences between insomnia types on sleep and daytime measures.

Results: We have collected data from 727 people, and we will have nearly 800 subjects by the meeting. At present, we have completed analyzing the data of 522 people, and their results follow. We performed 3 one-way MANOVAs, comparing insomnia types on the daytime functioning measures (i.e., ESS, SSS, FSS, IIS), mood measures (i.e., BDI, STAI), and the sleep measures (SOL, # awakenings, WASO, TST, SE, and Sleep quality). No significant differences were found between insomnia types on either daytime measures or mood measures. A significant MANOVA was found for the sleep measures, Wilk's Ë = .345, F(18, 345.553) = 8.775, p < .001. Univariate analyses found significant differences between groups on # awakenings per night, F(3, 127) = 11.528, p < .001, sleep quality, F(3, 127) = 4.268, p < .01, SE F(3, 127) = 15.883, p < .001, SOL, F(3, 127) = 29.557, p < .001, and WASO, F(3, 127) = 15.724, p < .001. Insomnia types did not differ on TST. Tukey's post hoc testing revealed expected results for SOL, WASO, and # awakenings, where those insomnia types that are characterized by the measure performed as expected (e.g., maintenance and combined had higher WASO, onset and mixed had higher SOL, etc.). However, the combined insomnia type scored worse than all other insomnia types on SE, and maintenance scored worse than onset on SE. Also, the combined insomnia group scored worse than the onset group on sleep quality ratings.

Conclusions: While it appears there are differences between groups on all of the sleep measures except TST, there does not appear to be differences on daytime or mood measures between groups. Therefore, it is possible that daytime and mood measures are less affected by SOL, # awakening, SE, WASO, and quality. Daytime and mood measures may be more sensitive to TST. The fact that the combined insomnia type group had worse SE than all other groups and the maintenance group scored worse than onset on SE may indicate that these two types of insomnia are more serious than mixed and onset.

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1661.K3

Do Frequency of Insomnia and Type of Insomnia Change with Age

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Introduction: Two common beliefs in the field of insomnia research are 1) older individuals report more insomnia than younger individuals (Bixler, Kales, Soldatos, Kales, & Healey, 1979; Mellinger, Balter, & Uhlenhuth, 1885), and 2) onset insomnia is more common in younger individuals and maintenance insomnia is more common in older individuals. We conducted this community survey to explore these premises.

Methods: We used random-digit dialing to solicit participation from at least 50 men and 50 women in each decade from age 20 to 80 and older. Individuals where asked to complete a 14-day Sleep Diary and seven questionnaires evaluating associated daytime functioning. We then assigned people to different insomnia groups based on 1) a report of insomnia for at least the past six months; 2) a sleep onset latency of >30 min at least three nights a week (Onset); 3) a time awake after sleep onset totaling >30 min at least three nights a week (Maintenance); 4) did not meet criteria of either 2 or 3 separately, but did have at least three nights a week where they met the criteria of either 2 or 3 (Mixed); or 5) met criteria for both 2 and 3 (Combined). The following analyses will focus on age groups and insomnia classification.

Figure 1. Presence of insomnia at each age group.

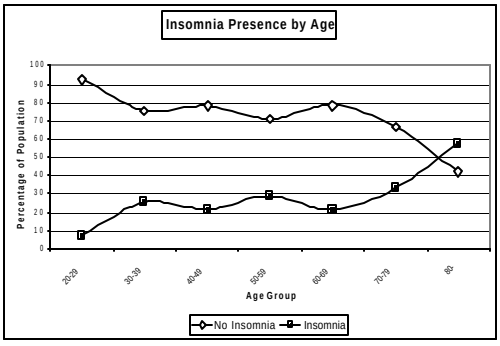
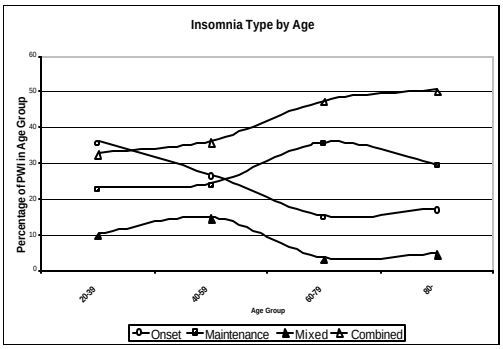


Figure 2. Insomnia type percentage at each age group.



Results: We have collected data from 727 people, and we will have nearly 800 subjects by the meeting. At present, we have completed analyzing the data of 522 people, and their results follow. Three Chi-square analyses were performed comparing insomnia presence and insomnia type to age group. A Chi-square Test of Independence found that insomnia presence does significantly change over age, c2 (6, N = 522) = 36.228, p < .001, with presence of insomnia being greater as age increas-

es. Because the numbers were so small in each 10-year age group for different insomnia types, we collapsed age into 20-year age groups (i.e., 20-39, 40-59, 60-79, and 80-). We then used Goodness of Fit Chi-square tests to examine if insomnia type was related to age. There were no significant differences in percentage of insomnia types at either the 20-39 year age group or the 40-59 year age group, but there were significant differences found at both the 60-79 year age group, c2 (3, N = 34) = 16.118, p = .001, and the 80- year age group, c2 (3, N = 24) = 11.000, p < .05. In both of these age groups, combined was the most common insomnia type, and maintenance was the next most common type. We then performed a series of Goodness of Fit tests to determine if onset and maintenance complaints differed within each age group, and found no significant differences.

Conclusions: These results indicate that as age increases so does the percentage of the population who complain of insomnia. The significant results for insomnia type at age groups indicates that there are some differences between insomnia type at different age groups, but further analyses of maintenance complaints verses onset complaints indicate that there is not an interaction between age and these two particular insomnia types.

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1663.K3

Behavioral Treatment of Insomnia: A Second Clinical Case Series Study

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Introduction: There is substantial experimental evidence that behavioral treatment of insomnia produces significant improvement. Less clear is whether behavioral treatment is effective when plied in clinical settings. Last year, we undertook a clinical case series study and found that behavior therapy for insomnia was effective[1] and appeared to produce outcomes comparable to those reported in two meta-analytic summaries of the clinical trial literature.[2,3] The present analysis was conducted to test the replicability of our earlier work.

Methods: Our Behavioral Sleep Medicine Clinic is staffed by 2 psychologists and 1 physician. One clinician is full time (AH). Patients are physician- and self-referred and are telephone triaged to the clinic. Patients are initially interviewed to establish ICSD diagnoses and to review clinical history. Patients with Psychophysiologic Insomnia or insomnia secondary to stable medical and/or psychiatric conditions are then assessed for a 1-2 week baseline period and are subsequently seen weekly for 4-8 sessions on average. Four procedures are used: Sleep Restriction, Stimulus Control, Sleep Hygiene and Cognitive Therapy. Sleep is monitored prospectively using sleep diaries throughout. 89 patients have been treated since November 1998. Of these patients, 32.6% completed treatment, 34.8% postponed treatment or were referred, 2.2% continue in therapy and 30.3% discontinued treatment. These groups did not significantly differ on demographic measures (e.g., age, sex), on psychological measures (e.g., BDI, BAI), or with respect to co-morbid medical or psychiatric diagnoses. 95% were Euro-American. Mean age was 46 (± 16); 65% were female.

Results: Baseline data were compared to end-of-treatment data for patients who completed an adequate trial of therapy. Outcome measures were difference and percent change scores for sleep latency, number and duration of awakenings, total sleep time and average percent improvement. All pre-post comparisons for this sub-sample were significant at p. < .005. Patients showed overall 33% improvement. This average corresponded to 34% reduction in sleep latency (effect size: 0.87), 13% decrease in number of awakenings (effect size: 0.54), 56% reduction in wake time after sleep onset (effect size: 1.14), and 29% increase in total sleep time (effect size: 0.55). In absolute numbers, patients, on average, fell asleep about 33 minutes quicker, woke up about 1 time less, stayed awake in bed for about 55 minutes less, and obtained about 49 more minutes of sleep per night.

Conclusions: This patient series replicated our earlier work: patients treated for insomnia in a clinical setting significantly improved in a magnitude comparable to recent meta-analyses on behavioral treatment for insomnia.[1,2] The most robust clinical gains in this patient series were reduction in WASO and sleep latency and increase in total sleep time. The between year variability may be due to differences in the focus for behavioral therapy. For example, these patients were older and may have had more sleep maintenance difficulties. Accordingly a greater focus would be on WASO to target this issue specifically. These data support the clinical efficacy of behavioral treatment independent of clinician and patient age.

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1675.K3

PSG and Subjective Estimates of Sleep Continuity in Patients with Primary and Secondary Insomnia

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Introduction: A variety of studies demonstrate that patients with insomnia overestimate sleep latency and underestimate total sleep time relative to PSG measures (e.g., 1,2). To our knowledge, no studies have concurrently determined whether such discrepancies 1) are unique to patients with insomnia, 2) apply equally to all sleep continuity measures, and 3) potentially are explained by how PSG measures are defined.

Methods: Three groups (n=9 per group) were compared: Primary Insomnia, Major Depression, Good Sleeper Controls (no history of psychiatric/ sleep disorders). Groups were matched for age, sex, height and weight. The sample was 66% female and the mean age was 37.5 (± 10.7). Subjects were studied for a minimum of two nights in the sleep laboratory and completed sleep diaries at each risetime. PSGs were scored in 30 second epochs according to Rechtschaffen and Kales criteria. The PSG definition of sleep onset was 2 consecutive epochs of Stage 1 or 1 epoch of stages 2,3,4 or REM. The PSG definition of an awakening was defined as more than 1 minute of wakefulness after sleep onset.

Subjective estimates were acquired for sleep latency, number of awakenings, wake after sleep onset time, and total sleep time. The first night served as an a baseline and these data were used in the present analyses. To evaluate subjective - objective discrepancies, difference scores were calculated by subtracting the PSG measures from the sleep diary estimates. One-way ANOVAs with post hoc Duncan tests were used to compare groups. To evaluate whether the awakenings that occur after PSG-defined sleep onset may account for subjective-objective discrepancies, amount of time awake during the first 1/3 of the night was correlated with subjective perceptions of sleep latency for each group.

Results: The groups tended to differ on all sleep continuity measures. The notable exceptions were PSG-measured total sleep time, subjective number of awakenings and difference scores for wake after sleep onset time. In all instances where trends were evident, patients with insomnia exhibited the worst sleep continuity profiles followed by depressed subjects and then good sleeper controls. Discrepancy scores revealed that patients with insomnia, compared to contrast groups, significantly overestimated sleep latency, underestimated total sleep time and number of awakenings, and tended to estimate amount of time spent awake after sleep onset accurately. Within-group correlations were .71 (Insomnia), .97 (Depressed), and .84 (Good Sleepers).

Conclusions: The finding that patients with insomnia underestimate number of awakenings while accurately assessing wake after sleep onset time suggests that 1) subjective- objective discrepancies cannot simply be ascribed to a uniform bias toward symptom exaggeration and 2) patients with insomnia may perceive time intervals that contain PSG sleep as continual wakefulness.[3] The correlational analyses suggest all subjects are prone to misperceive PSG defined sleep onset to the extent that "event" does not correspond to consolidated sleep.

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1044.K3

Treatment of Nightmares and Insomnia in Crime Victims

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Introduction: Crime victims commonly manifest symptoms of posttraumatic stress disorder (PTSD). Two common PTSD symptoms are insomnia and nightmares, both of which can disrupt daytime functioning as well as thwart efforts towards overcoming other stress symptoms. Clinical research has demonstrated that cognitive-behavioral treatments are effective in reducing nightmare and insomnia complaints. We hypothesized that crime victims would respond to imagery rehearsal therapy for nightmares and sleep hygiene instruction for insomnia.

Methods: Eligible clients reported symptomatic complaints of nightmares and insomnia, were victims of a crime at least six months prior to enrollment and 18 years or older. Treatment consisted of three, three-hour sessions and one brief follow-up session. Clients were trained to use imagery rehearsal (to alter dreams while awake and then to rehearse a new set of images) to treat nightmares and were instructed on sleep hygiene principles. To measure treatment impact, clients completed validated questionnaires on PTSD, sleep and nightmares before and 10 weeks after treatment. Nightmare frequency was assessed by nights and number of nightmares. Sleep improvement was measured by changes in sleep latency (SL) and sleep quality (SQ). Sleep quality (PSQI component 1) was measured with a four point scale, ranging from very good (0) to very bad (3). The Sleep Impairment Index (SII), a seven-item scale (each rated from 1 to 5; total range 7 to 35) reflects greater impairment with higher scores; >15 indicates impaired sleep (Morin, 1999). For sleep latency, four clients who endorsed values greater than 100 minutes were reported separately.

Results: To date, twenty-eight clients (23 females, 5 males) completed the within-group protocol with a 10-week follow-up. The mean (SD) age was 42 (12.5) years. The mean (SD) nightmare chronicity among clients was 13.3 (12.9) years. Ethnicity was 75% Non-Hispanic White. Paired t-tests revealed significant changes in all five variables, with clinically meaningful decreases in nightmares and sleep latency. The four outliers had a mean latency of 195 (113.6) minutes at intake, and a post-treatment mean of 110 (92.7). Sleep quality went from fairly bad (1.9) to fairly good (1.2). Sleep impairment scores improved but did not drop below Morin's cutoff of 15, indicating persisting sleep impairment.

Table 1

Sleep Variables	PRE *M (SD)*	POST *M (SD)*	Δ	*P*
Nights	3.75 (2.49)	2.12 (2.20)	-43%	.000
Nightmares	6.32 (5.92)	2.79 (3.36)	-56%	.001
SL (mins)	40.80 (24.70)	20.60 (11.70)	-50%	.000
SQ*	1.90 (0.90)	1.20 (0.80)	-17%	.001
SII	26.40 (4.10)	20.80 (5.90)	-21%	.003

**Decreased scores reflect sleep quality improvement; non-parametric sign test performed for significance.*

Conclusions: Crime victims, as well as other trauma survivors, who suffer from PTSD may benefit directly from improved sleep habits and decreased nightmares, although the persistence of sleep impairment in this sample suggests the need for an expanded differential diagnosis beyond insomnia. Notwithstanding the uncontrolled protocol, trauma survivors appeared receptive to simple cognitive-behavioral treatments and instructions. Given the brevity of these therapeutic approaches for nightmares and insomnia and their potential cost-effectiveness, they may serve an important supplemental role in treating PTSD patients. Further investigation is needed to determine whether or not they improve other PTSD symptoms as well.

Research supported by New Mexico Crime Reparations Commission (Victims of Crime Act), NIMH (MH 53932)

1055.K3

Prevalence of "Complex Insomnia"—Insomnia Plus Sleep-Disordered Breathing—in Crime Victims with PTSD

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Introduction: Difficulty falling or staying asleep, commonly termed "insomnia," is a frequent complaint of crime victims with posttraumatic stress disorder (PTSD) and is likely viewed as a psychiatric symptom rather than a sleep disorder. As such, other causes of insomnia may be

prematurely excluded from the differential diagnosis. For example, sleep-disordered breathing (SDB) is the chief cause of insomnia in as many as 5 to 10% of patients who present to sleep disorders clinics. The current study was undertaken to: 1) assess signs and symptoms of insomnia and SDB in a consecutive series of crime victims; and 2) assess the potential for the diagnosis of "complex insomnia" (i.e., both insomnia and SDB), utilizing validated sleep instruments. We hypothesized that insomnia in crime victims would be severe, but would also be coupled with an increased frequency of SDB symptoms, all of which might lead to greater impairment.

Methods: Forty adult crime victims (12 males, 28 females) with PTSD symptoms were recruited to participate in a program to treat insomnia and nightmares. Mean age was 43 and mean BMI was 27. Self-reported sleep assessments were divided into three categories (Table 1): 1) Insomnia symptoms: sleep latency (SL); total sleep time (TST); and, sleep efficiency (SE%); 2) SDB symptoms: loud snoring (SNORE); breathing cessation episodes (STOP); and, choking, gasping or struggling for breathe (CHOKE) observed by patient or bed partner; and, 3) Validated Sleep Instruments: Epworth Sleepiness Scale (ESS) measured daytime sleepiness; Pittsburgh Sleep Quality Index (PSQI) measured global sleep quality; and, Functional Outcomes of Sleep Questionnaire (FOSQ) measured daytime impairment due to sleepiness and fatigue.

Results: On average, crime victims suffered from severe insomnia as evidenced by markedly abnormal sleep parameters. Symptoms highly indicative of SDB were present in 50% of patients. Thirty-five percent of patients reported ESS scores > 10, a commonly used cut-off indicative of disorders of excessive sleepiness, such as SDB. PSQI scores were inordinately high, consistent with very poor sleep quality, exceeding values observed in insomniacs or depressives. Impairment scores (FOSQ) were equivalent or slightly worse than those obtained from obstructive sleep apnea patients.

Table 1

Insomnia Symptoms		
SL	TST	SE%
58.74	4.96	61%
SDB Symptoms		
SNORE	STOP	CHOKE
52.5%	47.5%	40.0%
Sleep Instruments		
EPWORTH	PSQI	FOSQ
7.03	13.88	71.94

Conclusions: Many crime victims in this sample reported paradoxical sleep symptoms, that is, both insomnia and SDB, or "complex insomnia." Through self-report, these patients had a mean sleep efficiency well below the norm of 85%, yet 50% reported symptoms consistent with SDB, such as loud snoring. Prior to enrollment in our study, many had attempted counseling, sleep hygiene instructions, or medications to combat their sleeplessness. Most reported limited success with these interventions. Conceivably, high levels of anxiety and hyper-arousal in these PTSD patients may have negated their capacity to discern the symptom of "sleepiness." This may explain why less than 10% had ever been referred or self-referred to a sleep center. Nonetheless, polysomnography appears to be an appropriate step in the evaluation of these crime victims, and such a prevalence study is currently in progress.

Research supported by New Mexico Reparations Commission (Victim of Crime Act), Oxnard Foundation, NIMH (MH53239).

1390.K3

Perception of Wake Instead of Sleep by Insomniacs Early and Late in the Non-REM Sleep Period

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Introduction: Insomniacs are more likely then good sleepers to report having been awake when woken following 5 minutes of Stage 2 sleep.[1] We found that this is related to insomniacs' global inability to distinguish between prior wake and Non-REM sleep upon awakening. However, 5 minutes following Stage 2 onset may be too early in the sleep cycle to accurately sample sleep/wake perception. The present study investigates whether sleep state misperception persists when awoken from Stage 2 sleep later in the sleep cycle.

Methods: Five insomniacs (4F, 1M) who reported SOL>30min, WASO>40min, and SEF<80% on a 7-day sleep/wake diary underwent 4 weekly laboratory PSG recordings and were compared to 7 good sleepers (3F, 4M, diary SOL<20min, WASO<20min, SEF>90%). Across the night subjects were presented with a 200Hz tone delivered through a speaker at the bed head. Following verbal acknowledgment of hearing the tone, a recorded question was presented through the speakers; "Just prior to hearing the tone, were you awake or asleep?" These sleep/wake probes occurred under four different conditions; Wake- after 5 minutes of wake without movement, Early Non-REM- 5 minutes after the first sleep spindle/K complex following sleep onset, Late Non-REM- 5 minutes after the return to Stage 2 following SWS, or 20 minutes of continuous Stage 2, REM- 5 minutes after REM onset. The schedule cycled through these four conditions to maintain sleep architecture and provide samples of each sleep/wake probe distributed evenly across the night.

Results: The table below presents the probabilities of reporting being awake just prior to probes during wake, early Non-REM, late Non-REM and REM sleep, and additional probabilities for total Non-REM sleep and total sleep. A two-way analysis of variance of responses to Non-REM probes indicated a significant main effect of condition (Insomniac vs Control, F= 9.72, p= .01) but no significant main effect of probe type (Early Non-REM probe vs Late Non-REM probe, F= .456, n/s), and no interaction of condition and probe type (F=.317, n/s).

Table 1

Measure	Controls	Insomniacs	Group difference *t*	Significance
P(W/w) -awake	.82 (.26)	.94 (.13)	.97	n/s
P(W/n1)- early Non-REM	.11 (.10)	.54 (.29)	3.70	.004
P(W/n2)- late Non-REM	.18 (.17)	.55 (.37)	2.32	.043
P(W/n1+n2)- Non-REM total	.14 (.11)	.53 (.29)	3.25	.009
P(W/r)-REM	.16 (.11)	.56 (.29)	3.43	.006
P(W/s)- all sleep	.15 (.08)	.54 (.25)	3.87	.003

Conclusions: These results further demonstrate that insomniacs are more likely than good sleepers to perceive having already been awake following nocturnal awakenings. The present study indicates that our previous findings on sleep state misperception early in Non-REM sleep extend to Stage 2 sleep later in the sleep cycle.

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1391.K3

A Comparison of SDQ Responses of Healthy Older Insomnia Complainers and Normal Controls

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Introduction: Given the widespread prevalence and potential health impact of sleep disorders, there is great need for an easily-administered and valid screening device for clinicians. The Sleep Disorders Questionnaire (SDQ) was designed to address this need. Below we compare responses of older insomnia complainers with data from normal controls on four SDQ clinical-diagnostic scales (Douglass et al., 1994): narcolepsy (NAR), periodic limb movement disorder (PLM), psychiatric sleep disorders (PSY), sleep apnea (SA).

Methods: 39 older insomniacs (mean age: males 64.4 ± 8.5 years; females 64.1 ± 6.9 years) met study eligibility criteria of > 55 years and a primary insomnia diagnosis. Participants were required to be free of acute or unstable physical illness, psychiatric disorders, and organic sleep disorders. They received overnight monitoring for SA and PLM (using cutoffs of >10/hr). Insomnia inclusion criteria were < 80% sleep efficiency, or sleep latency > 30 min, or total sleep time < 6 hr calculated as mean values on two weeks of sleep logs. The SDQ was administered to all study applicants. Using the scoring manual and software provided by Douglass et al., we analyzed our subjects' responses on four clinical-diagnostic scales derived from the SDQ.

Results: There was no difference between our healthy older insomniacs and the normal controls on PSY and NAR scales. However, insomniacs scored higher (indicating greater pathology) than controls on PLM. The median PLM score for our male insomniac participants is equivalent to the 75th percentile for male controls and the median PLM score for female insomniacs fell between the 75th and 90th percentile for female controls. For SA, our female insomniacs' median score again fell between the 75th and 90th percentile for female controls. However, median scores of older insomniacs, with the exception of PLM, are well below those of SDQ validation sleep disorders patients. For example, the SA median scores for sleep disorder patients are 42 and 40 for males and females respectively. Further, unlike patient groups and similar to controls, there was little gender difference on the four SDQ scales.

Table 1. Median SDQ Responses for Older Poor Sleepers and Normal Controls

	Male		Female	
	Insomnia	Controls	Insomnia	Controls
SDQ Scales	N=13	N=39	N=26	N=45
NAR	21	20	20	21
PLM	**21**	**14**	**23**	**14**
PSY	16	16	18.5	18
SA	24	21	**23**	**16**

Conclusions: Although study participants had a primary insomnia diagnosis and were screened for SA and PLM, they scored higher than controls on SDQ scales tapping these disorders. Several explanations are possible: 1) ambulatory recordings were not sufficiently sensitive to these disorders, 2) one-night recording missed or underestimated a clinically significant disorder, or 3) scoring for control subjects (males 28.4 ± 11.3 years; females 25.4 ± 9.1 years) was not appropriate for older subjects. Further, Douglass et al. note that the PLM scale may reflect an underlying sleep disruption. This is consistent with the sleep disruption present in our older subjects' sleep log and PSG data. Our subjects' highest PLM scale responses are on items indicating sleep disruption ("I wake often during night," "I feel I have insomnia," and length of longest wake period). These data suggest that except for greater sleep disruption, SDQ responses of healthy older insomniacs may not substantially differ from those of younger normal controls.

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1728.K3

Evoked EEG Activity in Patients with Insomnia and Good Sleeper Controls

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Introduction: The inability to initiate and maintain sleep has been hypothesized to be related to elevated somatic[1] and/or cortical[2] arousal. While it is not difficult to conceptualize how either type of arousal might interfere with the initiation of sleep, it is more difficult to conceive of how these factors are responsible for awakenings. One possibility is that elevated cortical arousal may cause patients with insomnia to be more sensitive to "environmental noise" and thus more likely to awaken. In the present study, we evaluated whether auditory stimuli administered during NREM sleep results in greater increases in fast frequency EEG activity in patients with insomnia.

Methods: 8 subjects with primary insomnia (5 females, age = 36.2 [range: 24-54], Pittsburgh Sleep Quality Index [PSQI] = 11 [±1.5], BDI = 5.9 [±3.2], BAI = 6.5 [7.3]) were compared to 7 good sleeper controls (4 females, age = 36.1 [range: 23-49], PSQI = 2.4 [±1.4], BDI = 1.0 [±0.9], BAI = 1.3 [1.9]). The groups did not differ in sex, age, race, height or weight. The groups significantly differed ($p<.05$) on the PSQI, BDI and the BAI. The latter two, however, were within normal limits for the patients with insomnia. Subjects were studied for two nights in the sleep laboratory. The first night was an adaptation night. The second night was a forced awakening paradigm. In this procedure, subjects were played single word stimuli across four time periods: at natural sleep onset (trial 1) and at sleep onset transitions following three forced awakenings from Stage 2 sleep. Pre-post intervals were analyzed using power spectral analysis (PSA) to determine if alpha blocking occurred in response to stimuli administration (validity check regarding procedures). PSA was also used to analyze all the stimuli presented during NREM sleep (Stages 1, 2). PSA was performed for 4 seconds prior to and after each stimulus administration. Relative activity at C3 and C4 were evaluated for the following frequencies: Alpha (7.5-12 Hz), Sigma (12-14 Hz), Beta (14-20 Hz), and 40 Hz (35-45 Hz). Average NREM profiles were created for all the stimuli administered during sleep for a mean of 24.4 word administrations per subject. Groups were compared using mixed model ANOVAs and post hoc t-tests.

Results: During wakefulness, pre-post changes for alpha occurred as expected and were significant for C3 ($p = .05$) and tended to be significant for C4 ($p = .07$); no group interaction was observed. During NREM sleep, main effects were evident for Sigma and Beta activity. Sigma activity significantly increased at C3 ($p=.02$), Beta activity significantly

increased at C3 (p = .02) and tended to increase at C4 (p=.06). During NREM, only Sigma activity distinguished groups; patients with insomnia exhibited significantly more activity at C4 (p=.02).

Conclusions: Our results suggest that patients with insomnia respond differently to auditory stimulation during "shallow" NREM sleep. Increased activity in the Sigma range suggests that thalamic related sensory inhibition may be increased in patients with insomnia. Whether this corresponds to increased activation of lower structures remains to be determined.

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1083.K3

A Causal Relationship Between Heritable Personality Traits and Chronic Insomnia

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Introduction: Abnormal features in personality test (Minnesota Multiphasic personality Inventory) have been reported in insomniac patients (Dorsey et al 1997). However, no specific factors were demonstrated among these. The Temperament and Character Inventory (TCI) provides an interesting model of inherited personality traits (Cloninger 1993). The four dimensions of temperament are: novelty seeking (NS), harm avoidance (HA), reward dependence (RD) and persistence (P). Does a specific personality trait increase the vulnerability for insomnia?. Therefore we explored the relationship between chronic insomnia and heritable personality traits by the TCI. Our working hypothesis is that there may exist a causal relationship between the temperament factors and chronic insomnia. We conducted the present study to test this hypothesis.

Methods: Subjects were 20 non-medicated patients with chronic insomnia (6 male, 14 female, ages 22-49). They underwent polysomnography for two consecutive nights, filled out the 226-item self questionnaire TCI (French version) during their stay in the sleep laboratory. In addition, the Hospital Anxiety and Depression scale (HAD), a self report rating scale designed to measure both anxiety and depression was also completed. In our sample, no patient presented sleep onset insomnia, but all had a high rate of wakefulness after sleep onset or a long period of intra-sleep waking. The relationship between TCI dimensions and sleep variables was tested using both the Pearson correlation method and the factor analysis method.

Results: The most evident result so far was the high correlation of 0.55 between HA and the anxiety subscale of HAD. The anxiety score was correlated to sleep latency (r=0.73). The depression scale of HAD was highly correlated to REM sleep (r=0.82). Novelty seeking was negatively correlated to both intrasleep waking (-0.7399) and anxiety scale (r=-0.40).

Conclusions: Results reveal that the high score of harm avoidance is present in insomniac patients. The harm avoidance scores suggest the presence of heritable bias such as pessimistic worry in anticipation of future problems, passive avoidant behaviors such as fear of uncertainty and rapid fatigability. The harm avoidance score in insomniacs patients was significantly related to anxiety subscale of HAD, suggesting that harm avoidance is associated with both anxiety and insomnia.. Another temperament dimension NS has shown a fairly high negative correlation with intrasleep waking. Novelty seeking is viewed as a heritable bias in the activation of behaviors in response to novelty, impulsive decision making and quick loss of temper. Our data suggest the hypothesis that subjects with higher harm avoidance have a greater probability of being affected by chronic insomnia. The study is still in progress. Nevertheless, present results are indeed encouraging. Moreover the relationship is causal i.e. the personality traits are a cause among others of the insomnia. Further studies could eventually establish a causal link between a genetic background and chronic insomnia.

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1747.K3

Subjective Experience of Sleep Onset Latency in Young Adults with Insomnia

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Introduction: It is generally reported that insomniacs overestimate sleep onset latency (eg. Perlis, Giles et al. 1997). There is also evidence that brief arousals from sleep may occur more frequently in insomnia, and evidence of increased high frequency EEG during sleep (Lamarche and Ogilvie 1997). The hypothesis that changes in the perception of sleep onset latency (SOL) are related to brief arousals from sleep was examined in young adults with insomnia.

Methods: 19 normal subjects (Control group), and 19 insomnia subjects were carefully screened for medical, psychiatric and sleep disorders. Subjects were matched for age (21.1±3.7), BMI (21.7±2.4), education, and gender. Subjects in the Insomnia group satisfied DSM-IV criteria for primary insomnia. Subjects also completed a self-report battery that included the MMPI-2 and the Sleep Disorders Questionnaire (SDQ). An average of 12 sleep onsets were obtained over two non-consecutive experimental nights using a nocturnal multiple sleep onset protocol. Subjective estimation of SOL and indices of sleep quality were assessed by self-report inventory after termination of each sleep onset. Sleep duration was 7.5-16 minutes of Stage 2 or greater sleep. Objective measures of SOL were assessed using traditional sleep stage scoring of standard overnight polysomnography (PSG). Brief arousals from sleep (1-15 seconds duration) were assessed using a visual scoring protocol. EEG power during sleep was assessed by automated analysis of occipital EEG.

Results: Subjects in the Insomnia group were clearly distinguished from those in the Control group in their self-reported levels of psychopathology (MMPI-2, $F(175,1) = 110.9$, $p<.001$) and sleep-related complaints (SDQ, $F(369,1) = 21.9$, $p<.001$). As expected, objective SOL to Stage 2 sleep was found to be longer for the Insomnia group than for the Control group ($F(325,1) = 22.41$, $p<.001$). Both groups tended to overestimate SOL, however, the Insomnia group did not overestimate SOL to a greater extent than the Control group ($F(36,1) = 0.54$, $p>.05$). Further, there was no significant increase in the frequency of brief arousals from

sleep in the Insomnia group ($F(36,1) = 1,90$, $p>.05$), and no increase in high frequency EEG activity after sleep onset ($F(239,1) = 2.02$, $p>.05$).

Conclusions: The absence of a difference in degree of overestimation of SOL between the two groups was contrary to previous reports, as was the absence of a difference in high frequency EEG power. Results suggest that overestimation of SOL is not a necessary feature of Insomnia in young adults defined by conventional criteria. However, the lack of a difference the frequency of brief arousals is still consistent with the concept of a physiological basis for sleep misperception in insomnia.

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1759.K3

Measuring Sleep Continuity: Is there a Definition that will Minimize Subjective vs Objective Discrepancies?

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Introduction: When self report measures of sleep continuity are compared to polysomnography discrepancies between the measurement strategies are apparent. These discrepancies are most marked in patients with insomnia, but are also evident across diagnostic categories.[1] Thus, it may be that subjective - objective discrepancies occur because PSG definitions are based on "cutoffs" that are below perceptual thresholds. The goal of the present study was to assess whether subjective - objective discrepancies could be minimized or eliminated by using more conservative PSG definitions.[2]

Methods: Data for this study were drawn from a larger investigation. Three groups (n=9 per group) were compared: Primary Insomnia, Major Depression, Good Sleepers (no history of psychiatric/ sleep disorders). Groups were matched for age, sex, height and weight. The sample was 66% female; mean age was 37.5 (± 10.7). Subjects were studied for a minimum of two nights in the laboratory and completed sleep diaries each morning. Subjective estimates of sleep were evaluated for their relationship to formal PSG definitions, using a threshold approach. To accomplish this, several PSG definitions for sleep latency and awakenings were calculated for each subject. PSG definitions for sleep latency used the following cutoffs: 30 seconds stage 1; 30 seconds stage 2; 90 seconds any stage; 8 of 10 minutes any stage; 10 minutes any stage; 15 minutes stage 2 or deeper. PSG definitions for "an awakening" used the following cutoffs: 30 seconds; 1 minute; 2 minutes; 4 minutes. If the subjective value of sleep latency was within 10 minutes of a given PSG value, it was assigned a value of "1"; larger discrepancies were assigned a value of "0". If the subjective value of intermittent wake time (IWT) was within 1 minute of a given PSG value, this was assigned a value of "1"; larger discrepancies were assigned a value of "0". Using this approach, percentage of subjects who exhibited a "close" correspondence between subjective and objective definitions was calculated for each PSG definition. Contingency analyses were used to evaluate within and between group differences.

Results: Within-group, subjects made very reliable and consistent subjective estimates of sleep latency regardless of the PSG definition (see table). There were also very reliable between-group differences. Good sleeper and MDD Ss were largely "accurate" in estimating sleep onset. PI Ss showed subjective - objective discrepancies even when PSG data indicated they were in stage 2 or deeper sleep for at least 15 minutes. For the awakening data, subjective-objective discrepancies varied in association with the various PSG definitions. The largest correspondence was for awakenings defined using a 4 minute threshold.

Table 1

GRP	STG1 30 SEC.	STG2 30 SEC.	STG1 90 SEC.	STG1 8 / 10 MIN.	STG1 10 MIN.	STG2 15 + MIN.
N	66	77.78	66.67	66.67	66.67	66.67
MD	77.78	77.78	77.78	77.78	88.89	88.89
PI	33.33	22.22	22.22	33.33	22.22	22.22
p	.13	.02	.04	.14	.01	.02

Table 2

GRP	IWT 30 SEC.	IWT 1 MIN.	IWT 2 MIN.	IWT 4 MIN.
N	33.33	55.56	77.78	77.78
MD	33.33	33.33	33.33	22.22
PI	0.00	0.00	33.33	55.56
p	.15	.03	.09	.06

Conclusions: Our results suggest that subjective-objective discrepancy differences for sleep latency in primary insomnia are not dependent on PSG definitions. The awakening data from the present study suggest that longer waking intervals are more readily perceived by subjects. These data lend support to the neurocognitive model[3] which suggests that factors not measured directly by polysomnography account for subjective-objective discrepancies as they present in primary insomnia.

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1764.K3

The Impact of Nonpharmacological Interventions for Insomnia on Cyclic Alternating Pattern Sequences (CAPS)

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Introduction: Cyclic Alternating Pattern Sequences (CAPS) are bi-phasic electrical expressions of arousal fluctuation during NREM sleep consisting of an arousal phase followed by a return to tonic activity. CAPS have been shown to be elevated in insomniacs, and drug treatments have been shown to reduce CAPS to normal levels (Terzano & Parrino, 1992). Nonpharmacological treatments for insomnia are effective in treating insomnia symptoms, but their effect on CAPS has not been assessed. In the present study, CAPS in a sample of sleep onset insomniacs were assessed before and after nonpharmacological treatments (i.e., stimulus control instructions and/or light therapy). Subjects' sleep was significantly improved for all treatment groups (Bootzin, Lack, & Wright, 1999), therefore it was hypothesized that CAP rates would improve following treatment.

Methods: Participants were 44 chronic sleep-onset insomniacs (44 female, 19 male; mean age=31.6 years). PSG and diary data were evaluated at baseline and at immediate post-treatment follow-up after 4 weeks of treatment. Treatments consisted of morning dim light (DL), dim light plus stimulus control instructions (DLSC), morning bright light (BL), or bright light plus stimulus control instructions (BLSC). The BLSC group was not analyzed due to logistical constraints. CAPS were scored using Terzano's criteria by a scorer who was blind to the condition and time of the record.

Results: Baseline and post-treatment data were compared using a two factor repeated measures ANOVA. The main effect of group and the interaction between group and CAP rate were significant (F=4.06 and F=3.80, p<.05, respectively, see Table 1). Within group t-tests revealed no significant changes in CAP rate as a result of treatment. Differences between groups both before and after treatment were tested using a simple effects ANOVA. The effect of group was significant at pretest (F=5.82, p<0.01) but not post-treatment (F=1.79, p=0.18); the DL group was found to have a significantly higher baseline CAP rate than the other two groups (p<0.013). Pearson Product-Moment correlations were conducted to assess the relationships between CAPS and improvement variables (sleep onset latency from diary reports and sleep efficiency from the polysomnography); none were significant. Pre- and post-CAP rates, however, were significantly associated with each other (r=0.62).

Table 1. CAP Rate (%) Means

Group	Pre-Tx (SD)	Post-Tx (SD)	t-statistic	p-value
DL	17.50 (9.07)	14.49 (6.48)	-1.76	0.10
DLSC	10.84 (5.91)	13.71 (7.05)	1.33	0.12
BL	9.35 (5.47)	10.38 (5.82)	0.93	0.37

Conclusions: CAP values were not found to be related to sleep, and their values were much lower than those found in previous research. Treatment had little effect on changing CAPS. It is possible that treatment of sleep onset insomnia, unlike treatment of sleep maintenance insomnia, does not affect physiological processes during sleep, and therefore would not affect CAPS. However, certain methodological constraints restrict strong conclusions about the relationship between CAPS and nonpharmacological treatment. The digital system used to record the data did not allow for flexibility in scoring arousal events. The present results do not preclude the possibility that nonpharmacological treatments can improve CAPS.

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1440.K3

Efect of Cognitive Behavioral Therapy on Polysomnography, Sleep Logs and Quality of Life in Patients with Primary Insomnia

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Introduction: Cognitive behavioral therapy (CBT) has been proven effective in treating primary insomnia. Few studies, however, have measured objective changes, nor has the influence of CBT on quality of life been established. In this ongoing two-centre study we investigated the effect of short-term CBT on polysomnography (PSG), sleep logs (SL) and quality of life (QOL) hypnotic-independent patients with primary insomnia.

Methods: Subjects were 28 patients with primary insomnia (18 females, 10 males) with a mean age of 45.5 years (range 25-66) and a mean duration of insomnia of 16.9 years (range 1-50). All patients were referred to the sleep centre by their general practitioner or specialist. Inclusion criteria were a sleep onset latency (SOL) and/or wake after sleep onset (WASO) of ≥ 30 minutes and a sleep efficiency (SE) ≤ 85% on more than 3 nights a week. Moreover, the insomnia had to exist ≥ 1 year. Exclusion criteria were excessive alcohol consumption (> 22 consumptions a week) and hypnotic use (≥ 3 nights a week). Psychopathology was excluded by anamnesis and questionnaires. Other sleep disorders were excluded by sleep history and PSG. Patients were not allowed to follow other treatments for insomnia during the study.Treatment: All subjects underwent cognitive-behavioral therapy (sleep hygiene, stimulus control, sleep restriction, relaxation exercises, and cognitive therapy) in 6 weekly sessions.Measures: Two nights of polysomnography, one week sleep/wake diary, and a questionnaire for quality of life were examined at 3 time points: at baseline, after 3 months waiting period, and one month after therapy. Outcome measures were sleep onset latency, total sleep time, sleep efficiency, wake after sleep onset and number of times awake as measured by PSG and SL, and the amount of slow wave sleep as measured by PSG. QOL was measured by a combination of the sickness impact profile (SIP) and the RAND-36.Statistics: General Linear Model factorial analysis was used to determine variances over different time points in PSG and SL. Kruskal-Wallis was used for the data from the QOL questionnaires, Wilcoxon signed rank test for related samples was used for the analysis between PSG and SL.

Results: No significant improvements were seen during the waiting period. After treatment, PSG showed significant decrease in sleep onset latency, wake after sleep onset and the number of times awake. In the SL, sleep onset latency and sleep efficiency were significantly improved. Large discrepancies are seen between PSG and SL. QOL data after therapy show significant improvements in the way patients feel, their social interactions, recreational activities and work or other daytime activities.

Conclusions: 1. CBT improves both objective and subjective sleep2. Large discrepancies are seen between objective and subjective sleep3. Quality of life improves when sleep improves

1780.K3

Comparative Meta-Analysis of Cognitive-Behavioral Therapy and Pharmacotherapy for Insomnia

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Introduction: There are three meta-analyses that support the efficacy of treatments for primary insomnia: two review cognitive-behavioral treatments (e.g., 1) and one reviews pharmacologic interventions.[2] To date, there are only two experimental studies that directly compare the two treatment strategies (e.g., 3). Both investigations found that cognitive-behavioral treatment (CBT) is as effective as pharmacotherapy (PT) in the short term and is better sustained over time. The objective of the present study was to evaluate whether the acute effects of treatment are comparable using data from the two treatment outcome literatures.

Methods: An initial pool of 190 treatment outcome studies of primary insomnia was identified by a Medline and PsychInfo search (1966- pres-

ent) and from reference lists provided by the authors from two of the previous meta-analyses. The 190 studies were reviewed for the following inclusion and exclusion criteria. Inclusion criteria: 1) duration of insomnia > 3 mos., 2) cognitive-behavioral treatments must include either stimulus control or sleep restriction. 3) pharmacological treatments must be either benzodiazepines or like GABAergic agents (e.g. zolpidem) 4) studies must use sleep diary measures and have pre/post data. Exclusion criteria were: 1) sleep continuity variables presented as ordinal data. 2) no mean or standard deviation data. Pre-post treatment means and standard deviations were calculated for major sleep continuity variables. Individual effect sizes were derived and weighted by sample size to calculate and compare average effect sizes formally (t-tests).

Results: 14 cognitive-behavioral studies involving 250 subjects and 8 pharmacotherapy studies involving 286 subjects met the inclusion/exclusion criteria. The two groups did not differ with respect to gender or age. The average number of CBT sessions was 4.9±2 over an average period of 5.3 ± 2.1 weeks. The average length of PT was 2 ± 2 weeks. Table 1 presents the Pre-post treatment means and weighted effect sizes for the following 4 sleep continuity variables: Sleep Latency (SL), Number of Awakenings (NA), Wake After Sleep Onset Time (WASO), and Total Sleep Time (TST). The overall mean effect size averaged over all sleep continuity variables was .79 for CBT and .80 for PT. For individual sleep variables, only the effect size for sleep latency was significantly different, with CBT showing greater reductions in sleep latency relative to PT (t = -2.85, p<.05).

Table 1

Efficacy of Pharmacotherapy Versus Cognitive-Behavioral Therapy in Studies of Chronic Insomnia

Diary	Pre-Tx	Post-Tx	Pre-PostTx	Subs	d^+
SL	(M,SD)	(M,SD)	(change)	(n)	
PT (N=6)	48.85 (29.73)	34.36 (26.26)	30%	129	.45
CBT (N=12)	53.99 (27.79)	30.93 (16.03)	43%	225	1.05*
NA					
PT (N=4)	2.94 (2.01)	1.80 (.99)	39%	174	1.03
CBT (N=4)	2.29 (1.87)	1.67 (1.59)	27%	58	.49
WASO					
PT (n=1)	55.09 (37.8)	29.49 (19.5)	46%	17	.89
CBT (N=5)	68.60 (40.27)	30.22 (23.98)	56%	81	1.18
TST					
PT (N=6)	332.08 (55.32)	372.59 (48.14)	12%	130	.83
CBT (N=8)	333.42 (62.08)	352.89 (44.24)	6%	146	.45

+ Weighted effect size = $\Sigma[(Mpretx-Mposttx)/pooled\ SD*n]/\Sigma(n)$
* p< .05; t=-2.85; N = # of studies; Subs = number of subjects

Conclusions: Cognitive-behavioral treatments for primary insomnia appear to yield results that are comparable to pharmacotherapy and may be superior for sleep initiation problems. A possible explanation for the sleep latency finding may be related the use of some benzodiazepines with long peak plasma level times in studies where drug administration was scheduled at or within 60 minutes of bedtime. Alternatively, CBT may have produced significantly better outcomes within this domain, because these studies tended to preferentially focus on patients with sleep initiation complaints.

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1468.K3

Autonomic Changes in Insomnia Patients Uncovered by Time Dependent Analysis of Heart Rate Variability

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Introduction: Insomnia is a frequent complaint with protean manifestations and major effects on well-being, health and performance. The assesment of this disorder is based on patient's complaints, questionnaires, actigraphy and polysomnography in selected cases. Insomnia patients display a range of physiologic changes, compatible with certain autonomic dysfunction. Previous work uncovered increased sympathetic activity in insomniacs[1] and in fatal familial insomnia.[2] Our objective was to asses the degree of physiologic impairment in insomniacs and follow up treatment results.

Methods: The sudy included seven subjets: one with chronic insomnia, one with transient insomnia and five matched controls with no sleep related problems.All subjects underwent whole night polysomnography for two nights, except the transient insomniac who had three studies: one during the insomnia time and two after recovery.The ECG tarce from the polysomnography was analyzed off line by means of a previously published method of time dependent spectral analysis.[3] The spectral varaiables of interest were: Total power (T), low frequency power (lf), high ferquency power (hf) and autonomic balance (defined as lf/hf=balance). The mean of each varaiable was calculated for the whole night, waking period before sleep onset, first episodes of slow wave sleep (sws1) and REM (rem1).

Results: (1) the average T for the whole night displayed great variability between subjects, and was almost the same for the second study in the same subject. (2) In the transient insomnia patient T decreased consistently with recovery from sleep disturbance: it was 50% higher when calculated for the insomnia period than for each one of the sleep studies after recovery. (3) The mean lf, hf, and T displayed great variability while awake before sleep onset and during sws1, with no difference between normal sleepers and insomniacs. (4) The only parameter that was strikingly different for insomniacs was the autonomic balance for the whole night as well as for sws1; it was lower in controls, pointing towards a less sympathetic autonomic activity in normal sleepers. During sws1 all subjects, the chronic insomniac excepted, had parasympathetic predominnce (balance<1).

Conclusions: (1) The study suggests that heart rate variability anlysis can be used in the assesment and follow-up of insomnia patients. (2)Transient insomnia does not cause the autonomic balance to be in abnormal limits, however, for the same patient, there is aclear and consistent decrese in sympathetic activity with recovery. (3) Chronic insomniacs present sympathetic predominance throughout the night, slow wave sleep included. In this regard insomnia patients are similar to patients with Obstructive Sleep Apnea Syndrome or with Periodic Leg Movements of Sleep.

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1147.K3

Memory Impairments Associated with Sleep Disruptions in Insomniacs

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Introduction: In addition to complaints of sleep disruptions, insomniacs frequently report memory impairments. Indeed, some studies reported deficits in episodic memory in insomniacs.[1] Other studies, using total or selective sleep deprivation in normal sleepers, have highlighted the importance of sleep in memory consolidation, especially in procedural learning tasks.[2] However, to our knowledge, procedural learning has never been studied in insomnia. The aim of the present study was to measure the impact of nocturnal sleep disruptions that characterize insomnia on episodic and procedural memory.

Methods: Twelve insomniacs (3M, 9F) (mean age: 42.9 ± 7.9 yrs,) participated. EEG, EOG and chin-EMG were recorded for two consecutive nights. Episodic (Auditory Verbal Learning Test (AVLT), Rey Figure (RF), Logical stories of the Wechsler-Memory scale) and procedural memory tasks (Tower of Hanoi (TH) , Rotor Pursuit (RP)) were administered before and after the second polysomnographic (PSG) recording. Memory variables included pre- and post-PSG measures of 1) the total number of items recalled for episodic memory tasks, 2) the mean number of moves necessary to solve the TH, and 3) the mean time (seconds) spent on the target for the RP. Sleep variables included % of stages 1 (%S1), 2 (%S2), and REM (%REM), sleep latency (SL), sleep efficiency (SE), REM sleep efficiency (RSE), total sleep time (TST) and the index of arousals/hour for stage 2 (A2). Partial correlations were used to assess the relationship between sleep disruptions and a) evening performance, b) next morning performance.

Results: For episodic memory, a higher %S1 was related to a better recall in the evening for RF (r = 0.68) and for W-M stories (r = -0.63) while an augmentation of A2 was negatively related to the number of words recalled on the AVLT in the evening (r = -0.65) and in the morning (r = -0.60). For procedural memory, a higher %S1 was negatively related to performance on the RP both in the evening (r = -0.63) and morning (r = -0.60). %REM and RSE were positively related to performance on the RP in the evening (r = 0.63; r = 0.66). Performance on the TH in the morning following PSG was positively correlated to TST (r=0.66) and negatively correlated to A2 (r = -0.62).

Conclusions: Poor sleep appears to have more negative consequences on procedural learning abilities than on episodic memory tasks. The greater the sleep disruptions, the worse was the consolidation of procedural tasks. These results suggest a greater sensitivity of procedural memory tasks to sleep disruptions and support previous findings showing poor performance on such tasks in normal subjects after sleep deprivation. These difficulties could be related to insomniacs' complaints of poor daytime functioning. Further studies are required to elucidate the nature of memory deficits associated with insomnia.

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1518.K3

Use of the Global Sleep Assessment Questionnaire to Identify Patients with a Sleep Disorder

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Introduction: Although sleep complaints are common, they often go undiagnosed, particularly within a primary care setting. Recognizing the need for a simple tool to screen for sleep problems, we developed a self-administered Global Sleep Assessment Questionnaire (GSAQ), to be used in a primary care setting to aid physicians towards a specific sleep diagnosis. The goal of this current study was to test the reliability and validity of the GSAQ, as well as its sensitivity and specificity to ensure that it can distinguish individuals with different types of sleep disorders.

Methods: 176 participants from 5 sleep centers in the US completed the GSAQ upon presentation to the center and were then evaluated by a certified sleep specialist. 66 primary care patients from 2 primary care practices completed the GSAQ at the primary care clinic and were then referred to the sleep center for a clinical evaluation. Primary care patients also completed a second GSAQ at the time of presenting to the sleep center (approximately 10-14 days after initial GSAQ).The GSAQ is a battery-style questionnaire that includes original items to identify the specific sleep disorders of interest (both a short and long version), the SF-36, a nine-item sleep scale from the Medical Outcomes Study questionnaire, and items assessing demographic characteristics. Using the final clinical diagnosis, including clinical judgment and confirmatory testing as appropriate as a gold standard, we also performed sensitivity and specificity analyses. The most common sleep disorders that were evaluated include Primary Insomnia Disorder (psychophysiologic insomnia, idiopathic insomnia, inadequate sleep hygiene, adjustment sleep disorder), Insomnia associated with a Mental Disorder, Obstructive Sleep Apnea Syndrome, Restless Legs Syndrome, Periodic Limb Movement Disorder, Parasomnias, and Shift Work Sleep Disorder.

Results: Patients presenting to the sleep center were predominantly males (54%), Caucasian (72%), with some college (80%), with a mean of 43.9 years of age.(Primary care patients were comparable except they were predominantly female (68%) and were less educated (65% had some college).)Our preliminary results suggest that an insomnia subscale consists of six items (sleep quality, number of nights with trouble falling asleep, number of total hours of sleep obtained, amount of worry about problems sleeping, number of minutes it took to fall asleep, and frequency of feeling downhearted and blue). An obstructive sleep apnea subscale consists of a series of 3 items (frequency of snoring, how loudly the snoring was, and frequency of breathing problems). The sensitivity and specificity for insomnia at the observed prevalence of 35% was 77% (52/74) and 64% (86/134), while the sensitivity and specificity for apnea at the observed prevalence of 30% was 83% (48/58) and 81% (112/139).

Conclusions: Our preliminary findings suggest that a well-designed self-report questionnaire, such as the GSAQ, can provide useful diagnostic information to improve the recognition rate of sleep diagnoses. Further analyses will focus on the psychometric properties of the scale

scores and ROC analyses. Future studies will then need to be undertaken to document its benefits in primary care settings.

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1832.K3

Daytime Sleepiness in Older Insomnia Complainers

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Introduction: Primary insomnia, as defined by the DSM IV, includes the complaint of difficulty initiating or maintaining sleep or nonrestorative sleep. The associated complaint of daytime fatigue is often elicited. The sleep disturbance must be distinguished from those associated with mental disorders, medical conditions, substance-induced disorders, circadian rhythm disorders or known organic sleep disorders. We recently completed a study of older adults meeting criteria for primary insomnia. Given that their sleep logs revealed significant sleep reduction and disturbance, this study was undertaken to objectively measure their degree of daytime sleepiness.

Methods: The subjects were older adults with complaints of insomnia who were recruited from the community. After rigorous evaluation, which included both apnea and PLM screening, 16 met criteria for primary insomnia and underwent three nights of attended polysomnography (PSG), i.e., one adaptation night and two data nights. The daytime Multiple Sleep Latency Test (MSLT) followed the second data night. Self-ratings of daytime somnolence were provided by the Stanford Sleepiness Scale and the Epworth Scale. The mean age of the sample was 62.8 years (range 55-75); 6 were males, 10 were females.

Results: The PSG data, summarized in the table below and derived from the night preceding the MSLT, do not support a clinically abnormal sleep onset latency. Rather, the amount of wake time after sleep onset (WASO) and the number of awakenings reveal significant sleep fragmentation. But despite this degree of sleep disruption, daytime sleepiness, objectively defined by the MSLT and subjectively rendered by the Stanford Sleepiness and Epworth scales, was well within the normal range. It is important to note, however, that the preceding night of sleep was not without influence. MSLT defined sleep latencies were influenced adversely by the number of awakenings (trend) and the proportion of stage I sleep in the preceding night; the proportion of stage 2 sleep was associated with greater alertness (trend). Nocturnal sleep latency was the best predictor of daytime sleep latency. There was a tendency for subjectively rated measures of daytime sleepiness to be inversely correlated with MSLT sleep latencies.

Table 1

N=16	Mean (Sr. Dev.)	Spearman Correlation with MSLT	
Age	62.8 (±7.48)	-0.22	ns
Stanford Sleepiness Scale	2.5 (±0.35)	-0.39	p<.11
Epworth Scale	9.6 (±1.30)	-0.32	p<.2
MSLT (min)	5.9 (±2.97)		
PSG measures:			
Sleep Latency (min)	6.2 (± 4.6)	0.45	p<.01
Total Sleep (min)	378.4 (± 63.8)	0.14	ns
% Sleep	83.4 (± 6.3)	0.14	ns
WASO (min)	53.5 (± 32.2)	-0.19	ns
# Wakes	24.1 (± 8.9)	-0.34	p<.10
Stage 1 %	22.6 (± 8.5)	-0.43	p<.05
Stage 2 %	51.0 (± 6.3)	0.37	p<.08
SWS %	1.7 (± 3.2)	-0.19	ns

Conclusions: A sleep maintenance insomnia characterized these older insomnia complainers rigorously screened for the diagnosis of primary insomnia. Their lack of daytime sleepiness is consistent with a hyperarousal etiology for this disorder. Daytime alertness was predicted by nocturnal sleep latency; it was also influenced to some extent by the dynamics of the preceding night's sleep.

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1566.K3

Racial Differences in Insomnia From a Normative Sample

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Introduction: There exists a substantial amount of data on self-reported disturbed patterns of sleep, but there is little data on racial differences in people with insomnia. The present study randomly sampled a metropolitan community and collected 2-weeks of sleep diary data to study patterns of sleep in people with reports of poor sleep.

Methods: We used random-digit dialing to solicit participation from at least 50 men and 50 women in each decade from 20 to 80 and older in the metropolitan Memphis (TN) area. Volunteers were paid between $15 and $175 (older adults were paid more) for completing a 14-day sleep diary and six questionnaires evaluating health, mood, and daytime functioning. Criteria for insomnia included: 1) insomnia duration of 6 months; 2) sleep latency > 30 minutes, or awake time during the night totaling > 30 minutes, at least three times per week; 3) a report of dissatisfaction with sleep. These criteria are consistent with the ICSD. Daytime functioning measures included in the sample were the Insomnia Impact Scale (IIS), the Epworth Sleepiness Scale (ESS), the Stanford Sleepiness Scale (SSS), the Fatigue Severity Scale (FSS), the State-Trait Anxiety Inventory (STAI), and the Beck Depression Inventory (BDI).

Table 1

	SLEEP MEASURES			
	African American		Caucasian	
Variable	M	(SD)	M	(SD)
WASO (min.)	56.9	(57.4)	41.8	(24.6)
TST (min.)	367.5	(76.4)	396.6	(66.9)
SE (%)	74.0	(12.4)	79.6	(7.9)
Naps (min.)	34.8	(29.7)	18.9	(23.0)

Results: We have collected data from 727 people and need approximately 50 older adults in order to complete recruitment. At present we have completed analyzing the data of 522 people, and their results follow. The sample is composed of 243 men and 279 women, ranging in age from 20 to 98. The racial breakdown is 70.0% Caucasian (CA), 26.8% African American (AA), and 3.2% Asian and Hispanic American. In the sample, there were 136 people with insomnia, 37 AA (27.6%) and 97 CA (72.4%). The prevalence of insomnia among AA (25.5%) and CA (21.4%) were proportional to their representation in the entire sample, $\div 2$ (1, N = 522) = 1.0, p = ns. We will report analyses on seven sleep measures: WASO, TST, SE, naps, SOL, # awakenings, and sleep quality rating. We will also report analyses on six daytime functioning measures: IIS, ESS, SSS, FSS, STAI, and BDI. For each category of functioning (sleep and daytime measures), a MANOVA was performed to compare AAs and CAs. The MANOVA for sleep was significant, Wilks' L = .77, F(9, 124) = 4.15, p <.001. Follow-up univariate tests were significant for WASO, TST, SE, and naps. As the table below indicates, for all these measures AAs were functioning significantly worse. Further, the magnitude of differences was clinically substantial. There were no

significant differences between groups on SOL, # awakenings, or sleep quality rating, although there was a trend towards poorer functioning in AA for these measures as well. The MANOVA for daytime functioning was not significant.

Conclusions: Based upon people's perceptions, these preliminary results find that (1) insomnia prevalence is not different across ethnicity; (2) insomnia severity is worse in AAs than in CAs; (3) daytime functioning, however, is not significantly different between ethnic groups. These results justify more careful investigation of the underserved AA population.

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1017.K4

Imagery Rehearsal ("New Dream") Therapy for Chronic Nightmares in PTSD: A Six Month Follow-up

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Introduction: Sexual assault survivors with chronic posttraumatic stress disorder (PTSD) often complain of nightmares, one of the most common symptoms of intrusion (reexperiencing the trauma). Although prior research has shown that non-PTSD nightmare sufferers respond to cognitive-behavioral techniques, direct treatment for PTSD related nightmares is not standard practice in sexual assault survivors. As previously reported, in the first controlled study to examine imagery rehearsal treatment for PTSD nightmares among sexual assault survivors, disturbing dreams were reduced at three-month follow-up. This work reports on a larger sample with a six month follow-up.

Methods: Eligible clients were recruited through flyers, advertisements, private therapists, and rape crisis centers and consisted of female sexual assault survivors, 18 years or older, with complaints of frequent nightmares (>once/week) for more than six months. Clients were randomized into treatment or wait-list control groups. Treatment consisted of two, three-hour group sessions and one brief follow-up session (seven hours of therapy). Imagery rehearsal involves learning how to "change a nightmare anyway you wish" while in the waking state, then rehearsing the "new dream". The basic premise is that while disturbing dreams are caused by traumatic experiences, they may be sustained through conditioning factors that cause the development of a "nightmare habit." Participants also learn several established principles about cognitive behavioral therapy, set within the framework of cognitive restructuring. However, desensitization or other overt forms of exposure to past trauma events or traumatic content of nightmares are not employed. In fact, discussion of past trauma is discouraged. Six month follow-up and post-treatment data are reported for control and treatment groups. T-tests were used for within and between group comparisons.

Table 1

Within-Group Results	PRE *M(SD)*	POST *M(SD)*	Δ	*P*
TREATMENT				
Nights	3.9 (2.2)	1.1 (1.4)	-72%	.000
Nightmares	7.2 (6.2)	1.7 (2.6)	-76%	.001
CONTROL				
Nights	3.8 (2.2)	3.6 (2.1)	-05%	.50
Nightmares	6.0 (5.5)	7.3 (7.3)	+18%	.36

Results: To date, 48 females (Treatment = 23, Controls = 25) were included in the analysis. Mean (SD) age was 35.9 (9.3); ethnicity was 79% non-Hispanic White, 21% Hispanic and other. On average, participants reported suffering from nightmares for 19 years. Significant decreases occurred within the treatment group, but there were no reductions in controls. Differences between groups were significant. The Mean (SD) change for the number of nights of nightmares was -2.86 (2.73) for the treatment group and -.24 (1.76) for the control group (t=3.9, df=37, p=.000). The Mean (SD) change for the number nightmares was -5.50 (6.73) for the treatment group and 1.22 (6.50) for the control group (t=3.5, df=46, p=.001).

Conclusions: Imagery rehearsal or "New Dream" Therapy resulted in clinically meaningful decreases in chronic nightmares in sexual assault survivors with PTSD. Preliminary results (not reported here) also suggest that decreases in nightmares are associated with improvement in sleep quality and decreases in other PTSD symptoms. Given the brevity of the technique, imagery rehearsal appears to be an effective treatment for the relief of chronic nightmares in sexual assault survivors. Caution is advised, however, in its use with PTSD patients who are susceptible to re-stimulation (through imagery exercises) and resultant exacerbation of waking and dream imagery

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1052.K4

Hypersynchronous Delta (HSD) Activity and Sudden Arousals From Slow Wave Sleep (SWS)in Adults Without NREM Parasomnias

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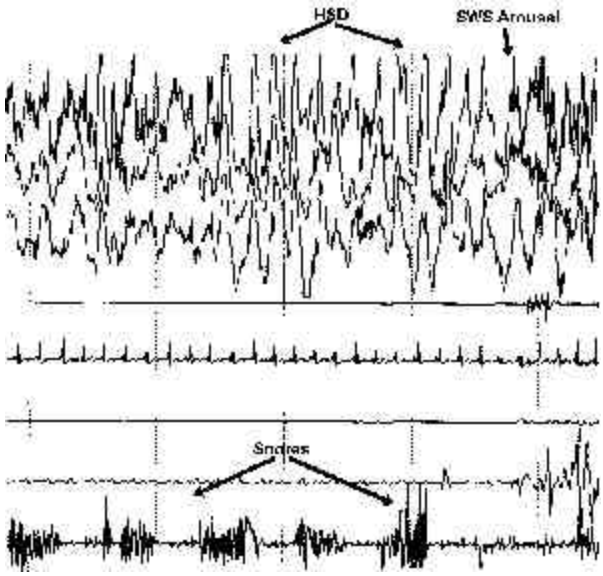
Introduction: HSD and sudden arousals from SWS are features of the microstructure of the NREM sleep EEG in patients with parasomnias such as sleepwalking (SW), night terrors (NT) and confusional arousals. Although HSD lacks any generally accepted definition it is usually reported to consist of several high amplitude delta EEG waves occurring immediately preceding and sometimes following sudden arousals from SWS. HSD has been variously interpreted as repetitive k-complexes or bursts of paroxysmal delta waves. HSD is reported to be a frequent feature of SW/NT in children, but is reported to be less frequent in adults with parasomnias.[1,2] SWS arousal/HSD have been reported in normal adult controls, but little research has been done on the frequency or significance of SWS arousals/HSD in adults with other sleep disorders.

Methods: A group of 82 consecutive clinical patients (57 males, 25 females, mean age 48+13.3, range 11-89 yrs.) admitted for evaluation of suspected sleep apnea from April-June 1999 were studied prospectively with standard all night diagnostic polysomnography. All patients had at least 30 seconds of visually scored stage 3 or 4 sleep. HSD was defined according to the method of Schenk and colleagues(2)-the only research paper to provide a working definition for HSD. This definition required the presence of 2 or more highest amplitude delta waves (as defined by standard R&K) within the 10 seconds preceding an arousal from SWS. A SWS arousal required the presence of an arousal as defined by the ASDA Atlas committee occurring from R&K defined Stage 3 or 4 sleep.

Results: All but 4 patients were found to have an RDI >5/hr. of sleep. Mean RDI for the group was 30+23.6 (range 2.7-117) per hr. of sleep. A total of 235 SWS arousals were noted. 70 of the 82 patients (85%) had >1 arousal from SWS. 37 of the 82 patients (45%) had >3 SWS arousals. Mean SWS arousals for the entire group were 2.9+2.7 (range 0-14). The

provoking stimulus was clearly visible for 215 of the 235 SWS arousals noted. 201 (85.5%) were secondary to snores or apneas/hypopneas and 14 (5.9%) SWS arousals were secondary to periodic movements. A total of 94 HSD episodes were noted for the group. 54 of the 82 (65.8%) patients had >1 episode of HSD. A mean of 1.4+1.6 (range 0-9) episodes of HSD were noted for the whole group. Amplitude of delta EEG waves during HSD was >100 uv for all episodes and exceeded 150 uv in >90% of all episodes. Fig. shows 1 of 4 SWS arousals and 1 of 3 episodes of HSD secondary to loud snoring in a 43 yr. old male without prior history of parasomnias. An RDI of 25.9 per hour was noted.

Figure 1. HSD IN Adult with OSA



Conclusions: SWS arousals and HSD occurred in a majority of these non-parasomniac adult patients studied. This suggests that HSD and SWS arousals are not definitive diagnostic characteristics of SW/NT or confusional arousals. Rather, this data suggests that SWS arousals/HSD may appear in other sleep disorders characterized by significant sleep fragmentation and sleep deprivation. The sleep deprivation and sudden arousals during SWS noted in these patients with obstructive sleep apnea are classic factors thought to underlie the occurrence of NREM parasomnias. Why then did these factors not result in NREM parasomnias in this group? A parsimonious explanation is that these patients lack another required factor that primes the parasomnia patient for the sudden appearance of sleep behaviors only when all prerequisites are met. A strong candidate for this remaining factor is the presence of an abnormally strong orienting response as has been documented in children with night terrors.[3]

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1420.K4

Type A-B Behabior, Nightmare Frequency, and Nightmare Distress

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Introduction: Past research has shown that nightmare frequency is associated with dimensions of personality, i.e., anxiety, thick and thin boundaries. In a recent study, Tan and Hicks (1995) demonstrated that Type A scorers reported a greater frequency of nightmares (fantastic nightmares, posttraumatic nightmares, and night terrors) than Type B scorers. The present study extended the work of Tan and Hicks (1995) and examined the relationships between Type A-B behavior and the two measures of nightmares, nightmare frequency and nightmare distress.

Methods: We asked 269 (106 men and 163 women, mean age = 19.0) university students to respond to the Belicki's Nightmare Distress Questionnaire (1992), the Spadafora and Hunt Scale (1990) which measures the frequency of different types of dreams (including nightmares), and the Glass' version of the Jenkin Activity Survey which measures Type A-B behavior. The three nightmare frequency items from the Spadafora and Hunt Scale were "Fantastic Nightmares," "Posttraumatic Nightmares," and "Night Terrors." The scores of these items and the Nightmare Distress Questionnaire were based on a 5-point Likert-type scale ranging from Never = 1 to Always = 5.

Results: Table 1 shows the means and standard deviations of the Type A-B groups for the nightmare frequency measures and the nightmare distress measure. A one-way analysis of variance was performed for each of the three nightmare frequency variables and the nightmare distress variable. Based on these analyses, there were significant differences between Type A and Type B scorers in the frequency of fantastic nightmares ($F1, 267 = 4.24$, $p < .05$) and posttraumatic nightmares ($F1, 267 = 8.34$, $p < .01$). However, our results indicated that there were no significant differences between Type A and Type B scorers in the frequency of night terrors ($F1, 267 = .92$, n. s.) and in the measure of nightmare distress ($F1, 267 = 1.31$, n. s.).

Table 1. Type A-B Behavior, Nightmare Frequency, and Nightmare Distress

Means and Standard Deviations of Type A (n = 130) and Type B (n = 139) Groups For Nightmare Frequency Variables and Nightmare Distress Variable

Group	Fantastic Nightmares		Post-traumatic Nightmares		Night Terrors		Nightmare Distress	
	M	SD	M	SD	M	SD	M	SD
Type A	2.42	1.09	1.70	.86	1.60	.92	21.00	6.59
Type B	2.17	.90	1.42	.70	1.50	.73	20.14	5.77

Conclusions: These results are consistent with those of Tan and Hicks (1995), that is, Type A individuals scored greater frequency of fantastic nightmares and posttraumatic nightmares than Type B individuals. However, our data show that there are no significant differences between Type A and Type B in night terror frequency and nightmare distress. These findings suggest that Type A individuals experience disturbing dreams more frequently than Type B individuals, but they do not experience more nightmare distress than Type B individuals.

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1551.K4

Sleep Related Eating Disorder or Bulimia Nervosa: A Case Report.

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Introduction: Sleep-related eating disorders (SRED) represent a distinct syndrome from daytime eating disorders with respectively distinct and overlapping nighttime and daytime features. The association of both disorders is uncommon. The authors report a case of nocturnal eating syndrome with bulimia nervosa (BN).

Methods: The authors report a 19 year-old female with nocturnal eating syndrome for 4 years with subsequent bulimia. Nocturnal eating behavior consisted of nightly consumption of large amounts of high-calorie ready-to-eat food. Four nightly episodes after sleep onset with partial or total amnesia was reported. Neither injuries nor dreaming but bodily discomfort. was mentioned. Past medical history revealed persistent concerns with her weight at age 13 years and a clear history of depression at age 17. Family history revealed somnambulism (mother, brother and grandmother). Laboratory work-up (biochemistry, head NMRI, EEG) were unremarkable. In-hospital sleep studies recorded two eating episodes emerging from stage2 NREM.(TIB=341min, SE=77.60%, SL=10min, stage1=7.48%, stage2=67.14%, SWS=5.46%, no REM sleep was recorded, WASO =19.50%.

Results: Clonazepan(1mg), carbidopa/levodopa(100/400mg), fluoxetine(60mg) alleviated the episodes and depressive symptoms. Two months later DSM-IV symptoms of BN with binge eating and severe purgative behavior emerged.

Conclusions: SRED with somnambulism and BN are distinct conditions. Sometimes differential diagnosis is difficult and we can observe occurrence of overlapping clinical features.

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1585.K5

Suggested Immobilization Test: Normative Values in PLMS/Non-PLMS Controls and in Treated RLS Patients

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Introduction: The suggested immobilization test (SIT) described by Montplaisir et al[1] has become a standard method for defining medication efficacy for RLS. Although some data have been presented for normal subjects with the SIT,[1] expanded data on what constitutes "normality" with this procedure would be both of considerable practical and heuristic value. For example, individuals without RLS but with periodic leg movements in sleep (PLMS) have not been studied with the SIT. Common neurobiologic substrates between RLS and PLMS are suggested by the fact that dopaminergic medication is effective for both conditions and reflex abnormalities suggesting interruption of descending motor pathways partially subject to striatal influence are present in PLMS. These allow for the possibility that patients with PLMS but without RLS might have subtle behavioral manifestations manifested in the SIT. In this study, we report preliminary results comparing SIT results from individuals without PLMS, individuals with PLMS but without RLS, and individuals with treated RLS, collected during the titration phase of a clinical trial examining the efficacy of ropinirole for RLS.

Methods: All subjects (7 Normal, 6 PLMS, 10 RLS) underwent a one hour SIT initiated between 1500 and 2100, except for one subject whose testing started at 1350. Normal and PLM subjects had undergone overnight polysomnography previously to document absence or presence, respectively, of periodic movements during sleep. Mean overnight PLMS Indices for the two groups were 0.1 mvts/hr and 33.3 mvts/hr respectively. RLS patients were all enrolled in an ongoing, randomized, clinical trial of a dopamine agonist (ropinirole) for RLS. RLS patient data presented here represent data from the initial (open label) titration phase of the trial prior to a double-blind, placebo-controlled, withdrawal phase. RLS patients underwent nocturnal polysomnography immediately subsequent to the evening SIT. Mean PLM Index in the RLS patients was 7.0 mvts/hr which was significantly lower than the PLM patients but, owing to the large standard deviation, not significantly higher than the Normals. We scored three types of EMG potentials from the SIT. These included: a) movements of duration greater than or equal to 0.5 sec and less than 10.0 sec, as originally described by Montplaisir et al;[1] b) movements of 10.0-15.0 sec duration; and c) PEM (phasic electromyographic metric), the proportion of 2.5 second intervals with phasic muscle activity of 100-500 msec, using the scoring system described elsewhere.[2] Channels were scored for left and right leg legs separately, as well as for simultaneous bilateral activity. Data for (a) and (b) represented hourly sums. PEM was expressed as the proportion of 2.5 sec intervals with phasic activity.

Results: Results indicated no significant differences among the three groups for either of the two categories of gross leg movements (0.5 sec-10.0 sec, 10.0 sec-15.0 sec) or for PEM activity. Across all three groups combined (n= 23), there were no significant correlations between PLMS in sleep and any measure of motor activity on the SIT. A number of subjects showed 10 or more mvts 0.5-10.0 sec in duration during the SIT on one or both legs (2/7 Normals, 1/6 PLMS, 3/10 RLS). Additionally, PEM rates of greater than 5.0% on one or both legs were seen in many subjects as well (3/7 Normals, 2/6 PLMS, 5/10 RLS).

Conclusions: These results have several potentially important implications for clinical utility of the SIT: 1) RLS patients titrated using a dopamine agonist show an apparent normalization of motor activity on the SIT relative to non-RLS patients; 2) individuals with appreciable PLMS during sleep did not show motor activity resembling untreated RLS patients when confronted with the task of remaining motionless for an hour; 3) several normal individuals showed some form of motor activity on the SIT. The significance of the latter warrants further investigation, particularly as it may differentiate specific neurologic/psychiatric pathologies , e.g., neuropathy, lower motor neuron disease, anxiety disorder, central dopamine loss.

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1890.K5

Memory Performance in Sleep-Impaired Patients with Parkinson's Disease

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Introduction: Patients with Parkinson's disease (IID) were shown to be impaired in their cognitive performance, Neuropsychological investigations revealed deficits of memory-, visuospatial-, and frontal lobe functions in earlier stages of the disease. In later stages of the disease dementia may occur. Impairment of sleep is frequently found in 13D patients. Their complaints often result from the main inherent symptoms like, akinesia, rigidity and tremor. Difficulties to get into Sleep, problems to sleep continuously and to move the body at night are often reported. Further complaints are feelings of restlessness, painful cramps, vivid dreams, a missing recovery effect of sleep and increased daytime weariness.

Methods: In order to explore the relation between sleep disturbance and cognitive impairment we examined 20 patients with Parkinson's disease and 10 control subjects. Both groups were instructed to rate their subjective sleep-quality on a scale from 1 (very good) to 6 (very bad). They had to answer to Beck's Depression Inventory and were subject to a standardized multiple word knowledge test, estimating their premorbid level of intelligence. Verbal learning increment, verbal interference as well as verbal long-term memory were assessed with the Rey Auditory Verbal Learning Test. The visual modality was tested with the Visual Design Learning Test and Gollin figures.

Results: While there was no difference in the premorbid level of intelligence between PD patients and controls, sleep-quality in the PD group was significantly worse than in the healthy control group. Depression was also significantly higher in PD patients than in healthy controls.Moreover intra-group (PD) comparison showed a significant correlation between increasing depression values and verbal proactive interference. Visual short-term memory as well as visual long-term memory performance seemed to deteriorate with increasing depression. Furthermore reduced sleep quality was associated with an impaired implicit memory.

Conclusions: Therapeutical intervention in depression and improvement of nighttime sleep is important in the treatment of PD. patients in order to enable better cognitive performance in daily live challenges.

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1254.K5

The Motor Pattern of Periodic Limb Movements During Sleep in Patients with Restless Leg Syndrome

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Introduction: Restless legs syndrome (RLS) is frequently associated with periodic limb movements during sleep (PLMS). The pathophysiology of the disease is unknown. The absence of any cortical potential preceding leg movements excluded a cortical origin. The typical PLMS periodicity, every 20-40, the same as periodic autonomic (blood pressure, respiration and heart rate) modifications during sleep, suggests a brainstem involvement. Other studies suggested that RLS might be caused by peripheral nerve disease. Recently a propriospinal origin of the daytime involuntary limb movements has been proposed. We studied the muscular activation pattern of the PLMS in patients with RSL in order to identify a probable generator.

Methods: We studied 7 RLS patients (5 men). In 2 cases family history was positive; in 2 cases there was a precedent of gastric ulcer. Disease duration varied from 1 to 37 yrs. In 2 cases RLS manifestations were confined to the pre-dormitum; in the other cases, symptoms appeared in ever relaxing situations. All patients underwent nocturnal laboratory video-polysomnographic recordings and MSLT the day after; EMG activity was collected from: right and left biceps brachii, triceps brachii, rectus abdominis, thoraco-lumbar paraspinalis, rectus femoris, biceps femoris, tibialis anterior and gastrocnemius muscles.EEG and EMG data were acquired at the same time by a computerised system (NEUROSCAN 3.0) for off-line analysis. Back averaging, somatosensory evoked potentials (SEPs), EMG/CVs, transcranial magnetic stimulation (TMS) and brain CT/MRI were also done. For each patient we considered 100 consecutive PLMS in order to study: how many times each muscles was involved in the contraction; how many times each muscle was the first to contract; the time delay between the first activated muscle and each of the others.

Results: Our patients presented a severe restless legs syndrome (PLMS index between 37 and 166), pathological sleep efficiency (80-25%), and a pathological or borderline MSLT (mean latency to sleep: between 4 and 8 minutes). Back averaging showed no EEG potential time-correlate with the motor event. Muscles most frequently involved in the contraction were inferior limb muscles (tibialis anterior, gastrocnemius, biceps femoris, quadriceps femoris). In particular, muscular contraction started in the tibialis anterior in about the half of the cases. Rarely the contraction began in axial muscles (rectus abdominis, thoraco-lumbar paraspinalis), sometimes in the upper limbs (biceps brachii, triceps brachii). There was no constant pattern of recruitment from one PLMS to another, even in the same patient, or a caudal and rostral propagation of EMG activity. The time delay between the first and last activation was extremely variable and long, up to 2 seconds.

Conclusions: PLMS activity starts more often in lower limb muscles and axial muscles are seldom involved; the starting muscle varies and the order and delay of the other muscle recruitment are not in accordance with a propriospinal propagation.

1269.K5

Propriospinal Myoclonus and Sleep-Wake Cycle

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Introduction: Propriospinal myoclonus (PSM) is a recently described type of spinal myoclonus characterized by flexor or extensor contractions of the trunk and limbs, spontaneous or evoked, arising in the spinal cord and spreading up and down the propriospinal pathways intrinsic to the spinal cord. Previously studies emphasized an exacerbation of the jerks when patients sat or lay flat. We recently described three cases in which the triggering factor could be traced to the reduction in vigilance level at the transition from wakefulness to sleep causing severe insomnia. Now we describe videopolysomnographic findings in 8 patients with propriospinal myoclonus.

Methods: We studied 8 patients with PSM (age between 35-71 yr) in which disease duration ranged between 1 and 31 yrs. In 6 cases jerks

were confined exclusively to the pre-dormitum, causing severe and persistent insomnia. In another case the jerks appeared also during intra-sleep wakefulness, when patient tried to fall asleep again and after awakening in the morning. In one patient, the jerks arose spontaneously and also during physical effort, after acoustic startle and by stimulation applied over the body surface. Neurological examination was normal in six cases. Chronic external ophthalmoplegia was present in one, and lower limb hypopallesthesia and asymmetric tendon reflexes in another patient. Cerebral MRI was normal in all patients. Spinal MRI was normal in six cases; in one patient there was a T8 root arachnoidal cyst and a C5-C6 disc protrusion in another case. All patients underwent diurnal and nocturnal videopolysomnographic studies with particular attention to postural effect and mental and somatosensory stimulations. EMG/CVs, SEPs and Transcranial Magnetic Stimulation (TMS) were also done.

Results: EMG/CVs, SEPs and Transcranial Magnetic Stimulation were normal in seven patients. In one patient Transcranial Magnetic Stimulation (TMS) disclosed increased motor latency with prolonged central conduction time to the left arm and SEPs from the lower limbs were altered. Back averaging never disclosed any cortical potential time correlated with the jerks. EMG analysis showed that jerks arose in the thoraco-lumbar paraspinalis or rectus abdominis or sternocleidomastoideus muscles with subsequent caudal and rostral propagation with conduction velocity of 3-16 m/s. In six patients the PSM appeared at the transition from wakefulness to sleep. EEG showed a spreading of alpha activity to the anterior regions, or its fragmentation, when theta activity appeared. In another patient PSM also reappeared during intra-sleep wakefulness and upon awakening in the morning. In these seven patients sleep efficiency was lower than normal. In the one patient in whom jerks were evoked by startle and stimuli applied over the body surface, PSM was unrelated to the wake-sleep cycle.

Conclusions: Our results confirm that PSM is a heterogeneous clinical condition but it appears to be related to the sleep-wake cycle. PSM could be included within the sleep-wake transition disorders.

1629.K5

Periodic Leg Movements During Sleep in Patients with REM Sleep Behavior Disorder

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Introduction: REM sleep behavior disorder (RBD) is characterized by the absence of muscular atonia that normally occurs during rapid-eye-movement (REM) sleep and by the appearance of motor behaviors associated with vivid dreams. The presence of periodic leg movements (PLM) during sleep in patients with RBD is considered a frequent manifestation of the disease. PLM during sleep (PLMS) and wakefulness (PLMW) are also known to be typical of restless legs syndrome (RLS), a sleep-related disorder characterized by leg paresthesia and motor restlessness. The aim of the present study was to evaluate both the prevalence and the polysomnographic characteristics of PLM in patients with RBD and to compare the latter with those of age-matched patients with RLS.

Methods: Thirty-six male patients diagnosed with RBD (67.0 ± 8.5 yrs.) entered the study. All patients except one presented the idiopathic form of RBD. Twenty of the thirty-six RBD patients (66.8 ± 6.5 yrs.) were matched for age and sex with twenty patients diagnosed with primary RLS (67.1 ± 6.5 yrs.) in order to compare the PLMS characteristics. None of the patients were taking any medication for at least two week prior to the polysomnographic recording. Sleep and PLMS were scored in the standard fashion.

Results: Twenty-two of the 36 RBD patients (61%) showed a PLMS index greater than 10 whereas 69% showed an index greater than 5. PLM characteristics was summarized in the Table. PLM characteristics were relatively similar in RBD patients and in RLS patients. However, one parameter differed significantly in the two groups, namely the PLMW index, which is greater in the RLS patients. The two groups showed similar sleep patterns. The only between-group differences were for total sleep time and sleep efficiency, which were greater in RLS patients.

Table 1. PLM characteristics of patients with RBD and patients diagnosed with primary RLS

Parameters	RBD Patients	RLS Patients	p
- PLMW mean index	28.1±30.2	53.0±34.3	0.010*
- PLMS mean index	44.3±29.8	65.8±52.2	ns*
- Stage 1	34.7±26.4	69.4±61.7	ns*
- Stage 2	52.3±38.3	64.9±50.7	ns*
- Slow wave sleep	54.6±66.8	48.8±59.8	ns*
- REM sleep	26.6±24.8	26.2±32.9	ns*

Mann-Whitney U test

Conclusions: The prevalence of PLMS in the RBD population obtained in the present study is in agreement with that of a previous study. Indeed, it has been shown that close to 65% of the RBD patients have PLMS during non-REM sleep.(Schenck et al., 1993) The prevalence of PLMS in RBD patients was found to be lower than that reported for RLS patients.(Montplaisir et al., 1997) The presence of a higher PLMW index in RLS patients can be explained by the importance of diurnal symptoms in this condition. The similarity between the PLMS index obtained in the two groups during REM sleep suggests that REM sleep atonia present in RLS but not in RBD patients has little influence on PLMS.

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1322.K5

Efficacy of Retarded Valproic Acid Versus Retarded Levodopa in the Treatment of Restless Legs syndrome: a randomized, cross-over, placebo-controlled double blind study.

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Introduction: We investigated the efficacy of retarded valproic acid (Ergenyl chrono) compared to retarded levodopa (Madopar depot) in patients with Restless legs syndrome (RLS).

Methods: 20 patients with idiopathic RLS (12 women, 8 men, mean age: 58.9±6.9 years, mean duration of symptoms: 16.9±15.2 years) were included if they have had typical symptoms of RLS every day for at least half a year and if they had at least five periodic limb movements (PLMs) per hour of total sleep time in their polysomnogram performed prior to the study entry. Exclusion criteria were polyneuropathy and specific sleep disorders other than RLS. Every patient received either 600mg Ergenyl chrono, 250mg Madopar depot or placebo for three weeks and

subsequently two nights of polysomnography (PSG). At the time of their PSGs, the patients rated their RLS symptoms (visual analogue scale from 1 to 10 and duration of RLS paresthesias during 24 hrs). After having completed the study, every patient received the drug, that had shown the best efficacy. Intraindividually, Ergenyl chrono vs. Madopar depot vs. placebo comparison was perormed.

Results: PLM-index (PLMI) and PLM arousal-index (PLMAI) were significantly reduced only with Madopar depot but not with Ergenyl chrono, whereas spontaneous arousals were significantly increased with Madopar depot, but not with Ergenyl chrono (table 1).The intensity and duration of RLS paresthesias was rated significantly reduced with Ergenyl chrono but not with Madopar depot (table 1).After having completed the study, seven patients were treated further with Madopar and 13 patients with Ergenyl chrono. After ½ to 11/2 year follow up period, 9 of the 13 patients with initial Ergenyl chrono treatment were still satisfied with Ergenyl chrono monotherapy, whereas 2 of the 7 patients with initial Madopar therapy were still satisfied with Madopar monotherapy.

Table 1

	PLMI (no/hr)	PLMAI (no./hr)	Spontaneous AI (no./hr)	RLS paresthesia intensity	RLS paresthesia duration (min./24 hr)
P	43± 37	21± 16	6± 3	6± 2	196± 224
VPA 600mg	38± 32	15± 13	7± 5	4± 3 *	104± 226 *
Levodopa 250mg	20± 23 *	10± 14 *	11± 4 *	5± 3	155± 235

*results are given as mean± SD, *: comparison to placebo: a p value of < 0.05 was considered significant, AI: arousal index, PLM: periodic limb movement RLS: Restless legs syndrome, P: placebo, VPA: valproic acid*

Conclusions: We conclude from our results, that both, Ergenyl chrono and Madopar depot improve RLS, Ergenyl chrono by reducing RLS paresthesias, Madopar depot by altering sleep structure.

1331.K5

Decreased Phasic Activity During REM Sleep in Untreated Parkinson´s Disease

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Introduction: Impairment of movement with akinesia, rigidity and tremor are cardinal features of Parkinson's disease (PD). REM Sleep Behavior Disorder (RBD), a disorder characterized by excessive muscle twitching and lack of atonia with injurious behavior during REM Sleep, is frequently associated to, and may precede the onset of Parkinsonism. When associated, both disorders may share motor dyscontrol during REM sleep. We have endeavoured to study both phasic and tonic motor activity in REM sleep in recently diagnosed - never treated – patients with Parkinson´s Disease before and after treatment with l-dopa and controls, in order to assess whether motor dyscontrol was already present at the onset of daytime PD symptoms and to investigate the putative effect of L-Dopa treatment on motor activity during REM sleep.

Methods: 6 consecutive patients (4 females, 2 males) suffering from Parkinson´s Disease underwent all-night polysomnographic (PSG) studies. All patients had been diagnosed recently and had never received antiparkinsonian treatment. Sleep studies were repeated following a 3 - month treatment period with l-dopa (mean dosage: 360 mg, range: 300-500 mg). Age (mean: 75.3 years, SD: 3.9) and gender-matched controls were recruited among subjects who had been refered to the Sleep Disorders Clinic for other reasons but failed to meet criteria for any condition according to the International Classification of Sleep Disorders. PSG- studies were recorded and scored according to standard methods. The tonic and phasic components of REM sleep were scored separately, according to the criteria used by Lapierre and Montplaisir (1992): 1. Tonic motor activity: Each 20 second-epoch was scored as "tonic" or "atonic" depending on whether tonic chin EMG activity was present for >50% or <50% of the epoch. 2. Phasic motor activity was quantified as:a. EMG twitches: The % of 2 seconds epochs containing phasic EMG twitches. The latter were defined as any burst of EMG activity lasting 0.1 to 5 seconds with an amplitude exceeding 4 times the background EMG activity. b. REM density: The number of Rapid Eye Movements (REMs) per minute of REM-sleep.Data were analyzed by means of non-parametric statistics (Wilcoxon and Mann-Whitney tests).

Table 1

	Untreated PD	L-dopa PD	Controls	Untreated PD vs Controls	Untreated PD vs treated	Treated PD vs Controls
Tonic Motor Activity+	0,21 (0,53)	1,89 (2,48)	1,56 (1,44)	n.s.	n.s.	n.s.
EMG Twitches+	1,05 (1,54)	3,83 (4,95)	3,63 (2,42)	*	n.s.	n.s.
REM Density+	6,26 (1,80)	7,14 (1,87)	10,43 (3,61)	*	n.s.	n.s.

+: see methods.
Results are represented as mean (SD).
*: $p < 0.05$

Results: No differences were observed between the groups or conditions regarding sleep architecture, PLM(periodic leg movements)-index or apnea-hypopnea-index.Preliminary results on 6 patients are shown on the table.

Conclusions: Phasic motor activity during REM sleep was dimished in untreated Parkinson's disease as compared to controls. Treatment with l-dopa not only improved daytime symptoms but increased phasic motor activity during REM sleep. There was an increase in phasic motor activity during REM-sleep following treatment with l-dopa, approaching the degree of activity observed in the control group.

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1332.K5

Parkinson´s Disease Patients do not Have a "First Night Effect" in the Sleep Laboratory

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Introduction: "First night effect" (FNE; Agnew 1966) refers to the

influence of the sleep laboratory setting on sleep variables during the first night of polysomnography. It is associated with longer sleep latency, higher amounts of wakefulness during the night, lower sleep efficiency, and a prolonged REM sleep latency with lower amounts of REM sleep. FNE has been found to vary in patients with different disorders (e.g.,Toussaint 1995, Hauri 1989). In this study, we examined whether there is a FNE in patients with Parkinson´s disease.

Methods: 22 non-demented patients (13 m, 9 f) with idiopathic Parkinson´s disease (PD), who unterwent polysomnography at one of both sleep centers were included. Mean age was 64.4 ± 9.5 years, median Hoehn and Yahr stage 2.5 (1-3). All patients were studied on their current dopaminergic and sleep medication: levodopa (n = 15), pergolide (n = 6), entacapone (n = 2), ropirinole, apomorphine, tolcapone, selegiline, amitriptyline, clozapine (n = 1 each), and benzodiazepines (n = 3). 3 patients were untreated. No drug changes were allowed between both nights. Polysomnography was performed in 2 consecutive nights according to standard methodology and scored according to standard criteria. Comparisons of the first versus the second night were done with paired t-tests.

Results: Results of the polysomnographies are shown in the table below. Sleep was disturbed with diminished sleep efficiency, high amounts of wakefulness during the night and low amounts of REM sleep in both nights. All differences were not significant. No trends could be detected either.

Table 1. Polygraphic sleep variables of 22 patients with Parkinson´s disease - first and second night in the sleep laboratory

	Night 1	Night 2	p
Time in Bed (min)	476 (18)	480 (8)	ns
Time of Sleep (min)	328 (86)	333 (96)	ns
Sleep Efficiency %	69 (17)	69 (20)	ns
Sleep Latency (min)	24 (21)	25 (28)	ns
REM Sleep Latency	132 (89)	129 (119)	ns
	Night 1	Night 2	p
Sleep Cycle Time	438 (37)	444 (31)	ns
Wakefulness %	27 (16)	26 (20)	ns
Stage 1%	14.3 (9.2)	12.3 (6.1)	ns
Stage 2 %	41.2 (14.8)	40.8 (15)	ns
Stage 3+4 %	6.5 (7)	6.7 (6.6)	ns
REM %	11.2 (6.4)	12.8 (7.3)	ns

Conclusions: No "first night effect" was found in any of the analyzed variables. Assuming that FNE reflects physiologic adaptation capacity of the brain to new sleep surroundings, these results suggest that this capacity is lost in patients with Parkinson´s disease. Alternatively, FNE may be masked by confounding influences such as medication. On the basis of these results we suggest, that for clinical purposes a sleep laboratory adaptation night could be omitted in some PD patients. Further studies are needed to determine if this holds true for treated and for untreated patients.

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1341.K5

Dissociation of Periodic Limb Movements and Restless Leg Syndrome After Renal Transplantation

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Introduction: Restless Leg Syndrome (RLS) and Periodic Limb Movements (PLMS) are often considered related conditions, with at least 80% of RLS patients having PLMS. However, the majority of patients with PLMS on a PSG do not give a history of RLS and PLMS are common in asymptomatic elderly subjects. PLMS may also be seen in other disorders, such as obstructive sleep apnea (OSA), narcolepsy and depression. RLS is a common sleep disorder in end-stage renal failure patients undergoing dialysis, and kidney transplantation usually leads to its resolution.[1]

Methods: We report a patient whose severe RLS resolved completely after cadaveric renal transplant but who later was found to have frequent asymptomatic PLMS, suggesting different mechanisms for the two conditions.

Results: A 61 year old male with polycystic kidney disease and chronic renal insufficiency on hemodialysis for 2 years complained of severe RLS for 5 years (crawling sensations in his legs, relieved by activity). Following cadaveric renal transplantation in 1987, renal failure and RLS resolved. The patient was reevaluated in 1999 for suspected OSA, but reported no complaints of RLS or PLMS. Examination revealed no evidence for peripheral neuropathy. Investigations revealed a hematocrit of 45% (21% pre-transplant) with MCV 93fl. Creatinine concentration was 1.3 mg/dl (14.8 mg/dl pre-transplant). A split-night PSG showed OSA during the diagnostic portion with DBE index 76/hr. PLMS occurred at a frequency of 125/hr (3% causing arousals). Nasal CPAP at 7 cm water eliminated disordered breathing events. However, PLMS continued at a frequency of 114 /hr (3% causing arousals). Treatment with n-CPAP alone resolved daytime sleepiness.

Conclusions: Our patient illustrates dissociation between RLS and PLMS, with RLS resolving after kidney transplantation, but a high frequency of asymptomatic PLMS being documented years later. This case provides further evidence that these are two separate (although related) phenomena, with probably different pathophysiology. Functional MRI studies have shown that RLS is associated with activation of the cerebellum and thalamus, while combined PLMS and RLS is associated with additional activation of the red nuclei and brainstem.[2] PLMS may be epiphenomena of other sleep disorders and care should be exercised before ascribing symptoms to PLMS alone.

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1707.K3

Clinical Associations and Severity of the Restless Legs Syndrome: A Split Group Comparison of Patients Attending a Patient Support Group

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Introduction: Last year, we reported the results of a questionnaire examination of 25 patients attending a support group for the restless legs syndrome (RLS). Subsequently, we were able to give the questionnaire to an additional 26 patients drawn from the same support group. We now investigate whether consistent results were found in both samples. In light of recent indications that there may be two distinct groups of RLS patients, an idiopathic, inherited group with early onset and a secondary group with later onset, we also examined whether clinical features and severity differed for those with early and late onset.

Methods: In addition to the patients examined last year (Group I), we now evaluated 26 patients in a second group (Group II). Questions analyzed included demographics and family association; disease course, features, and management; and questions drawn from the International RLS Study Group (IRLSSG) rating scale. We compared the two groups on these measures, a regression of SEVERITY (sum of 8 IRLSSG questions) on possible determinative variables, and a factor analysis of the 8 IRLSSG questions. We also sought differences between patients with earlier and later onset.

Results: On most measures, the two samples were comparable. Both were middle aged to elderly; predominantly female; had similar timing of maximal symptoms; had been given medications for RLS; had responded best to dopaminergic agents and benzodiazepines; found similar relief with motor activity and counterstimuli such as massages or hot baths; and were predominantly of European origin. A factor analysis of the 8 IRLSSG questions showed a dominant factor related to the severity and frequency of primary symptoms. Lesser factors differed between the two groups, but were related to questions that correlated inconsistently with severity, particularly the degree of relief from walking. In both groups, patients with early onset (up to age 35) were more likely to have known affected family members ; more likely to have arm involvement ; and more likely to have been treated with medications. However, only in Group II were the early onset patients distinctly more severe. In the combined group (N=51), we found a significant relation of SEVERITY to number of limbs affected, but not to either sex or known affected family members.

Conclusions: Our results indicate that repeated sampling of those RLS patients who attend support groups reveals largely consistent clinical features and relationships. In both groups studied, a factor analysis of 8 candidate questions for the IRLSSG scale showed one predominant factor that seemed to account for most of the variance in summed severity. This suggests that there may be one major core measure of symptomatic impact in RLS. In both groups, patients with younger age of onset reported more affected relatives and had more arm involvement. This last finding supports the hypotheses that there are two distinct groups of RLS patients differentiated by age of onset .

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1378.K5

Acute Onset of Restless Legs Syndrome Following Phlebotomy: A Case Report

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Introduction: Restless Legs Syndrome (RLS) is characterized by complaints of progressively distressing abnormal sensations in the resting legs alleviated by movement. The criteria for the diagnosis of RLS have been formulated by the International Restless Legs Syndrome Study Group (IRLSSG) and include: 1. Desire to move the limbs usually associated with paresthesias/dysesthesias. 2. Motor restlessness 3. Symptoms are worse or exclusively present at rest with at least partial and temporary relief by activity. 4. Symptoms are worse in the evening/night -circadian pattern (IRLSSG 1995). The Restless Legs Syndrome Rating Scale (RLSRS) is a ten question clinician-administered questionnaire currently under development by the IRLSSG with scores ranging from 0-40 (Walters AS, Chair, personal communication). RLS is divided into primary or idiopathic (usually familial) type and secondary, most commonly following neuropathy, uremia and iron deficiency. Stein and Tschudy (Stein et al 1970) have noted the association of RLS with acute intermittent porphyria. Ferritin levels within the lower normal range correlated significantly with RLS severity (Earley et al 1998). Phlebotomy is a first choice treatment for porphyria cutanea tarda, a relatively common condition characterized by fragility and blistering of light-exposed skin which is associated with increased transferrin saturation.

Methods: We reviewed the patient's record.

Results: Mr. K. an otherwise healthy 51 year old caucasian male with a history of heavy smoking and week end related alcohol abuse was diagnosed with porphyria cutanea tarda (PCT). A series of phlebotomies was performed, following which his serum ferritin level was 7 ng/ml and the PCT was controlled. Within one week Mr. K. developed complaints suggestive of severe RLS such as fatigue and distressing sensations in the lower extremities, prominent at rest prior to sleep time and interfering with sleep onset. Mr. K's work up included x ray and MRI of the spine, brain CT, 2D echocardiogram and cardiac stress test which were interpreted as essentially normal. EMG results suggested an L5 radiculopathy . Blood work showed an increased TSH (20.28 uIU/ml) and treatment with Synthroid 0.1 mg was initiated. Following the neurological consult suggested treatment with Clonazepam 1 mg HS was initiated. The distressing sensations in the lower extremities persisted, but sleep onset was improved. However, the patient complained of drowsiness following treatment and Clonazepam was discontinued. A trial with Zolpidem 10 mg HS was not successful. Sinemet CR 50-200 was helpful initially. However within several weeks, rebound occurred as suggested by complaints of distressing sensations in the legs during the day. After discontinuing the Sinemet, Mr. K. was placed on Temazepam up to 30 mg HS. Eight months after his first ferritin level (7 ng/ml) Mr. K.'s ferritin level was 10 ng/ml. He complained of daily RLS symptoms (RLSRS of 33 suggesting very severe disturbance). Temazepam was helpful in promoting and mainly maintaining sleep. However, Mr. K complained of drowsiness during the day. In accordance with the treating gastroenterologist, iron replacement therapy was initiated. Treatment with Pramipexole .125 mg 2 hours prior to bedtime was initiated as well. The patient started tappering off the Temazepam. Three weeks after iron replacement therapy was initiated serum ferritin level was 36 ng/ml and the patient had dramatically reduced complaints of RLS (RLSRS of 7 suggesting mild disturbance).

Conclusions: Acute onset of restless legs symptoms may suggest RLS

secondary to induced low levels of ferritin. Careful examination of patients at risk might be warranted. Protocols that combine iron replacement therapy with RLS therapy might prove useful in the treatment of patients with porphyria cutanea tarda. Further investigation may focus on the relationship between serum ferritin and secondary RLS.

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1070.K5

Can Periodic Limb Movement Disorder be Diagnosed without Polysomnography?

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Introduction: Periodic limb movement disorder (PLMD) is a common disorder characterized by repetitive, stereotypical movements during sleep associated with insomnia or hypersomnia. Unlike restless legs syndrome (RLS) which is a separate but related disorder defined by clinical criteria, the clinical correlates useful in diagnosing PLMD have not been defined. We sought to determine whether clinical data could predict the presence of PLMD in a group of patients without RLS presenting with sleep complaints. In addition, in the group of patients who were diagnosed with PLMD, we explored the relationships between the severity of PLMD and clinical data.

Methods: The study cohort consisted of 122 patients. All patients completed a detailed medical and sleep questionnaire which included 1) demographics, 2) major sleep complaint, i.e. insomnia and /or hypersomnia, 3) medical disorders (including diabetes, anemia, neuropathy, and spinal disease), antidepressant medications (including tricyclic antidepressants, selective serotonin reuptake inhibitors, and monoamine oxidase inhibitors), and habits (including use of nicotine and caffeine), and 4) history of abnormal motor activity at night and symptoms of muscle discomfort. All patients underwent standard polysomnography. The PLMD group included 61 patients with PLMD diagnosed according to American Sleep Disorders Association criteria (i.e. sleep disorders symptoms and PLM-index > 5) without coexistent obstructive sleep apnea or RLS. 61 patients without PLMs or RLS who presented to the center with a variety of other sleep disorders comprised the control group. Data are presented as mean ± SE and were analyzed by either t-test or Mann-Whitney-U test. A logistic regression model was created using the presence or absence of PLMD as the dependent variable and clinical data as independent variables. Multiple linear regression analysis was used to determine the effects of clinical data on the severity of PLMD as expressed by PLM-index.

Results: The PLMD group consisted of 48 males and 13 females with the control group including 43 males and 18 females (55.1 ±1.8 vs. 49.6 ±2.0 years, p = .04). 80% of the PLMD group and 77% of the control group had symptoms of disorders of initiation and/or maintenance of sleep. The prevalence of subjective sleepiness (Epworth Sleepiness Scale > or =10) was 57% in PLMD group and 54% in control group. The PLMD group reported more leg kicks (28%) during sleep than the control group (5%, p = .02). There was no statistically significant difference in the reported prevalence of medical disorders, antidepressant use, muscle tension, muscle aches, leg pain, body jerking, crawling sensation in legs, smoking and/or caffeine intake between the two groups. The logistic regression analysis showed that only age with an odds ratio of 1.027 (C.I. !.001-1.054, p = .037) and smoking and/or caffeine consumption with an odds ratio of 2.540 (C.I. 1.064 - 6.073, p = .033) were significantly related to the presence or absence of PLMD. Within the PLMD group, none of the symptoms or other clinical data had any correlation with the PLM-index except for age (p = .03).

Conclusions: Clinical data including detailed specific medical and sleep questionnaire are not useful in predicting the presence of PLMD in patients who do not have RLS. Aging, smoking and/or caffeine consumption were positively related to PLMD. PLMD was more severe in older individuals. Polysomnography is required for establishing the diagnosis of PLMD in patients with symptomatology of insomnia or hypersomnia.

1092.K5

Restless Legs Syndrome in 286 Patients: Associated Disorders

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Introduction: Restless legs syndrome (RLS) is a disorder characterized by disagreeable sensations in the legs that occur at rest and are relieved by movement. These symptoms, which are worse at night, may result in sleep onset or sleep maintenance insomnia. Most patients are found on polysomnography to have periodic limb movements in sleep (PLMS). The disorder, idiopathic in most cases, may be sometimes associated with specific disorders. We wondered what diagnoses the patients had received prior to definitive sleep laboratory evaluation in an attempt to shed light on the reason for delayed diagnosis and to see whether RLS was more common in groups of patients with certain diseases. We compared the diagnoses made in the five years prior to sleep laboratory evaluation of 286 patients with RLS and 1144 matched control subjects from the general population.

Table 1

	Females		
Diagnosis	Case(%)	Controls(%)	Odds ratio
Affective disorders[a]	36.1	10.7	4.9***
Arthropathy[b]	47.4	22.7	3.3***
Disorder of back[c]	36.8	14.8	3.5***
COPD[d]	27.8	17.1	1.9**
Asthma	15.8	6.6	2.5***
Acquired hypothyroidism	10.5	3.2	3.8***
Diabetes mellitus	6.8	3.9	1.8
Anemia[e]	12.8	4.9	3.1***
Peripheral vascular disease	1.5	0.2	8.0*
Renal failure[f]	0.8	0.6	1.3

a. affective psychosis, depressive disorder; b. osteoarthritis and allied disorders, other and unspecified arthropathies, other and unspecified disorders of joint, other disorders of synovium, tendon, and bursa; c. intervertebral disc disorders, other and unspecified disorders of back; d. chronic bronchitis, emphysema, chronic airway obstruction; e. iron deficiency anemias, other deficiency anemias, hereditary hemolytic anemias, other and unspecified anemias; f. acute renal failure,chronic renal failure, unspecified renal failure
*P <0.05 **P <0.01 ***P <0.001

Methods: We selected 286 patients (153 men and 133 women) diagnosed as having RLS at the St.Boniface General Hospital Sleep Disorders Center from 1990 to 1998. All patients met the diagnostic clinical criteria, and/or met the polysomnographic criteria for PLMS. These patients were matched to control subjects using the Manitoba Health Database. Each patient was matched to four controls selected at random from general population by postal code, age, and gender. All patients and control subjects were residents of Manitoba for the length

of the study period. We determined what physicians had diagnosed in the patients and control subjects in the 5-year period prior to the year in which the patient was diagnosed as having RLS. Statistical analysis of data was performed by Mantel-Haenszel chi-square test to determine what diagnoses were statistically more common in RLS patients compared to controls in the 5 year period.

Results: The tables show the percent of patients and control subjects who had been diagnosed two or more times for each diagnostic class in the 5 years before sleep lab evaluation. RLS patients had been more frequently diagnosed as having affective disorders, diseases of musculoskeletal and connective tissues, some endocrine and metabolic diseases, and anemia prior to being diagnosed with RLS.

Table 2

	Males		
Diagnosis	Case(%)	Controls(%)	Odds ratio
Affective disorders[a]	27.5	4.2	7.5***
Arthropathy[b]	36.6	23.0	1.9***
Disorder of back[c]	22.9	13.9	1.8**
COPD[d]	23.5	10.6	2.7***
Asthma	11.1	14.5	2.5**
Acquired hypothyroidism	1.3	0.8	1.6
Diabetes mellitus	9.2	6.0	1.6
Anemia[e]	7.8	2.8	2.9**
Peripheral vascular disease	5.9	1.6	3.9**
Renal failure[f]	3.3	0.8	4.0*

Conclusions: We conclude that RLS patients were far more likely than controls to have various disorders diagnosed in the five years before being diagnosed with RLS. They were more likely to have previously been diagnosed with musculoskeletal disorders, depression, and painful conditions such as joint and back disorders. It seems reasonable that a clinician should include a sleep history in evaluation of patients with these disorders.

1097.K5

Sleep Complaints and Restless Legs Syndrome in Adult Type II Diabetics.

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Introduction: Restless Legs Syndrome (RLS), a disorder of unknown etiology associated with a variety of medical disorders is a cause of insomnia and excessive daytime somnolence (EDS). An association between diabetes mellitus (DM) and RLS has not been rigorously established. This study examined the the prevalence of sleep complaints and symptoms of RLS in a group of type II diabetics and sex and age matched controls.

Methods: Consecutive adult type II diabetic outpatients and age and sex matched controls were recruited. Fifty-eight type II diabetics (29 males, mean age 57.2 years) and 48 controls (27 males, mean age 53.1 years) were enrolled. Data pertaining to diabetic complications, medication use and comorbidities were obtained during patient interview and chart review. Examination for sensory neuropathy was performed. A detailed sleep questionnaire, which focused on symptoms of insomnia, daytime somnolence (Epworth Sleepiness Score, ESS), and RLS symptoms (according to the International RLS Study Group), was administered. Hemoglobin A_1C, electrolytes, urea, creatinine, B_{12}, folate, iron, ferritin and complete blood count were measured. Baseline characteristics of the two patient groups were compared using unpaired t-tests and Chi-square analysis. Regression analysis was performed to determine which factors predicted presence of RLS among diabetics. A p value of 0.05 or less was considered statistically significant.

Results: The diabetics were more obese than controls (BMI, 30.1 vs. 27.2; p = 0.03); there were no significant differences between the two groups in other variables including biochemical indices. Sleep complaints were common among the diabetics compared with controls, with higher rates of insomnia (50% vs. 31%, p=0.04) and hypnotic use (26% vs. 6.0%, p=0.02). Nocturia (41.4% vs 18.8%, p=0.01) and nighttime muskulosketal discomfort (29.3% vs 12,5%, p=0.03) were more common in diabetics than in controls. There was a higher prevalence of hypersomnolence in diabetics (proportion with ESS >12: 15.5% vs. 2.1 %, p=0.02) compared to controls. The prevalence of RLS among diabetics was not significantly different than in controls (24.1% vs. 12.5%, p=0.10). Diabetics with RLS had higher ESS (8.2 vs. 4.8, p=0.02) than non-RLS diabetics. Rates of sensory neuropathy were similar among diabetic patients with and without RLS (43% vs. 34%, p=0.78). Age, BMI, duration of diabetes, Hgb, Hgb A_1C level, ferritin and creatinine did not predict the presence of RLS among diabetics.

Conclusions: Adult type II diabetics have high rates of insomnia, hypnotic use and daytime somnolence. Nocturia and muskuloskeletal discomfort are the most common nighttime complaints and are the most common cause of insomnia in this group. The prevalence rate of RLS among diabetics is higher than previously reported, but not greater than in age and sex matched controls. RLS in diabetic patients is independent of coexisting conditions (anemia, iron deficiency, and renal insufficiency) and unrelated to the duration of diabetes and the level of diabetic control. RLS was found not to be related to the presence of clinically detectable sensory polyneuropathy.

1755.K5

A Comparison of Periodic Limb movements and Arousals in Relation to Two Selective Serotonin Reuptake Inhibitors

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Introduction: Antidepressants have been shown to cause various sleep disturbances which may include alterations in sleep architecture, insomnia, altered arousal thresholds and increased periodic limb movements (PLMs). It has been noted that it would be beneficial to further break down antidepressants into subgroups to determine their effects.[1] We specifically examined the hypothesis that two of the selective serotonin reuptake inhibitors (SSRIs), fluoxetine (Prozac) and sertraline (Zoloft) may have different effects on PLMs and arousals.

Methods: We did a systematic chart review of 16 patients who have been seen in our sleep clinic within the past 2 years. Patients were excluded if they took other medications which may have affected sleep. Patients had a 16-channel overnight diagnostic polysomnogram (PSG). The records were hand-scored using Rechtschaffen and Kales' sleep scoring guidelines. The Prozac group consisted of 9 patients (6 males, 3 females, mean age 43.4). The Zoloft group consisted of 7 patients (3 males, 4 females, mean age 48.3). We compared the two groups regarding the following variables: PLMs per hour and arousals per hour. PLMs were further broken down into events causing arousals and not causing arousals. Comparisons were tested for statistical significance using t-tests.

Results: The results of the drug comparisons are shown in the table.

Conclusions: The average age of the two groups was not significantly different; nor was the spontaneous arousal index. However, the overall PLM index was significantly higher with fluoxetine than with sertraline group ($p < 0.5$); furthermore, PLMs were more likely to be associated with arousals ($p < 0.5$). The study is limited by the small sample size, but is suggestive that SSRIs may differ in their tendency to promote peri-

odic leg movements.

Table 1

Sex	Age	Spontaneous arousal index	PLM index	PLM index with arousals
		Fluoxetine		
M	48	9.0	20.6	4.3
F	27	20.6	21.8	8.4
M	50	16.5	0.0	0.0
M	44	0.0	0.0	0.0
F	47	10.2	5.5	2.0
M	62	16.1	45.8	5.3
M	35	4.2	38.1	12.5
M	40	13.5	7.1	3.6
F	38	12.1	26.5	10.9
Average	**43.4**	**11.3**	**18.4**	**5.2**
S.E.	*3.3*	*2.1*	*5.5*	*1.5*
		Sertraline		
F	49	5.9	5.6	4.4
F	40	16.6	0.0	0.0
F	46	10.2	0.0	0.0
F	45	7.5	2.1	1.3
M	65	8.8	5.2	2.1
M	41	7.2	2.1	0.3
M	52	5.4	0.0	0.0
Average	**48.3**	**8.8**	**2.1**	**1.1**
S.E.	*3.2*	*1.4*	*0.9*	*0.6*

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1423.K5

Effects of Cabergoline on Sleep and Morning Motor Performance in Patients with Parkinson´s Disease

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Introduction: It is well established that important causes for the sleep disturbance seen in patients with Parkinson´s disease are nocturnal akinesia and dopaminergic drug treatment, although multiple additional influences must be taken into account. In this study, we examined the effects of cabergoline, a dopamine D2 and D1 receptor agonist, on sleep and motor performance in patients with Parkinson´s disease. It was hypothesized that cabergoline would exert beneficial effects on sleep due to its distinct long elimination half-life (≥ 60 h).

Methods: 15 patients with idiopathic Parkinson´s disease (8 m, 7 f, mean age 63.9 (9.5) years) were included. Mean symptomatic disease duration was 4.6 (3.3) years, median Hoehn and Yahr stage 2.5 (1-3). 6 patients were de novo, 9 were pretreated (levodopa n = 9, tolcapone n = 1, budipine n = 1). Before begin of cabergoline treatment and 6-8 weeks later, after titration to 4-6 mg/d given as a single morning dose the following tests were performed: Polysomnography (two nights in both conditions; the second night was used for analysis), sleep log (VAS scale), and motor tests (UPDRS III and tapping tests) performed in the morning before drug intake.

Results: Sleep data are shown in the table below. There were significant increases in stage 1+2 sleep, and significant increases in awakenings and stage shifts. On cabergoline treatment, there were significant improvements in morning motor score (mean baseline score: 23.9 / treatment: 14.7 ($p < 0.001$), and significant increases in tapping rate (baseline mean: 147/sec / treatment: 172/sec; $p < 0.01$). Sleep logs revealed that patients self-rated the restorative quality of their sleep higher during cabergoline treatment on a VAS scale($p < 0.05$, paired t-test).

Table 1. Sleep data in 15 patients with Parkinson´s disease before (baseline) and during (treatment) cabergoline therapy

	baseline	treatment	p
Time in Bed (min)	480 (2)	481 (4)	ns
Time of Sleep (min)	360 (71)	373 (54)	ns
Sleep Efficiency %	74.9 (14.8)	77.7 (11.4)	ns
Sleep Latency (min)	27 (30)	15 (14)	ns
REM Sleep Latency	87 (79)	91 (67)	ns
Awakenings	22 (10)	32 (13)	< 0.05
Stage Shifts	119 (42)	147 (46)	< 0.05
	baseline	**treatment**	**p**
Sleep Cycle Time	445 (30)	454 (22)	ns
Wakefulness %	20.2 (14.2)	21.1 (9.5)	ns
Stage 1+2%	56.2 (10.8)	63.9 (9.7)	< 0.05
Stage 3+4 %	10.9 (15.9)	6.0 (7.1)	ns
REM%	17.6 (6.6)	13.7 (7.3)	ns

Conclusions: In contrast to our hypothesis, there was significant improvement of morning motor performance, but no overall improvement of objective sleep variables under cabergoline therapy. There was a small, but significant increase in stage 1+2 percentage, which may in part be due to the non-significant REM sleep suppression and decrease of slow wave sleep. The significant increase in stage shifts and awakenings points towards an increased sleep instability under cabergoline therapy. However, patients evaluation of the restorative quality of sleep was significantly better on cabergoline therapy.

1114.K5

Sleep and Night Motor Disturbances in Parkinson's Disease: The Role of Disability and Pathology CIC

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Introduction: Sleep disturbances in Parkinson's disease (PD) can result from lesions of neuronal systems involved in sleep control, from motor disability, or from both (Aldrich 1994). Continuous high frequency stimulation of the subthalamic nucleus (STN) (Limousin et al 1998), that reverses motor symptoms during the night, was used to distinguish reversible sleep disorders caused by motor handicap from irreversible sleep disorders caused by PD lesions.

Methods: Night-time sleep and motor symptoms in 10 PD patients, treated by bilateral high frequency STN stimulation, were compared, in a crossover order, to their sleep parameters and symptoms during a night without stimulation.

Results: A 66% reduction in night-time akinesia and the suppression of axial and early morning dystonia following nocturnal stimulation was accompanied by a mean 47 % increase in total sleep time, and a mean 51 minute reduction in wakefulness after sleep onset. Periodic leg movements (n=3) and REM sleep behavior disorders (n=5) observed during the control night were not modified by stimulation.

Conclusions: The results suggest that, in PD patients, insomnia predominantly results from night-time motor disability, whereas periodic leg movements and REM sleep behavior disorders from brain lesions

affecting systems other than the nigro-striato-pallido-cortical pathways.

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(2) Limousin P, Krack P, Pollak P et al. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 1998,1105-11,339.

1150.K5

Treatment of Periodic Limb Movements in Sleep with Selegiline

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Introduction: In a retrospective study, patients undergoing treatment with Selegiline HCl for Periodic Limb Movements in Sleep were examined with respect to specific sleep composition. Pre- and post treatment overnight polysomnographic recordingsd revealed a highly significant decrease in the number of PLMs per hour of total sleep time [$p < 0.0005$]. Selegiline was not found to have any significant effect on patients' sleep efficiency or sleep onset latency [$p > 0.10$].

Methods: Preliminary consultation notes were inspected in order to attain a baseline perspective of patients' PLM indices, onset latencies, and sleep efficiencies. Individuals diagnosed with PLMS who were commenced on Selegiline HCl were followed. Patients were prescribed selected dosages for various duration. Data from follow-up assessments allowed inference of PLM index, sleep efficiency, and sleep onset latency differentials.

Results: PLM indices were substantially reduced with all dosages of Selegiline HCl. The mean improvement for the overall treatment of the entire patient pool was clearly significant at 21.2/hour [$p < 0.0005$]. Sleep efficiency had a mean reduction of approximately four percentage points for the entire patient pool. Sleep onset latency was delayed by a mean of 9.71 minutes. Calculation p-values proved insignificant for both of the latter aspects.

Conclusions: Recent literature focuses on the administration of several medications in the treatment PLMS. Our results with Selegiline have added to the pharmacological possibilities. Although sample sizes were limited, medication proved to be encouraging at all dosage levels. Through prospective experimental study, perhaps the potential of this medication for clinical usage could be thoroughly explored.

References:
(1) Ohanna, N., Peled, R., Rubin, A.E., Zomer, J., Lavie, P. Periodic Leg movements in sleep: Effect of clonazepam treatment. Neurology 1985, 23, 408-411.

1814.K5

Periodic Limb Movements and Nasal CPAP

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Introduction: Periodic limb movements (PLMs) have been previously reported in association with application of nasal continuous positive airway pressure (CPAP). Leg movements resembling PLMs have also been reported with subtle hypopneas and arousals associated with episodes of increased upper airway resistance. The purpose of this study was to further investigate the relationship between PLMs and nasal CPAP administration.

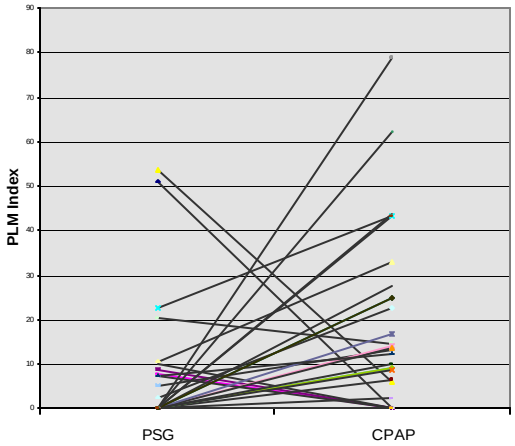
Methods: All polysomnograms performed at the University of Mississippi Medical Center Sleep Disorders Center between the dates 1/4/98 and 11/12/99 were included based on the following criteria: 1) apnea-hypopnea index (AHI) > 10 on the baseline recording, with subsequent CPAP titration polysomnogram (PSG), 2) AHI on the CPAP titration study of < 10 or reduced by at least 50% compared to the baseline study, and 3) periodic limb movement index (PLMi) > 5 on either the baseline recording or the subsequent CPAP titration study. Leg movements associated with EEG arousals following respiratory events were not scored as periodic leg movements. PSG's were excluded if an agent used to treat periodic limb movement disorder (PLMD) was started, or if an agent known to exacerbate PLMD was discontinued after the baseline recording and prior to the CPAP titration. Comparison was made between the PLMi during the baseline PSG and the CPAP titration study. A change of 5/hr or greater in the PLMi was considered significant.

Results: Twenty nine patients were identified based on the above criteria. PLMi increased in 20, decreased in 7, and did not change significantly in 2 patients. Patients were divided into 3 groups based on apnea-hypopnea index (AHI) on the baseline PSG: 1) AHI < 15, 2) AHI =15 - 40, and 3) AHI > 40. Of patients with AHI < 15 on the baseline PSG, 66.7% had a significant decrease in the PLMi with CPAP administration, while the majority of patients with AHI = 15-40 and AHI > 40 (69.2% and 90%, respectively) showed a significant increase in PLMi during CPAP administration. Additional data are summarized in the table and graph below:

Table 1

	Mean PLMi (PSG)	Mean PLMi (CPAP)	# Patients with PLMi Increase	# Patients with PLMi Decrease	# Patients without PLMi Change	Mean Change
AHI < 15	24.0 +/- 23.2	9.3 +/- 17.0	2	4	0	-14.7 +/- 29.0
AHI = 15-40	4.3 +/- 6.3	16.5 +/- 13.3	9	3	1	12.2 +/- 15.5
AHI > 40	0.8 +/- 2.4	27.1 +/- 25.9	9	0	1	26.3 +/- 26.5

Figure 1. PLM Index During Baseline PSG and CPAP Titration



Conclusions: Our data suggest that PLMs are more likely to occur during baseline polysomnography in patients with mild OSA, and during CPAP titration in patients with moderate to severe OSA. This may be due, at least in part, to two phenomena: 1) movements resembling PLMs may occur with EEG arousals following subtle hypopneas and episodes of increased upper airway resistance; this could explain the occurrence of leg movements not only during baseline recording in patients with mild OSA, but also during CPAP titration in patients with moderate to severe OSA (while at subtherapeutic pressures that approximate mild

OSA and/or upper airway resistance syndrome); 2) moderate to severe OSA may "mask" true PLMD (due to sleep disruption), which may more fully manifest during CPAP titration as respiration is improved. Further study of this matter could benefit from esophageal manometry during baseline and CPAP titration studies, and analysis of leg movement frequency at subtherapeutic versus therapeutic CPAP settings during titration.

1516.K5

Periodic Limb Movements Disorders (PLMD) in Two Siblings with Fragile X Syndrome.

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Introduction: Fragile X Syndrome is the most common genetically-inherited form of mental retardation and it is caused by a defect on the long arm of X chromosome. A repeated duplication of a small region of the gene (CGG) results in a lengthened DNA region of the gene. Fragile X Syndrome is X-linkage resulting in higher frequency in males than in females. The male individuals with the syndrome have common physical behavioral and mental features, such as: narrow face, prominent and large ears, macroorchidism and loose joints. The most prevalent behavioral disturbances are attention problems and hyperactivity and other characteristics are speech, language and learning disabilities. Twenty percent of males with this syndrome have generalized or partial seizures. Among medical problems they may show gastroesophageal reflux and sleep disturbances. Obstructive sleep apnea has been reported in Fragile X Syndrome as well nocturnal enuresis and insomnia. We describe two siblings with this syndrome associated with excessive daytime sleepiness.

Methods: We are describing polyssomnographic features of a 23 y.o (MCC) and a 32 y.o. (ALC) males siblings with daytime excessive sleepiness, hyperactivity and attention deficit in our sleep center. We perform clinical and polysomnographic evaluation in both patients under standard procedure. Samples of blood and urine was taken for laboratorial analysis. Both realized EEG and EKG. Diagnostic confirmation of Fragile X Syndrome was made by genetic studies.

Results: Polysomnographic findings from MCC showed excessive numbers of arousals, sleep fragmentation, short sleep latency, increased REM latency, low sleep efficiency, increased slow wave sleep, increased REM sleep and high PLM index of 70/h. The Epworth Sleepiness Scale was 15. Seric ferritin and hemogram were normal as well orther tests . ALC presented almost all MCC findings except for Snoring, PLMD index of 86 and 12 in the Epworth Sleepiness Scale.

Conclusions: Periodic Limb Movement Disorder (PLMD) may account for the sleep deprivation and daytime sleepiness in our cases. Otherwise PLMD may be associated with Attention Deficit Hyperactivity Disorder, one behavioral characteristic of Fragile X Syndrome.This is the first report that we know of PLMD associated with Fragile X Syndrome. In spite of the high PLMD Index, the finding of high proportion of slow wave sleep deserves mention.

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(1) Tirosh, E; Borochowitz, Z. Sleep apnea in fragile X syndrome. Am J Med Genet. 1992. Apr 15-May 1;43(1-2):124-7.

1843.K5

Restless Legs Syndrome. A Prevalent Disorder Associated with Neuropsychiatric and Somatic Complaints

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Introduction: Restless legs syndrome (RLS) was coined by Ekbom, Sweden, in 1945.[1] He estimated the prevalence of RLS to be 5,2%. The impact of RLS on daytime symptoms has not been thoroughly studied. This study investigates the prevalence of RLS among Swedish men, and whether there is an association between RLS and neuropsycluatric and somatic complaints among these men.

Methods: A random sample of 4000 men, 18 - 64 years of age,(mean age 48 yr) living in a county in mid-Sweden, was sent a 100-item questionnaire that included questions about sleep habits, symptoms of sleepiness and somatic complaints. Four symptom questions determinated by The International Restless Legs Syndrome Study Group[2] as minimal diagnostic criteria for RLS were also included. A positive response to all four questions indicates RLS. Odds ratios (OR) with 95% confidence intervals were calculated by means of multivariate logistic regression. The odds ratios were adjusted for differences in age, witnessed apneas, smoking and alcohol consumption.

Results: Twotousendsixhundredeight (66%) of 3961 eligable men responded to the questionnaire. A random sample of 10% of non-responders was contacted by telephone, resulting in additional responses comparable to those obtained by questionnaire. The primary reason for not responding was the opinion that resarch on sleep disturbances did not personally concern them. Twohundredthirtyone men had the diagnosis of RLS. Thus the prevalence of RLS was estimated to be 5,8%. Sleep related complaints were about three times more frequent among men with RLS as compared to those without RLS. The OR for not being refreshed at awakening was 3,8 (95% CI 2,8-5,3) among the men with RLS. The OR for scores > 10 on the Epworth scale among med with RLS was 1,6 (95% CI 1,1-2,3). The men with RLS had a more depressed mood, OR 2,6 (95% CI 1,8-3,8), and complained more often of reduced libido, OR 2,2 (95% CI 1,4-3,3) The odds ratio for morning headache was 4,7 (95% CI 2,9-7,6). Hypertension (OR 1,5, 95% CI 0,9-2,4) and heart problems were more often reported among the men affected by RLS (OR 2,5, 95% CI 1,4-4,3)

Conclusions: This study, using internationally accepted RLS criteria,[2] shows that restless legs syndrome is as prevalent among Swedish men as originally reported 55 years ago.[1] The study also shows that insomnia and sleepiness during wakefulness are greater among those suffering from RLS. Men with RLS seems to be affected by severe neuropsychiatric complaints such as depressed mood and impotence together with headache, hypertension and heart problems.These data support the conclusion that RLS is not just a harmless symtom.

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POSTER PRESENTATIONS

1867.L

Exploring Relationships Among Pain Variables and Sleep Disturbances in Cancer Patients

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Introduction: It is becoming increasingly clear that symptom experiences are often interrelated and that pain is a specific clinical factor that may significantly interact with sleep disturbances (e.g., Chokroverty, 1999; Wooten, 1994). However, few studies reported in the literature specifically address sleep problems in cancer patients, particularly cancer patients with pain problems. This ongoing study, originally designed to examine the reliability, validity, and response variability of different scales used to measure patient satisfaction with cancer pain management, has revealed that sleep disruption is a significant problem for many oncology patients with moderate to severe pain. Thus, a second objective of this study is to explore in more detail the nature of sleep complaints and to explore relationships between sleep alterations and pain variables.

Methods: Using the Brief Pain Inventory (BPI) (Cleeland, 1989), 143 cancer patients have been surveyed regarding their cancer pain history, etiology, intensity, quality, and the extent to which pain interferes with daily activities, including sleep, with the most recent 57 patients also completing the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS). The analyses conducted focused on examining possible interactions between selected sleep and pain variables. Because of the ordinal level data, a Spearman's rank order correlation was employed to assess these relationships.

Results: As the BPI Pain Interference Composite Score increased, (a) sleep quality decreased ($r=.673$, $p \leq .01$), (b) sleep duration decreased ($r=.450$, $p \leq .01$), (c) habitual sleep efficiency decreased ($r=.396$ $p \leq .01$), (d) daytime dysfunction increased ($r=.386$, $p \leq .01$), and (e) trouble sleeping because of pain increased ($r=.435$, $p \leq .01$). As the BPI Pain Severity Composite Index Score increased, (a) sleep quality decreased $r=.477$, $p \leq .01$), (b) sleep latency increased ($r=.291$, $p \leq .05$), (c) sleep duration increased ($r=.339$, $p \leq .05$), and (d) trouble sleeping because of pain increased ($r=.542$, $p \leq .01$).

Conclusions: These preliminary analyses suggest important interactions between pain problems and sleep disturbances. Further exploration will help to identify strategies to improve the health care of cancer patients in pain who experience sleep disturbances.

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1871.L

Chronic Pain, Sleep Disturbance, and Depression: A Consideration for Assessment

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Introduction: The high incidence of depression among people who experience chronic pain has been well established. However, there has been controversy concerning the use of the Beck Depression Inventory (BDI) in a population with chronic pain. It has been suggested that in chronic pain populations some elevations on the BDI may be attributed to the somatic component of pain rather than a mood disturbance.[1] Both chronic pain and depression may be associated with fatigue, sleep disturbance, and/or diminished engagement in activities. The presence of sleep disturbance in depression has also been well established.[2] The current research sought to determine the strength of the relationships between pain severity, sleep related factors, and depressive symptomatology.

Methods: Twenty participants (mean age = 58 years, SD = 14.2 years) with a medical illness or injury associated with pain previously diagnosed by a physician were included in the study. Participants were excluded if the presence of a sleep disorder or major psychiatric illness was indicated or the duration of the chronic pain condition was less than six months. Participants were recruited on a volunteer basis from aquatic exercise programs and chronic pain support groups in the southeastern United States. Participants completed a questionnaire packet that included the Epworth Sleepiness Scale (ESS), West Haven-Yale Multidimensional Pain Inventory (WHYMPI), and the BDI

Results: A significant positive correlation was observed between pain severity (PS), indicated by a sub-scale of the WHYMPI, and daytime sleepiness, as measured by the ESS. Pain severity was also significantly correlated with the global (BDI/G), cognitive/affective (BDI/CA), and somatic/performance (BDI/SP) scales of the BDI. Daytime sleepiness was significantly correlated with the BDI somatic/performance scale (Table 1).

Table 1

Pearson Correlation Coefficients

	ESS	BDI/G	BDI/SP	BDI/CA
PS	**.380***	**.797*****	**.788*****	**.567****
ESS	**-**	**.285**	**.530****	**.095**

* $p<.05$ ** $p< .01$ *** $p<.001$

Conclusions: As postulated there were significant correlations between pain severity, daytime sleepiness, and depressive symptoms. Significant positive correlations between pain severity and the BDI emphasize that pain and depression share a number of symptoms. A positive correlation between the ESS and the BDI somatic/performance scale suggests a relationship between daytime sleep propensity and depressive symptoms related to health and/or engagement in activities. Elevations on the BDI somatic/performance scale could lead to higher depression scores than might otherwise be expected on the BDI global scale. Because of the relationship between the BDI somatic/performance scale and ESS, daytime sleepiness may ultimately elevate the BDI global scale. This indirect relationship between daytime sleepiness and the BDI global scale emphasizes the importance of considering daytime sleepiness in the assessment of depressive symptoms in a chronic pain population. Based on these findings it is suggested that the consideration of both pain

severity and daytime sleepiness are essential in the assessment of depression in a chronic pain population.

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1886.L

Absence Epilepsy Presenting with Hypersomnolence

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Introduction: Epilepsy patients suffer from a variety of sleep complaints. As many as 61% of epileptics complain of hypersomnolence and 42% of non-restorative sleep (Vaughn, et al 1996). Epileptic children may have an increased Sleep Latency, decreased Total Sleep Time, and increased daytime somnolence. The frequency of seizures directly correlates with the frequency of sleep complaints in epileptics (Hoeppner, et al). Anticonvulsant therapy is associated with stabilization and normalization of sleep in most epileptics (Johnson, et al 1983). We present a case in which a 21 year old male presented with a five year history of hypersomnolence. He complained of non-restorative sleep that worsened with a sleep period longer than six hours. He continually fought off sleep during his wake period, he took I to 2 hour planned naps, he frequently dozed during quiescent periods, and occasionally dozed during inappropriate circumstances. He had a habit of taking caffeine tablets to fight-off sleep during critical daytime activities. He presented after dozing off in stop-and-go traffic and bumping the car ahead of him.

Methods: The patient kept a sleep diary for two weeks. He then underwent a twelve lead nocturnal polysomnogram (NPSG) (adjusted to his sleep schedule), followed by a Multiple Sleep Latency Test (MSLT). A 21 channel electroencephalogram (EEG) was performed on the same day as the MSLT. An MSLT was performed after the initiation and optimization of his anticonvulsant regimen.

Results: His sleep diary showed a bedtime extending from 2:00 a.m. to 9:30 a.m., with a short Sleep Latency and few nocturnal awakenings. He averaged two, sixty minute daytime naps per week. The NPSG documented a Sleep Latency of 62 minutes, a Total Sleep Time of 394.5 minutes, a Total Bed Time of 462.5 minutes, and a REM Latency of 68 minutes. Sleep stage distribution was: 11% Stage 1, 36 % Stage 2, 27% Stage 3/4, and 26% Stage REM. He had a Disturbance Index of 5/hour and Periodic Limb Movement Arousal Index of 4/hour. There were frequent seizure discharges noted throughout the sleep period and during all MSLT naps. He had a Mean Sleep Latency of 8.5 minutes and two REM onset naps on the MSLT. EEG revealed classic 3/sec spike and slow wave epileptiform discharges consistent with Absence type seizures without apparent clinical manifestations. Treatment with Divalproex sodium was associated with resolution of the epileptiform discharges on EEG. Mean Sleep Latency was greater than 20 minutes and there were no REM onset naps during the MSLT. The patient experienced clinical improvement in sleep quality and resolution of Hypersomnolence.

Conclusions: Our case suggests that frequent epileptic discharges during sleep may intrinsically produce sleep disruption resulting in non-restorative sleep and significant daytime somnolence. Seizures should be included in the differential diagnosis of hypersomnolence. Hypersomnolence in epileptic patients may be an indication of persistent nocturnal seizures.

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1252.L

Changes of Interictal Spikes in the Medial Temporal Lobe in All-Night Sleep Recordings in Partial Epilepsy with Subdural Electrodes.

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Introduction: It has been known that sleep has facilitating effects on epileptic seizure. Therefore, the relationship between epilepsy and sleep has long been studied. Most past studies used surface electroencephalogram (EEG) for the monitoring of interictal epileptic discharges (IIEDs). However, it has been known that only a part of ictal discharges could be detected by surface EEG. We have performed all-night sleep recordings in seven epileptic patients by medial temporal lobe subdural electrodes and examined the relationship between sleep stages and epileptic spike counts.

Methods: Subjects were 7 patients (4 male, 3 female; age 24 – 46 years) with clinically intractable partial epilepsy, six were temporal lobe epilepsy (TLE), among them, one was bi-temporal focus. One was frontal lobe epilepsy (FLE). All underwent presurgical evaluation in Tokyo Metropolitan Neurological Hospital. Recordings were carried out approximately one week after surgical placement of subdural electrodes that were attached to bilateral parahippocampal and basal temporal cortex. In addition, a Cz-A1 scalp EEG, an oblique electro-oculogram and a chin electromyogram were recorded. Two days before recording, antiepileptic drug treatment were restarted. All signals were recorded on a digital data recorder and later downloaded on a computer hard disk. The data were decimated to make 750 Hz sampling files. To detect IIEDs, we developed an automatic spike-detection algorithm. To evaluate the reliability of automatic detection, visual spike detection were carried out in the same 10 epochs (of 16.4 second) of each sleep stage, and high correlations were obtained. To calculate spike numbers during sleep, the most active lead of medial and basal temporal montage were selected. Spike densities (total spike number of each sleep stage divided by total duration of each sleep stage) were calculated. FFT analysis was also performed on the Cz EEG to examine the relationship between each frequency power and spike counts in the medial temporal lobe (MTL).

Results: In uni-lateral TLE, the spike density of MTL of affected side was high in any sleep stage. In bi-lateral TLE, laterality of spike density was uncertain. In FLD, spike density of the MTL was remarkably low. With regard to the relationship between sleep stage and spike density, the spike density was high in deep NREM sleep except in one subject, who showed high spike density during stage 1. The spike densities in REM sleep were not always the lowest. Sigma activity measured by FFT showed parallel fluctuation pattern with spike counts in some subjects.

Conclusions: In the studies used surface EEG, interictal discharges on partial epilepsy increased in deep NREM sleep.[1] Our results support the former results with some exception. Regarding the relationship between EEG spectral power and spike counts, one study indicated that delta activity was closely related to IIED distribution.[2] But another study

revealed a higher correlation between sigma activity and IIEDs. Our preliminary results suggest that the sigma activities were closely connected to the spike-index than delta activities. However, more detailed examination will be needed to obtain the final conclusion.

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1628.L

A Large Multi-center Trial for the Treatment of Sleep Disturbances in Persons with Alzheimer's Disease: A Progress Report

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Introduction: The Alzheimer's Disease Cooperative Study (ADCS), an NIA-funded consortium of Alzheimer's Disease (AD) research centers, has undertaken an investigation in the treatment of insomnia in patients with AD. Results of early studies[1] indicated that 50 subjects would be needed in each arm of a three-arm, parallel design trial comparing two melatonin formulations with placebo, making this the largest melatonin trial yet attempted. Given the expense, importance and delayed completion of this much-anticipated study, we are reporting our progress to date.

Methods: Entry criteria for the trial include a diagnosis of AD and specific wrist-actigraph documentation. Actigraphic measures must demonstrate an average of less than seven hours of sleep, between 8:00PM and 8:00AM, over a minimum of five full days per week of proper data collection amidst a two-week screening period. Subjects meeting criteria are then randomized to placebo or either 2.5mg or 10mg of melatonin given one hour before habitual bedtime. Study medication is taken at the same time every night for eight weeks, followed by a two-week placebo washout. Twenty-four hour actigraph monitoring continues throughout the protocol. Recruitment at 32 NIA Alzheimer's Disease Research Centers across the country began in November 1997.

Results: Recruitment into the study has been much slower than anticipated. Obstacles to recruitment have included caregivers' need for standard, albeit unproven, therapies such as trazodone and commercially available melatonin. As of late November 1999, aproximately 240 people have been screened for the trial and 125 randomized to study medication. Primary reasons for exclusion have included failure to meet actigraph criteria for sleep disturbance (49), medical instability (12), diagnostic exclusions (9), and miscellaneous (29, including 7 refusals to wear the actigraph). To date, 96 subjects have completed the study. There have been no serious adverse events attributed to study medication.

Conclusions: Although others have noted how difficult it can be to recruit AD subjects into sleep studies[2], we nevertheless expected faster progress than we have made. Recruitment rate has been improved by making special efforts to draw from nursing homes and assisted living facilities, conducting community education programs and bringing on additional, non-academic research sites. We hope to meet our recruitment goal of 150 subjects within the next few months.

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1644.L

Stroke During Sleep & #61498; Recurrence Risk of Multiple Vascular Events

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Introduction: Stroke is the first cause of death in many Brazilian regions. Its high morbidity and social cost have stimulated researchers to look for other associated factors than the classic risk factors for stroke.Many patients wake up with neurologic deficits pointing that the ischemic event occurred during sleep. REM sleep and apneas are physiologic and pathologic sleep events that might be related to stroke or cardiac ischemia, once not recognized such conditions may lead to stroke recurrence.OBJECTIVE The aim of the present study was to investigate the relationship between the patients with stroke occurring during sleep or waking state and the follow up.

Methods: Sixty-seven patients (31 female and 36 male) underwent this study. The age ranged from 40 to 88 years old (average of 66.6 years old). They come from Neurovascular Disease Department since November 1998 until November 1999. The follow up was 6.7 months in average. We asked them "what they were doing when the stroke came up". We have presumed that the stroke occurred during sleep if the patient woke up with the deficit installed.

Results:

Table 1

STROKE DURING SLEEP: RECURRENCE RISK OF MULTIPLE VASCULAR EVENTS

Results

PARAMETER		STROKE FURING SLEEP YES	NO	X^2 Test
AGE	More than 45	20	42	p = 0.5340844
	Less than 45	2	3	
GENDER	Male	12	24	p = 0.8670339
	Female	10	21	
SITE OF STROKE	Unilateral	10	26	p = 0.4698173
	Bilateral	10	15	
ECOCARDIOGRAPH	High risk	12	22	p = 0.8612796
	Low risk	10	23	
NUMBER OF EVENTS	Single	7	20	p = 0.0425400 *
	Multiple	15	2	
PSYCHIC SYMPTOMS	Yes	16	24	p = 0.209505
	No	6	21	

* statistically significant

Conclusions: The sleep installation of stroke was not statistically significant associated with age, gender, psychic symptoms after stroke, CT scan localization of the lesion or high ecocardiograph risk for cardioembolic stroke.Patients with at least one coronarian or cerebral clinic

ischemic event during sleep had higher chance of recurrence.People with sleep installation of stroke may carry a poor outcome.

1654.L

Psychological Disturbance is Associated with Both Gastrointestinal Symptoms and Sleep in Patients with Functional Gastrointestinal Disorders

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Introduction: Functional gastrointestinal disorders are often viewed as psychosomatic disorders with significant psychogenic components. Epidemiological studies have shown increased complaints of poor sleep in these patients. It has been controversial whether objective sleep abnormalities are present, or whether there is an over-reporting and/or a misperception of sleep symptoms.[1-3] The association of psychological factors, sleep complaints and gastrointestinal symptoms also remains unclear.

Methods: 17 women with functional upper (dyspepsia-like) and/or lower (IBS-like) symptoms and 13 healthy women underwent polysomnographic (PSG) monitoring on one night. Psychological disturbances were assessed with the SCL-90-R; the Pittsburgh Sleep Quality Index (PSQI) measured subjective sleep quality during the past 2 weeks; state anxiety was measured with the STAIS in the evening and morning of the sleep study, together with an assessment of gastrointestinal symptoms. In the morning after the sleep study, a modified insomnia questionnaire assessing sleep dissatisfaction regarding the past night was completed. In addition to standard PSG scoring, brief arousals (<15 seconds) in addition to awakenings (>15 seconds) were scored.

Results: Although individuals with a current psychiatric disorder or on psychotropic medication were excluded, patients scored significantly higher on almost all symptom dimensions of the SCL. Patients also scored significantly higher on the PSQI. PSQI scores were significantly correlated with SCL variables (e.g., PSQI global score with Positive Symptom Distress Index (PSDI): r=.7, p<.001), but not with gastrointestinal (GI) symptoms. Instead, GI symptoms were correlated with STAIS (r=.5, p<.05) and the SCL (e.g., GI symptom score and Positive Symptom Distress Index r=.5, p<.05). Patients' sleep stage distribution, sleep efficiency, sleep onset latency, and arousal index data were well-within normal limits, and not significantly different from the controls. Of interest is the fact that the patients showed an increase in the number of awakenings (11 vs. 6, p=.054), although the total wake time across the night was similar in patients and controls (27 min. in patients vs. 30 min. in controls). In addition, the number of movement episodes was increased in patients (14 vs. 9, p<.05). With regard to sleep dissatisfaction of the past night, patients rated their sleep quality significantly worse (p<.05) and reported feeling significantly less rested (p<.05).

Conclusions: (1) Patients with functional gastrointestinal disorders report greater dissatisfaction with sleep, which may be related to subtle differences in sleep continuity (i.e., arousal responses) in the absence of gross abnormalities in sleep architecture. (2) There is an association between patients' reporting of psychological disturbances and their reporting of sleep dissatisfaction. (3) There does not seem to be an obvious relationship between sleep and GI complaints in these patients.

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1681.L

Wrist Actigraphy as a Method of Sleep Detection in Persons with Parkinson's Disease

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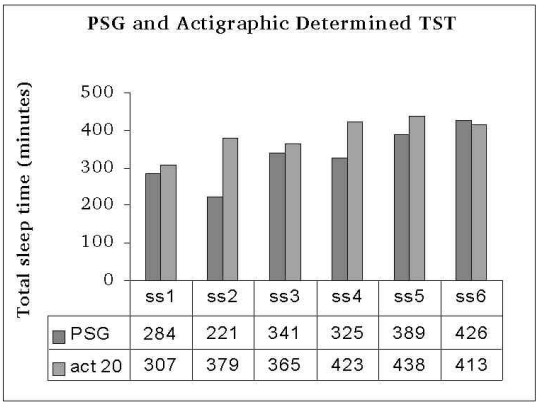
Introduction: We are conducting a multi-center investigation of melatonin for the treatment of insomnia in persons with Parkinson's disease (PD). This study provides an opportunity to compare actigraphic and polysomnographic (PSG) measures in this population. While there are numerous reasons to employ actigraphy in PD sleep research, nocturnal akinesia may affect actigraphic sleep/wake determinations. Validation of actigraph methodology by PSG in this population is important[1], and we present initial findings in this report.

Methods: Overnight data were collected using the MiniMitter Actiwatch (AW64 series) employing a digital integration method. If asymmetric arm tremor was present, the actigraph was placed on the less affected limb. Concurrent polysomnographic recordings were performed using Sandman software. Actiwatches and PSG equipment were synchronized prior to data collection to maximize epoch-by-epoch analyses. An experienced certified sleep technician, utilizing a 12-channel montage, scored PSG records by standard R&K criteria. The sleep technician was blind to actigraphy scored data.

Results: To date, six subjects (mean age = 68.7 years) with PD and sleep related complaints have been studied. Comparisons of actigraphy and PSG data for total sleep time reveal an agreement rate of 0.85 and a Spearman's rank correlation coefficient of 0.48 (ns) (SE ratio = 1:1.15, PSG:ACT). Overestimation of total sleep time occurred in 5 of 6 subjects using the "high sensitivity" setting of the actigraph software algorithm (Fig.1).

Figure 1



Conclusions: As expected, analysis of actigraphy data resulted in a higher estimate of total sleep time in persons with PD despite use of a "high sensitivity" setting for the sleep algorithm[2]. Parkinsonian tremor was present during the daytime in four of six subjects and we attempted to minimize its effect by placing the actigraph on the less affected arm. Given the decrease in tremor with sleep[3], placement of the actigraph on

the more tremulous arm would increase wakeful activity counts, therefore improving actigraphic sleep/wake determinations. We chose placement on the less tremulous arm to minimize this effect with the understanding that not all PD patients experience tremor. The 0.85 agreement rate of actigraphy with PSG is within acceptable limits for many situations where longitudinal sleep data collection are important.

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1348.L

Prevalence and Characteristics of Sleep Disturbance in Patients with Chronic Hepatitis C Treated with Interferon a-2b and Ribavirin

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Introduction: Studies report insomnia in 20 to 39% of the patients receiving interferon α-2b plus ribavirin therapy for chronic hepatitis C (HCV). The studies, however, did not quantify or characterize the nature of the reported insomnia. Insomnia may involve a variety of noctural sleep disturbances and is often associated with a variety of sleep disorders, including restless legs syndrome, periodic limb movement disorders and sleep-disordered breathing. Excessive daytime sleepiness (EDS) may result from intrinsic sleep disorders, including those which may also cause insomnia. The aims of this study were to evaluate the prevalence and characteristics of sleep distrubances in patients with HCV receiving concomminent interferon α-2b plus ribavirin therapy.

Methods: Cross sectional study using the Epworth Sleepiness Scale (ESS) and the Sleep Quality Profile (SQP). The ESS is composed of a 8 item 4 point Likert scale (response range 0-3) designed to measure daytime sleepiness. The range of scores is from 0 to 24 with scores greater than 10 indicating significant daytime sleepiness, and scores greater than 16 indicating extreme daytime sleepiness. The SQP is composed of 10 item dichotomous scale designed to identify groups of daytime and noctural sleep distrubance symptoms. The ESS and SQP are reliable and valid tools for the assessment of daytime sleepiness and noctural sleep disturbance (Cronbach's alpha = 0.83 and 0.79, respectively).

Results: Fifty-three (53) chronic HCV patients, 25 (45%) females and 28 (55%) males, ages ranging from 26 to 60 (mean age 46.2 + 8.52 SD), with compensated liver disease and no concomitant uncontrolled physiologic illnesses, receiving interferon α-2b plus ribavirin at The Texas Liver Center, a university affiliated outpatient facility, were evaluated using the ESS and the SQP. **Begin The mean ESS score was 9.6 + 5.1 with 22 (54%) having ESS scores > 10, indicating daytime sleepiness.** End Six (15%) had ESS score > 16 indicating a high level of daytime sleepiness. Of the HCV patients with ESS scores <10, symptoms of insomnia predominated with 53% having four or more reported symptoms of sleep disturbance (SQP > 4). The mean SQP score was 4.7 + 2.6 with 27 (66%) reporting at least three symptoms of disturbed sleep. Analysis of responses to the SQP indicated that **Begin 77.5% are tired and unrefreshed when they wake up, 72.5% reported arm or leg movements during sleep, 75% had restless sleep,** End 55% snored, 57.5% had difficulty sleeping at night, 20% woke up gasping or choking during the night, and 10% had witnessed apneas.

Conclusions: According to scores computed from both the ESS and SQP, the patients being treated for chronic hepatitis C with interferon α-2b plus ribavirin, experience a heavy burden of symptoms related to daytime sleepiness and disturbed noctural sleep. **Begin Symptoms of limb movements during sleep** End and, to a lesser extent, sleep-disordered breathing **Begin are predominant in patients with chronic hepatitis C on interferon a-2b.** End Further study using polysomnography and multiple latency sleep testing is needed to confirm and characterize these disturbances.

1689.L

Quantification of Symptoms in Kleine-Levin Syndrome: Evidence for Mood & Cognitive Disturbances and Preceding Illnesses

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Introduction: Kleine-Levin Syndrome (KLS) is a disease of unknown etiology that has a significant impact on the lives of patients. Two cases of KLS have presented recently in our center and in both cases: 1) symptoms of mood and cognitive disturbance were prominent and 2) another illness had preceded the first symptomatic episode. We subsequently performed a thorough review of published case reports of KLS with a focus on quantifying the symptoms, duration of episodes, evidence of mood and cognitive disturbances, and preceding illnesses and events

Methods: Cases were selected by using the classical criteria established by Critchley.[1] Sixty nine cases of KLS in the English Language literature from 1936 to 1999 were evaluated. Gender, age of onset, symptoms, length of episodes, outcomes, and events preceding the onset of the KLS episodes were all recorded and analyzed. In one third of the cases, symptom quantification was reviewed by independent raters yielding an agreement of 78%(a range of 54% to 100% agreement) on key variables.

Results: The average age of onset of KLS was 15.3 years (s.d. = 4.3) with a range of 9-33 years; 61 cases (88%) occurred in males. Hypersomnia, the primary feature of KLS was documented in 97.1 % of cases, however the degree of objective verification of reported hypersomnia was quite variable. Hyperphagia occurred in 91.3 % of cases. Hypersexuality, which historically has been considered part of the diagnostic triad for KLS, was only present in 33.3% of cases. Psychotic symptoms (delusions, paranoia, or hallucinations) were present in less than 15 % of cases. The average length of symptomatic episodes was 13.2 days (s.d.= 8.2) and ranged from 3.5 days to a maximum of 52 days. Complete return to baseline functioning after the episode was documented in 73.1 % of cases. The mean number of episodes was 4.2 per year (s.d.=3.4). Changes in mood were described quite frequently, with some agitation/irritability reported in a majority of the cases (58 %). Withdrawn isolative behavior was present in 36% of cases. Generalized mood disturbance (20 %) and depression/anhedonia (17 %) were also reported during episodes. Cognitive changes were also prominent with 44.9% of cases described as involving significant confusion during wakeful periods. After patients returned to their baseline level of functioning 37% had amnesia for the episode. In our clinical experience it was difficult to disentangle the mood, cognitive changes, and extreme hypersomnia that coexisted during episodes.A preceding illness was described in 30 cases (43.4%), with most being identified or presumed to be viral (14 cases) or an unspecified febrile illness (10 cases); there were also two cases with otitis media, one case with tonsillitis. Episodes

of headache (5 cases), heavy alcohol use (4 cases), and head trauma (4 cases) were also identified as occurring in the interval preceding episodes.

Conclusions: 1) Consistent with previous summaries, KLS is most frequently characterized as periodic episodes of hypersomnia and hyperphagia lasting typically 5-21 days with complete return to baseline function following each episode. 2) The third symptom of the classic triad, hypersexuality however, appeared to be less common than more general symptoms of mood and cognitive changes. 3) The frequent presence of some type of infectious disease prior to the first episode raises several questions about possible etiology-particularly given recent evidence for other post-infectious neuropsychiatric disorders.[2] 4) This review and quantification of symptoms also provides some basis for suggesting slight revisions in the diagnostic criteria for KLS.

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1726.L

The Influence of Sleep on Gelastic Seizures with Hypothalamic Hamartoma

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Introduction: Objective: To study the influence of sleep on gelastic seizures (GS) and the influence of hypothalmic hamartoma (HH) on sleep.Background: Intrahypothalamic regulation of sleep exists depending on the antagonism between the anterior and posterior hypothalamic regions. Lesions in the posterior hypothalamus will cause hypersomnia while lesions in the pre-optic hypothalamic-basal forebrain region results in insomnia. HH associated with GS frequently arises from the posterior hypothalamic regions. We studied influence of these lesions on sleep and the effect of sleep on GS.

Methods: We studied 13 patients (age range 2-13) with magnetic resonance imaging (MRI) evidence of HH and history of GS. All patients underwent continuous Video-EEG monitoring for 4 days including overnight recording.

Results: All patients reported having had GS during sleep. Eleven (84%) patients have an increase in gelastic seizure frequency within 15 minutes at onset of sleep and within 15 minutes after awakening. EEG showed increased epileptiform activity during periods of drowsiness and sleep in all patients. Two patients experienced transient hypersomnia (1-2 weeks) after partial resection of their HH. Five patients who underwent a trial of regular caffeine intake (average dose of 2mg/kg/day) reported a significant reduction in seizure frequency.

Conclusions: There is an intensification of GS activity during periods of drowsiness and sleep. The location of the lesion may possibly influence the intrahypothalmic regulation of sleep and seizure indirectly. Suppressing sleep with stimulant may possibly reduce the seizure frequency. The complex relationship of the HH to GS and sleep remains unknown. Understanding these relationships may help us to understand the effect of sleep on epilepsy and the effect of a hypothalamic lesion on sleep. Polysomnogram studies should be considered in patients with HH and GS.

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1077.L

Therapies are Needed for Cognitive/Motor Impairment in Healthy Patients with HIV on HAART

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Introduction: Cognitive/motor deficits have been reported during all stages of HIV infection, contributing to disability as HIV progresses.[1,2] In the course of studies on potential treatments for this disability, we have begun to quantify the degree of cognitive/motor impairment in patients with HIV infection and on highly active anti-retroviral therapy (HAART), relative to healthy HIV negative control subjects.

Methods: We performed between-groups comparisons of performance data gathered from a consecutive series of otherwise healthy HIV positive subjects who were clinically stable and on HAART versus a sample of control subjects at the Green Hospital General Clinical Research Center having no risk for HIV infection. Baseline performance data from a series of clinical trials were pooled on 25 HIV positive patients who, by physical examination, clinical laboratory findings and medication, were on stable HAART and 10 controls of comparable ages and educational background. Performance data came from a computer-based battery that assessed reaction time, memory, spatial orientation, grammatical reasoning, and motor skills. Using t-tests, we contrasted the performance between HIV+ individuals on HAART and controls.

Results: The 25 patients performed significantly less well ($p < .05$) on: Code Substitution, Word Memory Task, the Manikin Task for spatial orientation, reaction time as tested by the Psychomotor Vigilance Task, Word Memory Task, Grammatical Reasoning and three of five Driving Task measures (steering wheel angular velocity, maintenance of lane position, and variability of the accelerator pedal while trying to maintain constant speed).

Conclusions: Patients with HIV infection on HAART continued to have the cognitive/motor disabilities associated with HIV infection. The cognitive/motor impairment we observed may be the result of residual central nervous system effects of HIV, side effects of HAART drugs, or a combination of the two factors. Regardless, adjunctive therapies that improve cognitive/motor function need to be identified.

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1106.L

Sleep-related Respiratory Disturbance in Mitochondrial Encephalopathies

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Introduction: Mitochondrial encephalopathies are a diverse group of

disorders which present clinically with a variety of cerebral and brainstem syndromes.The association between sleep-related respiratory disturbance (SRRD) and mitochondrial encephalopathies is poorly characterized, and often not recognized.This is a case-series based report of the types of sleep-related respiratory disturbance seen in patients with mitochondrial encephalopathies.

Methods: We reviewed the clinical presentations of six patients with known mitochondrial encephalopathies (MELAS (2), Leigh`s (1), MNGIE (1), cerebral lactic acidosis (1) and oxidative phosphorylaton disorder (1)), who were evaluated for acute excacerbations of their underlying disease.Focal neurological deficits, seizures, feeding difficulties and mental status changes were the presenting symptoms.Three patients had clinically reported SRRD at or prior to admission.

Results: One patient with previous evidence of brainstem involvement succumbed to severe apnea and seizures during the acute phase.Two patients had nocturnal hypoventilation following metabolic strokes, and required supplemental oxygen (1) and ventilatory support (1).Two patients had clinically reported respiratory pauses and periodic breathing, and one of these patients was placed on an apnea monitor and supplemental oxygen.One patient had multiple strokes and developed feeding and respiratory difficulties as terminal complications.

Conclusions: Sleep-related respiratory disturbances may herald the onset of acute excacerbations of mitochondrial encephalopathies.If SRRD is due to seizures and hypoventilation, appropriate interventions may be instituted.In the presence of extensive cerebral or brainstem involvement, the occurence of SRRD appears to be an adverse prognostic factor.

1112.L

The Relationship of Dyspnea and Fatigue to Subjective Sleep Quality in COPD Patients

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Introduction: Poor sleep quality, dyspnea, and fatigue are the most frequent complaints among people with COPD. The Theory of Unpleasant Symptoms proposes that symptoms are interrelated: one symptom may affect another. The purpose of this study was to examine the characteristics of sleep quality in people with COPD and determine their relationship with dyspnea and fatigue. This abstract reports on preliminary data from a study of symptoms in people with COPD.

Methods: Twenty-nine men and 21 women with COPD (age = 69.2, SD=11.6 years)were interviewed in their homes. Their mean FEV1% of predicted for gender, age, and height was 46.9 (SD=18.9) and the mean FEV/FVC was 65 (SD=21.3), indicating moderate to severe airway obstructive disease. Each subject completed the Pittsburgh Sleep Quality Index and 100 mm. Visual Analog Scales for dyspnea and fatigue. Descriptive statistics and correlation coefficients were determined for each subscale of the PSQI, dyspnea, and fatigue.

Results: The mean Global PSQI score was 9.10 (SD=4.68). Mean subscale scores were: sleep quality 1.02 ± .87, latency 1.3 ± 1.16, duration 1.59 ± 1.53, sleep efficiency 1.40 ± 1.23, use of medications .64 ± 1.17, disturbance 1.58 ± .57, and daytime dysfunction 1.72 ± .86. The most frequent sleep disturbances reported were waking up in the middle of the night or early morning (91% of subjects) and getting up to use the bathroom (94%). Only 27.5% of the sample could be considered good sleepers (global PSQI < or =5). The mean dyspnea score was 51.2 (SD=23.2) and the mean fatigue score was 58.4 (SD=19.2). Dyspnea was significantly related to the global PSQI (r=.42, p=.002) and to five subscales: duration (r=.30, p=.035), latency (r=.32, p=.021), sleep efficiency (r-.38, p=.006), disturbances (r=.38, p=.006), and daytime dysfunction (r=.37, p=.06), but not to sleep quality (r=.23) or to use of sleep medications (r=.11). Fifty-one per cent of the sample responded positively to the item regarding breathing difficulty interfering with sleep. Fatigue was related to disturbances (r=.24, p=.09) but not to any other subscale or to the global PSQI. Fatigue and dyspnea were positively moderately correlated (r=.50, p<.001).

Conclusions: In people with COPD, dyspnea is significantly, moderately and negatively related to subjective sleep quality as measured by the PSQI. Fatigue is not related to subjective sleep quality.

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1432.L

Sleep Disorders in Scleroderma Patients

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Introduction: Progressive systemic sclerosis, a generalized disease affecting connective tissue, is characterized by endothelial lesions and by immune cell and humoral activation causing fibrosis of the skin and other organs. The onset and course of the disease are heterogeneous, permitting us to classify the systemic, diffuse, and limited forms according to the extent of cutaneous and visceral involvement. The patients' quality of life and life expectancy are determined by the intensity of pulmonary, esophageal, cardiac, and renal involvement. Pulmonary involvement through fibrosis, hypertension or even aspiration pneumonia leads to respiratory discomfort and cardiac insufficiency. These clinical circumstances most likely trigger sleep disorders among this group of patients.

Methods: Criteria of Inclusion: Patients of either sex with systemic scleroderma (limited and diffuse systemic forms). No age limit. Patients who fulfil the American College of Rheumatology's (ACR) criteria for diffuse or limited systemic scleroderma. Criteria of Exclusion: Patients who do not consent to take part in the study. Patients who cannot remain in the sleep laboratory overnight. Patients with overlap scleroderma, or scleroderma concomitant with systemic lupus erithematosus, rheumatoid arthritis, and/or inflamatory muscular disease. Material and Methods. A polysonograph examination (Neurotec System) was conducted in 12 consecutive female patients (age ranged from 35 to 50 years), in which electrical activity of the brain, eye movements, muscle tone, leg movement, EKG, and respiration (using an abdominal belt and an oronasal thermal transducer) were monitored. The sleep analysis was done under standard procedure.

Results: Total sleep time was normal in 4 patients, elevated in 3 and diminished in 5. The sleep latency was normal in 6 patients, elevated in 3 and diminished in 3. The REM latency was normal in 3, elevated in 7 and diminished in 2. The amount of stage 2 was normal in 6 and diminished in 6. The amount of slow wave sleep was normal in 2 patients, elevated in 9 and diminished in 1. The amount of REM was normal in 1 patient and diminished in 11. We find mild OSAS just in 1 patient (AHI: 12,6) and PLMS (moderate and severe) in 4 patients.

Conclusions: PLMS had high prevalence in our sample despite of low average age. Slow wave sleep was surprisingly increased and we suspect that such find has some relationship with Grow Hormone (GH) level. Almost all patients had less REM sleep.

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1117.L

Effects of Vagal Nerve Stimulator (VNS) on Sleep

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Introduction: Vagal nerve stimulator (VNS) is an approved treatment for epilepsy but its effect on sleep is unknown. We have evaluated two patients with intractable seizures before and three months after VNS to see if vagal nerve stimulators create any effects on sleep.

Methods: Two patients with intractabe partial seizures were identified before vagal nerve stimulator placement. They were tested with a standard polysomnogram protocol utilizing a Telefactor Sasssy system with Grass amplifiers. They were tested one week before and three months after VNS placement. The VNS settings were .1m amp, 30 seconds on, 3 minutes off. Variables measured were sleep efficiency, respiration disturbance, limb movement, arousal index, sleep latency, REM latency, percentage of REM sleep, and percentage of slow wave sleep. Both patients had partial complex seizures with secondary generalization since early childhood and were now in their twenties. The frequency was 1-5 events/month despite multiple drug regimens. Both EEGs showed bilateral independent spikes.

Results: Both patients demonstrated poor sleep efficiency before VNS and improvement thereafter. Patient 1 went from sleep efficiency score of 46% to 71% after VNS. Patient 2 went from a sleep efficiency score of 84 to a 96%. Respiratory disturbance index and arousal index were normal before and after. Limb activity was slightly increased before the VNS and was normal after placement. Patient 1 had a limb movement index score (LMI) of 6/hour before and 3/hour after VNS. Patient 2 had a LMI score of 12/hour before and 4/hour after VNS. Sleep and REM latency, % stage 3 & 4 was unchanged. Spike frequency was not calculated.

Conclusions: 1. There may be improvement in sleep efficiency and sleep characteristics with VNS placement. However, that may reflect a first night effect. 2. No other changes were noted.

1118.L

Approaches to Scoring Sleep Stages in Polysomnographic Studies Containing Epileptic Activity

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Introduction: Sleep-EEG recordings in epilepsy patients are useful in enhancing interictal epileptiform discharges (interictal spikes) (Malow et al, 1999). However, these sleep studies may be challenging to score, because interictal spikes and abnormal background activity may interfere with the interpretation of sleep waveforms. In conjunction with standard criteria (Rectschaffen and Kales, 1968), our purpose is to offer suggestions for scoring studies of epilepsy patients.

Methods: Patients with partial epilepsy undergo sleep studies as part of a research protocol at the University of Michigan Sleep Disorders Center. A 16-channel EEG is recorded along with ocular movements, chin EMG, and other conventional polysomnographic parameters. The 16-channel EEG allows for the accurate detection of interictal spikes. For our purposes, interictal spikes are defined as both a spike or sharp wave (<200 msec) and its slow-wave component. These studies are scored in 30-second epochs, using ocular movements, chin EMG, and C3-A2 with the suggestions below. Since the central EEG (e.g. C3-A2) is often corrupted by interictal spikes, having additional EEG channels allows for maximal flexibility in analysis.

Results: The following suggestions were developed for scoring non-rapid eye movement (NREM) sleep in epilepsy patients. Rapid eye movement (REM) sleep is not included in this abstract because interictal spikes are relatively suppressed by REM sleep and pose less of a problem. 1) Determining the wake to NREM stage 1 transition: The awake EEG may be slow at baseline or may be contaminated with interictal spikes. We examine the awake EEG carefully to establish the normal amount of alpha present in an individual patient. Then, we use an occipital channel without interictal spike artifact to determine when alpha dropout occurs. 2) The NREM stage 1 to stage 2 transition: Interictal spikes can resemble K-complexes or occur simultaneously with K-complexes. We confirm the presence of K-complexes by reviewing non-involved channels. 3) The NREM stage 2 to stage 3 transition: The slow wave component of the interictal spike discharge may mimic physiologic delta. We confirm physiologic delta by reviewing other EEG channels that are not contaminated by interictal spikes. Delta due to interictal spikes is often localized. In rare instances, if epochs are highly contaminated with spikes, we modify the proportion of delta necessary to score NREM stage 3/4 sleep. We score NREM stage 2 if six seconds (20%) or more of the epoch lacks delta.

Conclusions: We have found the above suggestions useful in scoring abnormal EEG-sleep recordings in epilepsy patients. The evolution of our work continues as we gain experience scoring sleep in a variety of epilepsy syndromes. Our aim is not to provide definitive rules, but to provide accurate and consistent staging. We welcome feedback on the validity and usefulness of these suggestions.

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1770.L

Visualization of Neural Activity by Functional Magnetic Resonance Imaging to Hyperoxia in Congenital Central Hypoventilation Syndrome.

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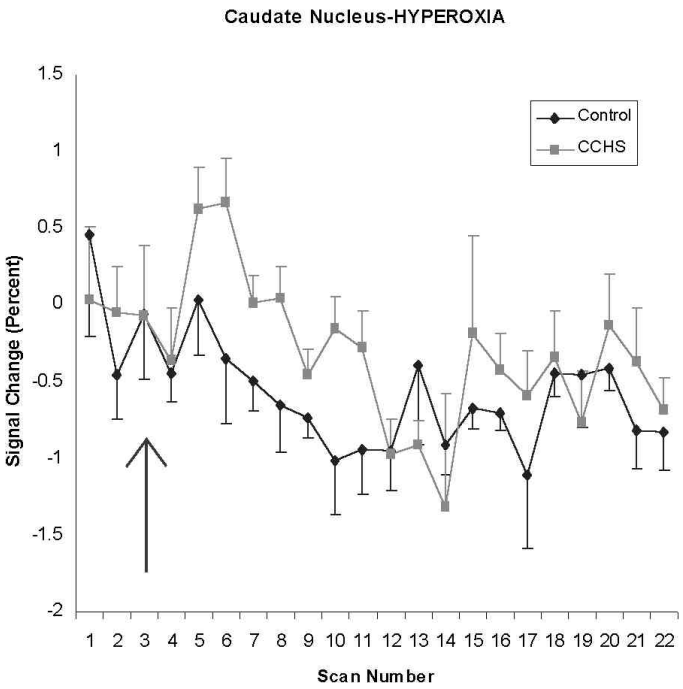
Introduction: Congenital Central Hypoventilation Syndrome (CCHS) is a rare disease of unknown etiology. Affected children exhibit an absence of respiratory drive during sleep and abnormal ventilatory responses to CO_2 and O_2 while asleep and awake. The deficient neural structures involved in this syndrome may be revealed by visualizing activity evoked by ventilatory challenges. We administered hyperoxic stimuli to CCHS patients and their controls while obtaining functional magnetic resonance images of the entire brain.

Figure 1. Averaged (+SE) signal changes in the caudate nucleus of 11 CCHS and 11 control subjects during a hyperoxia challenge (onset at the arrow).



Methods: Eleven CCHS patients without Hirschsprung's Disease, ventilator-dependent only during sleep, and eleven age- and gender-matched control subjects were used (mean age=10.7±2.0 yrs, 5 male pairs). For 30 s, all subjects breathed room air through a mouthpiece; the gas mixture was then switched to 100% O for 120 s. A series of 20 image slices (25 repetitions, Echo Planar technique) through the entire brain was collected during the challenge. All voxels in the images collected under experimental conditions were compared to voxels obtained under baseline condition (room air) on a scan-by-scan basis, and subjected to multiple paired t-tests with Bonferroni correction ($p<0.01$) using MedX software. Selected areas were identified from previously determined relationships to breathing, and the time course of signal changes assessed. Mean values for the caudate nucleus, amygdala and cerebellar fastigial nucleus were selected.

Results: Two aspects of signal change emerged in different neural regions, overall signal changes and transient responses. In the cerebellar fastigial nucleus, increased signal changes emerged in CCHS subjects over control values for virtually the entire challenge. However, the caudate nucleus of CCHS cases (Fig. 1) showed only an early transient response in signal increase over controls. In the amygdala, controls showed a rapid signal response to increased oxygen which was not present in the CCHS subjects. Several areas, e.g., the hippocampus, showed no group differences to the challenge.

Conclusions: The findings suggest that particular brain regions mediate the breathing characteristics found in CCHS. The cerebellar fastigial nucleus shows sustained enhanced activity in CCHS with hyperoxia, and may contribute to late-developing transient breathing responses to hyperoxia in CCHS patients (Macey, et al., 2000). The rapid response of the amygdala in the control group to the challenge suggests a role for normal peripheral chemoreception in that site. Although CCHS patients show an accentuated respiratory response to the peripheral stimulation, neural signal changes in the amygdala are muted; peripheral chemoreceptor activity in CCHS may be mediated by other neural sites. The caudate shows an accentuated response in the CCHS group that may regulate the early neural activity associated with peripheral chemoreception. The findings suggest that cerebellar and rostral limbic and motor areas participate in the deficient respiratory responses of CCHS.

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1775.L

Sleep Efficiency, Actigraph Amplitude, and Behavior in APOE E4 Positive and Negative Alzheimer Disease Patients

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Introduction: In an ongoing longitudinal study we are collecting actigraphic data that follows Alzheimer's disease (AD) patients over the course of their disease. The patients are also genotyped for presence of the apolipoprotein E4 (APOE E4) allele and rated by their caregivers on the Time-Based Behavioral Disturbance Questionnaire (TBDQ; Bliwise et al., 1992). Therefore we can compare the course of behavioral, sleep, and circadian disturbance in APOE E4 positive and negative AD patients.

Methods: All patients had a diagnosis of probable AD by NINCDS-ADRDA criteria. There were 38 AD patients (63% male) who had multiple observations and had moved from AD stage 2 to 3, or from AD stage 3 to 4. The stages are clinically identifiable levels of severity of AD based on MMSE scores: 2 (Mild: MMSE = 15-23); 3 (Moderate: MMSE = 8-14); 4 (Moderately Severe: MMSE = 4-7). Subjects' average age at initial actigraphic testing was 70.4 years (SD = 7.8) and did not differentiate E4 positive from E4 negative patients. Mean MMSE score at initial testing was 17.3 (SD = 3.7). At approximately 6-month inter-

vals, MMSE; Time-Based Behavioral Disturbance Questionnaire (TBDQ, a caregiver's report for the previous month of seven disruptive behaviors, e.g., combativeness); and approximately 6 days of 24-hr actigraphic recordings were collected. Calculation of the circadian activity measures and nocturnal sleep are described in Friedman et al., 1997. APOE genotyping using genomic DNA from blood was performed with standard restriction isotyping methods.

Results: The table presents sleep efficiency (SE, %), actigraph amplitude (AA, difference of the highest and lowest counts), and the TBDQ scores (0 to 1, with 1 being the most disturbed) for variable numbers of E4 positive and E4 negative patients who had data from two consecutive stages. The N's are small but the data by inspection and t-test do not show any significant differences in behavior or sleep and circadian rhythms between E4 positive and negative patients. This does not replicate our earlier cross sectional analysis (Murphy et al., 1997) which showed significantly more deterioration on the TBDQ for E4 positive patients. Inspection of the medication records did not indicate any difference in the use of sedative hypnotics, antianxiety, or antipsychotic medications by E4 status.

Table 1. Consecutive Stages For 38 AD Patients

			Stage 2	Stage 3
Genotype	Measure	N	Mean	Mean
E4	SE	6	72.6 + 15.9	74.1 + 13.3
	AA	7	44.0 + 9.5	42.0 + 11.8
	TBDQ	15	0.23 + 0.18	0.34 + 0.18
Non E4	SE	5	82.1 + 7.0	74.3 + 17.5
	AA	7	44.2 + 9.8	42.0 + 17.0
	TBDQ	17	0.16 + 0.18	0.20 + 0.14

			Stage 3	Stage 4
Genotype	Measure	N	Mean	Mean
E4	SE	3	71.1 ± 20.0	63.9 ± 14.4
	AA	3	39.7 ± 11.1	38.5 ± 11.8
	TBDQ	7	0.32 ± 0.26	0.45 ± 0.28
Non E4	SE	5	72.3 ± 9.5	68.6 ± 12.4
	AA	6	49.7 ± 10.0	48.6 ± 17.5
	TBDQ	7	0.21 ± 0.13	0.37 ± 0.14

Conclusions: This preliminary analysis suggests that the APOE E4 allele may not be a risk factor for circadian, behavioral, or sleep disturbance in probable AD. It also points up the need to check the "conclusions" from cross sectional analyses against longitudinal data. The possibility remains that APOE E4 would be shown as a risk factor with larger N's or in the earlier (pre-clinical) or later AD stages.

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1779.L

Human Forebrain Devoid of Brainstem Influences Exhibits EEG and Neuroendocrine Rhythms.

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Introduction: Neural substrates that are both necessary and sufficient to generate electrophysiologic correlates of specific sleep-wake states and their ultradian and circadian rhythmicity remain ill-defined. Desynchronized alpha frequency EEG activity alternating with synchronized delta has been frequently noted following brainstem vascular accidents (viz., alpha-coma). This suggests that circuits intrinsic to the forebrain are adequate to generate electrophysiologic correlates of specific sleep-wake states. These reports, however, provide little detail concerning the precise neural circuits responsible for such activities because: 1) vascular territories were either incompletely involved or poorly delineated; 2) knowledge of the brain regions involved in sleep-wake control as they relate to these vascular territories was incomplete. Case Report: An 80 year-old woman presented with an alteration in consciousness and suddenly became comatose. Initial CT scan revealed diffuse atrophy, a left frontal, periventricular hypodensity, and a calcified basilar artery. Serial scans confirmed complete infarction along the basilar artery, and its tributaries, including the right superior cerebellar artery, and branches supplying the paramedian midbrain and entire right thalamus. Thus, the combined lesions resulted in a forebrain devoid of influences arising from principal components of the "ascending reticular activity system" including the raphe nuclei, pedunculopontine tegmental nucleus, and locus coeruleus.

Methods: Polysomnographic recording commenced seven days after presentation. One recording began at 11pm and lasted 6.75 hours. And a second session began at 1pm the following day and lasting 7.5 hours. Hourly tympanic membrane temperatures were recorded and endogenous melatonin and thyroid stimulating hormone (TSH) rhythms were assessed by immunoassay.

Results: Periods of EEG desynchronization/synchronization occurred with an approximate 90 minute total cycle. Transitions between states were more explicit over the left hemisphere. Sensory stimuli failed to produce any change in the EEG over either hemisphere. Temperature (range 36.6-37.6°C) with an evening peak (6pm-10pm) coinciding with a subtle TSH peak (0.49uIU/mL; nadir = 0.41uIU/mL). REM-sleep was undetectable. There was a dissociation between polygraphically defined states in the forebrain and brainstem; a total of 18 epochs of periodic leg movements of sleep (PLMs) (mean duration = 3.72 min) in the right leg did not correspond with forebrain desynchronization and occurred irregularly. Low serum melatonin levels were consistent with age; and the absence of an endogenous rhythm was consistent with complete separation of the hypothalamus from preganglionic circuits known to modulate the pineal gland.

Conclusions: This striking experiment of nature confirms that in humans a forebrain devoid of brainstem influences is sufficient for: 1) generating both synchronized/desynchronized EEG states; and 2) maintaining their rhythmicity. State related neural subpopulations such as the magnocellular basal forebrain and posterior hypothalamic area may therefore be sufficient to support cortical arousal even lacking an intact thalamus. The neuroendocrine axis devoid of brainstem influences similarly appears to be able to maintain circadian rhythms. As evidenced by the presence of trains of PLMs, the isolated medulla and spinal cord also exhibit less well-delineated rhythms consistent with previous reports that PLMs can occur following spinal cord transection and that cardiorespiratory rhythms are evident in animals with mid-pontine transec-

tions.

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1458.K6

Sleep-Wake and Vegetative Functions in Thalamic Stroke

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Introduction: There is increasing clinical evidence for a key-role of the thalamus in the regulation of sleep-wake (Bassetti et al 1996; Cortelli et al 1999) and vegetative functions (Cortelli et al 1999).

Methods: Two patients (pts) with MRI-proven bilateral paramedian thalamo-mesencephalic stroke were prospectively studied by means of clinical examination, one–week actigraphy, and prolonged nocturnal polysomnography (PSG). Sleep EEG was subjected to visual and spectral analysis. Rectal temperature over 24 hours and nocturnal growth hormone and melatonin secretions were measured in one patient each (in collaboration with Dr. G. Printzen, Bern, and Drs. P. Cortelli and G. Pierangeli, Bologna-Italy).

Results: Patient 1: This 60 year-old man presents a moderate subjective sleepiness with increased sleep like-behavior (12-15 h sleep/day), severe amnesia, and bilateral complete ophthalmoplegia. Actigraphy shows sleep behavior over 56% of the recording time. A first PSG 4 days after stroke shows 1) abnormal wake EEG activity consisting of high-voltage 2-3 Hz rhythmic activity and intermingled 7-9 Hz activities; 2) increased sleep stage 1 NREM sleep (24% of total recording time = TRT); 3) nearly absence of sleep spindles; 4) reduced slow-wave sleep (4% TRT); and 5) absence of typical REM sleep (no rapid eye movements=REMs, low chin EMG with little modulation during sleep). Spectral analysis reveals a low level of slow-wave activity with no apparent decline over the night and no clear sleep-cycle modulation. Core temperature recording shows a nocturnal minimum. Two months later the patient's hypersomnia has improved and a second PSG shows 1) abnormal wake EEG activity consisting of monomorphic 5-6 Hz rhythms; 2) increased sleep stage 1 NREM sleep (27% TRT); 3) nearly absence of sleep spindles; 4) some recovery of slow-wave sleep (9% TRT); and 5) REM sleep (12% TRT). Spectral analysis reveals a lower level of slow-wave activity (maximal value <200 microvolt square) with decline over the night and clear sleep-cycle modulation. Patient 2: This 69 year-old man presents a severe subjective sleepiness with increased sleep-like behavior (>15 h sleep/day) with vertical upgaze palsy, and dementia. A PSG 4 days after stroke shows 1) abnormal wake EEG activity consisting of low voltage 6-9 Hz activity and theta-delta waves; 2) severe reduction of sleep spindles; 3) reduced slow-wave sleep (6% TRT); 4) nearly absence of typical REM sleep; 5) features of dissociated sleep (REMs with mixed frequency EEG, and variable chin EMG). Nocturnal growth hormone and melatonin secretions are normal.

Conclusions: Bilateral paramedian thalamo-mesencephalic strokes lead to 1) subjective sleepiness and increased sleep-like behavior, 2) profound alteration of EEG correlates of wakefulness, NREM and REM sleep (making conventional sleep scoring difficult), and 3) preservation of circadian endocrine and vegetative activities. The effects of vascular lesions of the thalamus show similarities but also major differences with those reported in fatal thalamic (familial) insomnia.

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1796.L

Predicting Nocturnal Hypoxemia in Patients with Primary Pulmonary Hypertension

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Introduction: Primary pulmonary hypertension (PPH) is a rare disease with an incidence rate of 1 in 500,000. Untreated hypoxemia increases pulmonary vasoconstriction and can cause a more rapid progression of the disease. Sleep can cause hypoxemia in patients with pulmonary disease, by its effect on ventilation, respiratory drive, airway stability, and ventilatory mechanics. We have previously shown that hypoxemia can occur in PPH patients.[1] The purpose of this study was to determine which clinical factors could predict nocturnal hypoxemia in PPH patients.

Methods: Eleven patients with PPH had an initial evaluation with spirometry, diffusing capacity, resting oxygen saturation and exercise oxygen saturation measurements. All patients then underwent a formal polysomnogram study in the sleep lab.

Results: Seventy-three percent (8/11) of our study patients had oxygen desaturation or needed oxygen supplementation during sleep. The oxygen desaturations were noted to occur independently of apneas and hypopneas. When compared to PPH patients without nocturnal desaturations, there was no significant difference in the FEV1 %predicted (71 ± 9 vs. 98 ± 15, p=0.07), FVC %predicted (80 ± 13 vs. 99 ± 23, p=0.28), and diffusing capacity (66 ± 15 vs. 76 ± 18, p=0.45). Among the patients who had nocturnal hypoxemia, 38% (n=3) were hypoxemic at rest, and 75% (n=6) had oxygen desaturation with exercise. Among the patients who did not have nocturnal hypoxemia, none needed supplemental oxygen either at rest or with exercise.

Table 1

	FEV1*	FVC*	DLCO*	O2 Sat at rest	Walking O2 Sat	AHI	02 Saturation during Sleep
1	114	124	97	100%	96%	4	No Oxygen Desaturation
2	96	96	68	93%	94%	0.2	No Oxygen Desaturation
3	84	78	64	100%	96%	1	No Oxygen Desaturation
4	58	67	44	83%	91% on 2L O2	12	78% less than 90%, on 2L O2 via NC
5	78	88	–	98%	96%	0.2	No O2 desat with 2L O2 via NC
6	79	102	76	97%	93%	3.4	50% of sleep time with O2 Sat < 90%
7	68	80	54	92%	87%	1.5	No O2 desat on 2L O2 via NC
8	77	80	68	96%	88%	3.9	84% of sleep time with O2 Sat < 90%
9	78	82	54	82%	89% on 6L O2	2	No O2 desat with 6L O2 via NC
10	58	57	83	86%	89% on 6L O2	11	69% of sleep time with O2 Sat < 90%
11	70	81	84	91%	80%	3.7	65% of sleep time with O2 Sat < 90%

*% Predicted

Conclusions: Significant nocturnal hypoxemia, unrelated to apneas and hypopneas, can occur in patients with PPH. Nocturnal hypoxemia is best

predicted by the occurrence of oxygen desaturation with exercise. The presence of an oxygen saturation greater than 95% with exercise makes the presence of nocturnal hypoxemia unlikely.

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1154.L

Epworth Sleepiness Scale (ESS) in Partial Seizures Patients

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Introduction: Daytime sleepiness and disturbed nocturnal sleep are common complaints of epileptic patients.[1] Antiepileptic drugs (AEDs), diurnal/nocturnal seizures or sleep fragmentation caused by abnormal brain electric activity during sleep play a role in determining sleepiness. This study determines: 1. Subjective sleepiness in epileptic subjects. 2 The influence of non-sedative AED and seizure control period in subjetive sleepiness.

Methods: A Portuguese version of the Epworth sleepiness scale was applied to 79 epileptic outpatients. Patient inclusion criteria in the study were: clinical and EEGraphic diagnosis of partial seizures, a seizure-free period of at least 3 months, and no current use of sedative AEDs, opioids or hypnotics. 79 subjects were included. M =45; F=34. Average age = 36,3 ± 13,6 (SD).

Results: Average ESS =8,54 ± 4,53 (SD). Average Reported Sleep Time (RST)=7,59 ± 1,98 (SD) hours. An ESS> 10 points prevalence rate of 26.60% was recorded Subjects on CBZ or DPH did not statistically differ for the ESS average score (8,25 ± 4,23 (SD) Vs 7,17 ± 5,04 (SD), t=0,82; tcritical =2; #61537;<0.05) as with RST (7,95 ± 1,87 (SD) Vs 7,22 ± 2,25 (SD),t=1,24; tcritical =2; #61537;<0.05). Seizure-free period of either shorter or longer than 1 year produced no statistical difference in ESS average scores (8,29 ± 5,85 (SD) Vs 8,80 ± 3,50 (SD), t=0,31; tcritical =2,04; #61537;<0,05), as well as for RST (7,53 ± 1,92 (SD) Vs 8,34 ± 2,53 (SD), t=1,01; tcritical =2,04; #61537;<0,05). Average ESS score is statistically similar to a similar study with epileptic subjects (2) (7,6 ± 5 (SD), t=0,06; tcritical=1,96; #61537;<0,05)..

Conclusions: Epilepsy patients display a significantly higher ESS scores when compared to age-matched controls.[2] Abnormal eletric brain activity-induced sleep fragmentation plays a role in determing this finding. The ESS scores and ESS>10 points prevalence rate of this population is similar to the ESS scores and ESS>10 prevalence rate of the Michigan series.[1] The ESS in our epilepsy population is not influenced by AED type, seizure-free time and age. However, the Michigan population was not controlled for seizure-control status, use of sedative AED, hypnotics and age. Nonetheless, it displayed a similar average ESS scores compared to the population in this investigation. Subjective sleepiness in epileptic subjects seems to be multifactorial where AED, seizure frequency and sleep fragmentation due to abnormal brain electric activity play a role.[1,2]

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1809.G

Evidence of Sleep Disturbance in Children With Chronic Recurrent Abdominal Pain

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Introduction: This study is a preliminary investigation of a hypothesized association between childhood chronic pain and sleep disturbance. The central goal of this study was to quantify and describe sleep disturbance associated with chronic Recurrent Abdominal Pain (RAP), a common pediatric condition. Pain has been shown to have a deleterious impact on the initiation and maintenance of sleep.[1] The combined effects of chronic pain and illness are likely to have an even greater negative impact on sleep continuity and sleep quality. Insufficient sleep has been shown to increase the perception of pain.[2] Furthermore, the cognitive and affective deficits resulting from chronic insufficient sleep may interfere with an individual's ability to manage pain and other stressors associated with chronic illness. These effects may be amplified in pre-adolescents whose cognitive abilities and affective regulation are at an early stage of development. An understanding of the reciprocal effects of pain and insufficient sleep is likely to have important implications for intervention strategies.

Methods: Subjects were 23 children (15 girls and 8 boys), aged 4 to 12 (mean age=8.6, standard deviate=3.1 years), who were referred to a gastroenterology specialty clinic in an urban children's hospital. Parents of children who had no prior diagnoses of systemic illnesses and developmental disorders completed a battery of measures including sleep and abdominal pain questionnaires, and standard instruments used to assess behavioral, affective and psychiatric disturbance. Insufficient sleep was defined as difficulty initiating and maintaining sleep, poor sleep efficiency (total sleep time divided by time in bed multiplied by 100), and subjective reports of poor sleep quality. Children with functional (having no known underlying cause) abdominal pain (n=9), Crohn's Disease (n=5), Gastroesophegeal Reflux Disease (n=2), and other functional RAP disorders (e.g., Irritable Bowel Disease, Gastritis)(n=7) were included in the sample.

Table 1. Sleep , Pain, and Psychiatric Measures

Variable	Mean (s.d.)	Range
Sleep Efficiency	94.1 (5.4)	79.0 - 98.6
Sleep Onset Latency (mins.)	23.3 (18.4)	5 - 60
Wake After Sleep Onset (mins.)	12.4 (15.1)	0 - 60
Abdominal Pain Index (%tile or T)	18.7 (7.3)	0-31
Children's Depression Inventory	6.2 (5.1)	0 - 20
Children's Rating Trait Anxiety	12.7 (6.3)	0 - 23
CBCL Anxious and Depressed Scale (T-score)	54.1 (5.9)	50 - 72

Results: Parental reports of their children's average sleep onset latency (SOL), minutes awake after sleep onset (WASO) and sleep efficiency are

reported in Table 1. Parental ratings of the frequency and intensity of children's abdominal pain symptoms and children's and parents' reports of anxiety and depression symptoms are also reported in Table 1 (a score of 10 on the Children's Depression Inventory and a t-score >60 on the Anxious and Depressed Scale of the Parent's version of the Child Behavioral Checklist are clinically significant). Significant associations were found between composite ratings of children's pain, and sleep efficiency (Rho= -.55, p<.03), SOL (Rho= .50, p<.05), and WASO (Rho=.55, p<.02). A significant association between the anxious and depressed scale of the CBCL and WASO was also noted (Rho=.62, p<.02). Other findings worth noting were that 21.7% of the sample resisted going to bed on 3 or more nights a week; 17.6% had difficulty waking up in the morning; 17.4% of the sample had difficulty falling asleep on more than three nights a week; 17.4% of the sample had night awakenings lasting greater than 10 minutes; and 30% of children had recent parasomnias occurring at least once during the prior month. Age, gender and diagnoses (i.e., functional vs. non-functional) were not associated with increased pain, sleep problems, or psychiatric symptoms.

Conclusions: Based on parental ratings of subjects in their home environments, RAP patients have mild sleep disturbance (i.e., increased SOL and WASO) compared with prior reports of children's normative sleep during overnight PSG.[3] Most notably, there was a significant association between pain chronicity and severity and the major indices of sleep disturbance. Objective assessment of sleep disturbance and healthy comparison groups will be important in future studies. These results raise important questions about the role of anxiety in the association between sleep and RAP and the potential benefit of addressing sleep problems when providing interventions for this population.

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POSTER PRESENTATIONS

1519.L

Sleep and Quality of Life of Pre-Operative Cardiac Surgery Patients

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Introduction: Quality of life is a significant concern for cardiac surgery patients, who also frequently report post-operative sleep disturbances. However, there has been no systematic study of the the characteristis of pre-surgical sleep disturbance in this population or the relationships between sleep and quality of life. Habitual sleep disturbance may have an impact on post-surgical sleep and recovery. The purposes of this study were to examine the characteristics of pre-operative sleep quality and the relationships between characteristics of sleep quality and quality of life of patients who were awaiting elective cardiac surgery.

Methods: The sample included 38 (33 men, 5 women) patients who were awaiting elective coronary artery bypass surgery (CABG), valve replacement, or combined valvular and CABG surgery (M age = 63, SD = 9.4 years) at home. NYHA functional classifications were I (n = 11), II (n =20), III (n= 6) and IV (n = 1). Subjects completed the Pittsburgh Sleep Quality Index (PSQI) and the Medical Outcomes Study SF-36 during the week prior to CABG, as indicators of sleep quality and quality of life over the past month as part of a larger, longitudinal study of sleep, emotional wellbeing, and quality of life in cardiac surgical patients.

Results: Means, standard deviations, and Pearson's correlations appear in the table. Sixty-one percent of subjects (n = 23) were poor sleepers, as indicated by a Global PSQI > 5 (Buysse et al, 1989). The most commonly reported causes of sleep disturbance reported to occur at least once per week were having to use the bathroom (n = 29), waking up in the middle of the night (n = 27), coughing or snoring loudly (n = 16), and feeling too cold (n=10). Global PSQI was moderately negatively correlated with physical function, role physical, bodily pain, social function, and vitality. None of the sleep quality components were correlated with mental health or role emotional dimensions. Six of the eight PSQI subscale scores were correlated with physical function, and 4 were correlated with bodily pain. Age was not associated with sleep or quality of life dimensions.

Table 1. Descriptive Statistics for Study Variables and Correlations between Sleep and Quality of Life

	Quality of Life Dimensions (SF-36)							
Sleep	Phys Func	Role Phys	Gen Hlth	Bod Pain	Soc Func	Role Emot	Men Hlth	Vital
PSQI M (SD)	54.2 (24)	42.9 (39)	64.6 (18)	80.6 (17)	73.7 (27)	73.5 (40)	65.6 (.7)	55.0 (20)
Qual 1.02 (.7)	-.36 *	-.14	-.45 **	-.32	-.23	-.22	-.20	-.21
Durat 1.29 (.9)	-.23	-.25	-.08	.08	-.38 *	-.04	-.10	-.31
Effic .6 (1.1)	-.34 *	-.33	-.18	-.43 **	.28	-.21	-.18	-.20
Meds .21 (.6)	-.26	.28	-.30	-.39 *	-.27	-.28	-.05	-.21
Day Dysf 1.0 (.8)	-.34 *	-.43 **	-.21	-.27	-.41 *	-.22	-.23	-.52 ***
Laten 1.31 (.9)	-.40 **	-.27	-.27	-.44 **	-.06	-.25	.06	-.10
Distur 1.32 (.5)	-.41 **	-.08	-.51 ***	-.30	-.07	-.08	-.15	-.24
Glob Dist 7.0 (4.4)	-.44 **	-.36 *	.25	-.49 **	-.34 *	-.25	-.16	-.34 *
* p < .05; ** p < .01; p < ***.001								

Conclusions: Sleep disturbance is common in pre-operative cardiac surgery patients and is associated with selected dimensions of quality of life. Interventions to improve sleep may also improve quality of life. Continued study is underway to explore relationships between pre-operative sleep, post-operative sleep, and long term quality of life.

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1522.L

Sleep Abnormalities in Classic Creutzfeldt-Jakob Disease

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Introduction: "Classic" Creutzfeldt-Jakob disease (CJD) is a human prion disease characterized by the subacute onset of progressive dementia, myoclonus, and pseudoperiodic EEG activities. Insomnia and progressive loss of NREM and REM sleep are considered typical for the „thalamic variant" of CJD called fatal familial insomnia (FFI).

Methods: Two patients (pts) with autopsy-proven „classic" CJD and clinically profound sleep-wake disturbances were prospectively studied by means of a standard protocol including actigraphy, EEG, and polysomnography (PSG). Sleep EEG was subjected to visual and spectral analysis. The topography of neuropathological changes was assessed in both pts (analysis performed in collaboration with Dr. A. Kappeler, Bern). Immunohistochemistry and genetics are being analyzed.

Results: Patient 1. This 64-year old man first experienced painful lower limb paresthesias, increased sleep needs (up to 12-13 hours/day), visual hallucinations at sleep onset, gait difficulties, and increased irritability. Apathy, aphasia, apraxia, dysarthria, tremor, and multifocal myoclonus (particularly during sleep) appeared within three weeks. There was no hyperhidrosis, tachycardia or hyperthermia. Brain-MRI showed bilateral, slight T2-hyperintensities of both basal ganglia and cerebrospinal fluid (CSF) an elevation of the 14-3-3-protein and neuronic specific enolase (54 ng/ml, normal < 35). The patient died five weeks after onset of symptoms. Patient 2. This 50-year old man first reported lower limb burning paresthesias, sleep maintenance insomnia with increased nocturnal motor activity, gait difficulties, and depressed mood. Apathy, aphasia, apraxia, dysarthria, and multifocal myoclonus appeared within one month. There was tachycardia, but no hyperhidrosis or hyperthermia. Brain-MRI revealed an old caudate stroke and CSF an elevation of the 14-3-3-protein and neuronic specific enolase (162 ng/ml). The patient died 10 weeks after onset of symptoms. Actigraphy: In the one-week actigraphy motor activity was almost continuous with only a few hours of reduced activity either irregularly distributed over the 24 hour (patient 1) or every second night (patient 2). EEG: In the first patient the EEG performed 4 weeks after onset of symptoms showed a diffuse 6 Hz activity with frequent, about 1/sec pseudoperiodic, sharp activities. In the second patient the EEG performed 8 weeks after onset of symptoms showed a diffuse 5-7 Hz activity with frequent 1-2/sec pseudoperiodic, sharp activities. Polysomnography: In both patients a single all-night sleep EEG recording showed the absence of sleep spindles and REM sleep. Spectral analysis revealed a general high level of slow wave activity (main peak at 3 Hz, with a shoulder at 3-5 Hz) with no apparent decline over the night and no sleep cycle modulation. Neuropathology: findings were in both pts typical for „classic" CJD with involvement of frontal (+++ in patient 1 / ++ in patient 2), parietal (++/++), temporal (+/++), and occipital lobes (±/++); caudate nucleus (+++/+++), pallidum (+/+), putamen (+/++), pons (-/+), and cerebellar cortex (+/+). Thalamic involvement was present in both patients (+/++) and homogeneous in all nuclei.

Conclusions: We report the occurrence of early and severe sleep abnormalities in two patients with sporadic CJD. These observations document the possibility of a significant overlap in clinical and electrophysiologic findings of classic CJD and FFI.

1856.L

Daytime Sleepiness and Cirrhosis: Clinical Aspects

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Introduction: In patients with cirrhosis excessive daytime sleepiness (EDS) has always been described as an initial symptom of hepatic encephalopathy; recently EDS has been interpreted as a part of a disorder of sleep-wake rhythm (i.e. delayed sleep phase) independent from the cognitive impairment. We studied daytime somnolence in patients with hepatic cirrhosis in order to determine its prevalence, characteristics and to identify possible causes of this problematic hypersomnia.

Methods: We evaluated 154 patients with cirrhosis: 99 males (64.3%) and 55 females (35.7%); mean age was 51.9). The etiology of cirrhosis was viral hepatitis in 76.9% (HBV 15.1%; HCV 55.9%; HBV+HCV 5.9%), autoimmune diseases in 10.5%, other causes 12,5%; patients with alcoholic cirrhosis were excluded. The severity of hepatic dysfunction was graded with Child-Pugh score system: 17% of the patients was in stage A, 65.3% was in stage B, 17.7% was in stage C. A neurologist clinically evaluated all patients. Biochemical data on hepatic function were available. Sleep features and EDS were evaluated by means of subjective questionnaires: the Basic Nordic Sleep Questionnaire (BNSQ) modified and Epworth Sleepiness Scale (ESS). We decided to classify somnolent patients on the basis of BNSQ rather than ESS, because it reflected better the clinical picture in cirrhosis. We considered " Sleepy (S)" those who reported "daytime sleepiness occurring at any time during the day, at least 3-5 times per week"and as "pts with postprandial sleepiness (PPS) those who complained "daytime sleepiness only after lunch at least 3-5 times per week".

Results: Thirty pts (19.5%) reported EDS, forty-eight (29.2%) postprandial sleepiness, 79 (51.3%) were not somnolent (NS).ESS greater than 10 was found in 25 subjects (53.3%); distribution of ESS score among the three groups are shown in table 1.We found no differences among the three groups in terms of age, gender and severity of hepatic dysfunction (table 1). Pts with EDS and PPS complained more about their sleep than NS: they more often referred disturbed sleep and reported difficulties in initiating and maintaining sleep. On the contrary no subjective evidence of delayed sleep-phase was found in somnolent subjects (bedtime and wake-up hours).

Table 1

	AGE yrs.	ESS Score	>10 % pts	C-P mean	B-A Mcg/dl	H-E % pts	GENDER M %	F%
S	53.9	11.8	53.3	8.4	75.9	43.4	50	50
PPS	53.2	7.1	15.5	8.2	60.8	35.5	71	29
NS	50.4	5.2	2.5	9.1	61	26.5	66	34
p	n.s.	0.0001	0.0001	n.s.	n.s.	n.s.	n.s.	n.s.

C-P =Child-Pugh; B-A=Blood Ammonia; H-E= Previous or Actual Hepatic Encephalopaty

Table 2

	INSOM. % pts	D.F.A. %pts	AW.>1 %pts	TST Min	BED-T. hrs	FIN.AW. hrs	SNOR. %pts	NAP %pts
S	56.6	40	80	371	23:00	7:35	26.6	80
PPS	22.2	26.6	60	396	23:06	7:10	28.9	84.4
NS	16.4	13.9	49.3	404	23:18	7:00	17.7	27.8
P	0.0001	0.01	0.005	n.s.	n.s.	n.s.	n.s.	0.0001

D.F.A.=Difficulty Falling Asleep; AW>1= >1 awakening/night

Conclusions: Our data seems to demonstrate that EDS is quite common in cirrhotic patients (48.1%) but it can have two different clinical

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aspects: excessive somnolence occurring at any time of the day or excessive postprandial somnolence. Subjective complaints of disturbed and fragmented nocturnal sleep seem to be the main cause of EDS in cirrhosis.According to the literature we found that EDS was never related to the severity of liver dysfunction. On the contrary we didn't find any evidence of delayed sleep phase in our cirrhotic patients, probably because the BNSQ is not reliable for evaluation of sleep-wake rhythm.

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1561.L

Symptom and Mood Correlates of Activity-Rest in Cardiac Surgery Patients

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Introduction: Disturbances in activity-rest and sleep are common during the first week following cardiac surgery and appear to change rapidly. Using actigraphy, Redeker et al. (1994, 1996) reported increased consolidation of sleep into nighttime hours and increased daytime activity during this time period. These changes may be influenced by symptoms, such as pain and mood disturbances, which are often experienced during the early post-operative period (Redeker, 1993). The purpose of this study was to examine changes in activity, pain, and self-reported sleep during the early postoperative period (days 2-4) and the relationships among activity, pain, self-reported sleep, and mood state. This preliminary study is part of a larger longitudinal study of sleep, emotional well-being, and quality of life of cardiac surgery patients.

Methods: Forty-two cardiac surgical (coronary artery bypass, valve, and combined bypass and valve) patients (35 males, 7 females) between the ages of 39 and 83 (mean age 63.84, SD 9.64) were recruited. Fifteen of these participants completed a full 72 hour cycle of data collection in a semi-private hospital room setting. They wore wrist actigraphs (MiniMotionlogger, Ambulatory Monitoring) continuously from days 2-4 after surgery, and completed daily sleep diaries and numeric ratings of pain (0-10) and sleep quality (0-10). The Profile of Mood States (POMS) and Symptom Distress Scale (SDS) were completed once during the entire 3-day period. Descriptive statistics, repeated measures analysis of variance, and correlations were computed.

Results: There was a significant increase in 24-hour activity [$F(2,13)=4.02$, $p=.04$], a significant decrease in daily pain intensity [$F(2,19)=5.13$, $p=.02$], and a non-significant increase in sleep quality [$F(2,19)=1.4$, $p=.26$]. Activity and pain were moderately negatively correlated on post-operative day 2 ($r=-.62$, $p<.01$), but not related on days 3 and 4. Anxiety was negatively correlated with day 2 activity ($r=-.44$, $p=.08$) and day 3 activity ($r=-.48$, $p<.05$), but not with day 4 activity. Vigor was moderately and positively correlated with activity on days 2,3, and 4 ($r's=.57-.61$, $p<.05$). Daily sleep quality was not correlated with activity, pain, or the mood state variables.

Conclusions: These preliminary results indicate the dynamic nature of activity-rest patterns, sleep quality, pain, and mood disturbances after cardiac surgery. There are rapid increases in activity, and decreases in pain intensity over days 2-4. There appears to be a non-significant trend toward improvement in sleep quality. Correlations among pain, mood state, and activity are highly variable during the early post-operative period, with the largest relationships occuring on postoperative day 2, the time of highest pain intensity. These data will be used to guide the appropriate timing and intensity of interventions to promote activity and sleep and reduce pain during the early postoperative period.

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1222.L

Survey of Sleep Disturbance in a College Transitional Brain Injury Program

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Introduction: Reports of sleep disturbances after acquired brain injury (ABI) have been prevalent, but largely anecdotal. Presence of sleep disturbance was surveyed in a group of forty-one students with ABI who were enrolled in a community college transitional support program.

Methods: Subjects were a heterogeneous population drawn from a community reentry program. The students ranged in age from 19 to 70 (44.7 ± 13.3) and were an average of 8.6 ± 6.1 years post-injury. All subjects were given the Pittsburgh Sleep Quality Index (PSQI). The PSQI is a multi-dimensional scale designed to detect disturbances in sleep patterns. Analysis is reported relative to the original standardization sample.

Results: Overall PSQI Global Score for this sample was 8.7 ± 4.9 (range 1-20). Sixty-six percent of the sample were above the cutoff for diagnosis of poor sleep (PSQI Global >5). Thirty-nine percent of those surveyed had a Global Score greater than 10 (equivalent to >4 s.d. above the literature control mean), and 10% of the total sample presented with a Global Score greater than 15 (>7 s.d. above the control mean). Analysis of the PSQI Component Subscales revealed that the most common complaint was difficulty initiating sleep. Fifty-one percent reported a Sleep Latency >2 s.d. above control levels, and 19% reported >3 s.d. above controls. Forty-one percent of the ABI sample reported a frequency of Nocturnal Sleep Disturbances >2 s.d. above the control mean. Twenty-five percent reported their Sleep Duration at less than 6 hours, and twenty-seven percent rated their Sleep Efficiency at less than 65%. Thirty-nine percent of the total sample were taking sleep medications 3 or more times a week, with the majority of the remainder (51% of total group) denying the use of any sleep aids. Of subjects currently reporting sleep difficulties (Global Score >5), 30% remained unmedicated. Of the patients currently taking sleep medications 3 or more times a week, 94% remained above the Global Score cutoff for poor sleep (>5), and 62% of this medicated subgroup reported a Global Score >10. Difficulty staying awake during the day was significantly correlated with subjective perception of sleep quality ($r2 = 0.174$), but not with any of the other component scores.

Conclusions: Administration of the PSQI to subjects with ABI in a com-

munity college transitional program demonstrated significant sleep disturbance in the participants. The results of this sleep survey affirms the reports by neurologists and primary care physicians of sleep complaints in this population. The reported frequency and severity of sleep disturbance in this population, the possible relation to daytime fatigue, along with the apparent inadequacy of current treatments, indicates the need for further research and attention to the sleep patterns of this population.

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1571.M

Polyssomnographic Features in Manic Patients

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Introduction: The relationship between mood regulation and sleep physiology has clear theoretical and clinical consequences in the understanding of the mood disorders. In addition to genetics, neurochemistry and neuroimaging studies, the understanding of sleep disturbances is a relevant line of research into the neurobiological basis of mood disorders. Despite its relevance, there has been only a few sleep studies in manic patients. The authors report the sleep features of manic patients.

Methods: Twelve subjects (7 females, 5 males), age range 22 to 73 (mean age=40 years) with a DSM - IV diagnosis of Affective Bipolar Disorder in manic phase (Young Mania Rating Scale > 20 points) were included. All subjects were free of psychoactive medications, alcohol or illicit drugs for seven day before sleep testing. In-hospital sleep studies consisted of one night at the sleep laboratory. Sleep measures were divided in three categories: 1.Sleep continuity measures; 2. Sleep architecture. 3. REM sleep measures. The results were compared with healthy, sleep disorders-free age- and gender-matched subjects.

Results: Sleep continuity (reduced total sleep time; increased number of arousals; increased total wake time; reduced sleep efficiency); Sleep Architecture (increased stage 1 and reduced stage 3 e 4) and REM Sleep Measures (reduced REM latency, (3 patients showed Sleep Onset Rapid Eyes Movements Periods – REM latency less than 20 minutes).

Conclusions: These data are similar with the reported literature features of sleep changes in manic subjects. As well as similar to PSG sleep studies of subjects with endogenous depression.[1,2] This is suggestive of a final common pathway for sleep changes in mania and depression.

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1872.M

A Case of Hypersomnia/Hyposomnia with a 30-Year Follow-Up

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Introduction: Ms. P, a 36-year-old professional, contacted a sleep laboratory in 1968 complaining about severe alternating hypersomnia (10-14 hours) and hyposomnia (4-5 hours). During the 3 previous years, she had experienced episodes of 2-5 weeks of excessive somnolence at least 3 times per year. During them, sleep was simply overwhelming, there was no way to avoid it. During long sleeps, she usually gained 50-100 pounds over her baseline weight of 250 pounds on a 59" frame, and there was excessive sexual arousal. There also were month-long stretches of very short sleep (4-5 hours) without mania. Diagnostically, although the presentation was suggestive of Kleine-Levin syndrome, she did not fit the criteria (only 14 hours of sleep during EDS, late onset at age 33, periods of hyposomnolence not typical for Klein-Levin). The patient was then studied in the laboratory for 29 PSG nights (see companion abstract), which confirmed her complaint.

Methods: Medical Issues:Increased somatic complaints around age 12 (headaches, pain). A positive Wasserman was also found at age 12 and followed without manifest disease. At follow-up 30 years after the study, she reported a hysterectomy one year after the study, a spinal fusion 4 years later, and her current need for 2 knee replacements. At follow-up, she was arthritic, treated with NSAIDs and Ultram p.r.n. No other meds.Psychological Issues:Born into a dysfunctional family. Mother severely disturbed psychologically, father left when she was 5 years old. Sister, 18 months younger, later died of alcoholism. Largely raised by relatives. Apparently was always outspoken and a difficult child. Relatives' favorite punishment was locking her in a closet for long hours, where she promptly slept. Entered 3 -years professional training at age 20. At age 22, weighed 215 pounds, treated with Dexedrine (15 mg). Depressed and hospitalized at age 25: "Numerous electroshock treatments, to the point of considerable amnesia and confusion," per hospital report. Parnate helped; no other drugs did.At the time of her sleep evaluation, Ms. P was single, functioning well at a responsible job. Psychological evaluation (Rorschach, MMPI, TAT, Becks) suggested a lonely person devoid of nurturant human interactions, with considerable anger and depression.

Results: Follow-up Evaluation:In 1998, 30 years after the sleep evaluation, Ms. P, now retired, was recontacted. She reported that the excessive fluctuations in her sleep had spontaneously disappeared in her 40's (after about a decade of severe impact). She now typically slept well for about 7 hours. Current weight is 250 pounds, blood pressure 134/70, cortisol 176, no other abnormalities. She characterizes her long sleeps 30 years ago as "escape."

Conclusions: We report the case of a professional woman who in her 30's and 40's, had a decade of severe fluctuations in the length of her sleep, on a background of severe psychological distress since early childhood. Thirty years later, now in her mid 60's, she is comfortably retired, not on psychotropic medication, with normal sleep.

1896.M

The Relationship Between Alpha EEG Asymmetry and the Presentation of Depressed Mood in Obstructive Sleep Apnea (OSA)

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Introduction: Previous studies indicate a relationship between OSA and

depression (e.g., Cassell, 1993). In clinically depressed subjects, level of resting and active alpha asymmetry reliably predicts depressive symptomatology (Benca et. al., 1999). These asymmetries appear to be trait-like characteristics in adults and present since childhood. This study aims to determine if levels of alpha EEG asymmetry predict depressive symptomatology in OSA subjects. Specifically, we predicted that OSA subjects who present with depressed symptoms are more likely to have strong right-sided frontal alpha activation.

Methods: All subjects (n=18) between ages 18 and 65, who presented to the LIJ Sleep Disorders Clinic with symptoms of OSA, were eligible for study inclusion. Subjects were excluded if they met criteria for comorbid medical and psychiatric disorders (other than depression). Prior to the first diagnostic sleep study (NPSG), all subjects responded to questionnaires and a structured interview to assess current mood state (i.e., Personality Assessment Inventory (PAI) and Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D)), subjective sleepiness (Epworth Sleepiness Scale (ESS)), and perceived locus of control regarding general medical and specific sleep disorder conditions (Multidimentional Health Locus of Control (MHLC)). Prior to bedtime, subjects were monitored for EEG recorded at 8 scalp sites (F3/4, F7/8, C3/4, O1/2), EOG, and bipolar chin EMG. The EEG and EOG were all referenced to the contralateral mastoid (A1/A2). During EEG monitoring, subjects were exposed to resting (eyes open/closed) and active (video designed to evoke emotional experience: neutral, disgust, sadness, anger, happy) conditions. EEG collection and analysis was performed using the Stellate Harmonie (Version 4.0) system and asymmetry analysis emulated the "Alpha Asymmetry Scores" (log right – log left power density) developed by Benca and colleagues (1999). The NPSG assessment included nasal/oral airflow, chest and abdominal plethysmography, ECG, and pulse oximetry. Sleep was staged in 30-s epochs according to R&K criteria.

Results: Subjects were divided into 2 groups based on PAI depression scores (T-Score>60 = depressed): (1) Depressed Group (DG) (n=9) and (2) Non-depressed Group (NDG) (n=9). Both groups were matched evenly in terms of all demographic and sleep related variables: age (DG = 46±11, NDG=45±10), education (DG=14±3, NDG=13±2), ESS (DG=16±4, NDG+12±6), RDI (DG=50±45, NDG=41±25), Low SaO2 (DG=80±11, NDG=79±9), Sleep Onset (DG=32±33, NDG=33±30), Stage 1% (DG=10±5, NDG=13±10), Stage 2% (DG=54±14, NDG=49±14), Stage 3% (DG=3±4, NDG=5±6), Stage 4% (DG=1±1, NDG=2±7), and REM% (DG=10±7, NDG=12±7). Analysis of the mean alpha asymmetry scores indicated that the DG (mean log (\propto power) in $\mu V^2/Hz$ = -3.01±1.75) had significantly greater right-sided frontal activation compared to the NDG (mean log (\propto power) in $\mu V^2/Hz$ = 1.36±2.24) during the sadness/depressed condition (t-test = 4.52, p<.000). No other EEG conditions were significant.

Conclusions: OSA Subjects with depressive symptoms demonstrate greater right-sided frontal activation than their non-depressed counterparts when challenged with depressing stimuli. In contrast, there were no alpha asymmetry differences between groups when presented with other challenging and neutral stimuli. Right-sided frontal activation appears to be a vulnerability marker for depressive symptoms in OSA patients. Future research needs to elucidate how this right-frontal hypoactivation interacts with other biological stressors such as hypoxia and/or sleep fragmentation and psychological factors such as perceived locus of control.

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1613.M

Effects of Neonatal Clomipramine Administration in Rat on Density of [3H]-8-OH-DPAT ligand in the Dorsal Raphé Nucleus and Hippocampus

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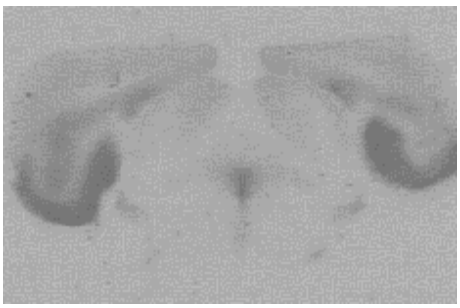
Introduction: A rat model of human endogenous depression (ED) produced by neonatal treatment with clomipramine (CLI) has shown multibehavioral abnormalities including decreased sexual activity, decreased aggressive activity, decreased or increased locomotor activity, and decreased pleasure seeking activity (1). It has been reviewed that decreased 5-HT neurotransmission is involved in the pathogenesis of ED and that increased 5-HT neurotransmission is involved in the improvement of ED. The discharge rate of 5-HT neurons in the dorsal raphé nucleus (DRN) is significantly less in adult CLI rats than that in control rats (2). 5-HT1a inhibitory autoreceptors are situated on the cell bodies of 5-HT neurons in the raphé nuclei and inhibit raphé cell firing, which reduces 5-HT neurotransmission. 5-HT1a receptors are also present in the hippocampus (Hipp) and may be involved in many behaviors. This current abstract reports the results of 5-HT1a receptor density as determined by autoradiography with the ligand, [3H]-8-OH-DPAT, in the CLI neonatally treated rat.

Methods: Neonatal treatment with CLI (CLI rat, 40 mg/ kg /day) or an equal volume of saline (SAL rat) was done from post-natal day 8 through day 21. Rats were sacrificed by decapitation at 5 months old. Brains were rapidly removed, frozen with dry ice and cut in 40 mm sections at -20 °C. [3H]-8-OH-DPAT binding to detect 5-HT1a receptor performed was based on published methods (3). Briefly, sections were fixed for two minutes in 0.1% buffered paraformaldehyde (pH 7.4) and were preincubated in 0.17 mol/L TRIS/HCL, pH 7.6 containing 4 mmol/L CaCl2 and 0.1% ascorbic acid for 30 minutes at room temperature. Subsequently sections were incubated with 2 nmol/L [3H]-8-DPAT for 60 minutes, washed in preincubation buffer (2 X 5 min) at 4°C and dried under cold air. Non-specific binding was determined in the presence of 2 mmol/L 5-HT. Sections apposed to HyperfilmTM (Amersham) for two weeks. Autoradiograms were analyzed using a computerized image analysis system. Specific 5HT1a receptor density was calculated by subtracting the density of the non-specific binding from the total binding. 5 sections were analyzed per region and matched for rostrocaudal level to produce a single value for each rat. All values were converted to nCi/mg using a standard curve produced from [3H] microscales (Amersham).

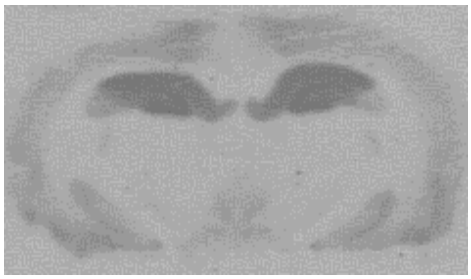
Figure 1



Results: The following graphs show autoradiographic localization of 5-HT1a receptors in rat DRN (Fig. 1) and Hipp (Fig. 2) visualized by bind-

ing of [3H]-8-OH-DAPT. Sections selected for DRN measurement was at the level of Bregma -7.5 and for Hipp was Bregma -3.0 of the atlas of Paxinos and Watson. Mean density of [3H]-8-OH-DPAT binding sites in DRN was 11.5 ± 0.67 nCi/mg in CLI rat and 11.5 ± 1.2 nCi/mg in SAL rat. Binding sites of paradorsal raphé nucleus (PDR) was lighter than DRN. Overall density of PDR and DRN was 8.39 ± 0.76 nCi/mg in CLI rat and 7.97 ± 0.94 nCi/mg in SAL rat. The binding density of Hipp was 9.93 ± 0.56 nCi/mg in CLI rat and 9.83±1.0 in SAL rat. Comparison of 5-HT1a binding density yielded no significant differences (P>0.05) between treatments in all neuroanatomical sites examined.

Figure 2



Conclusions: A rat model of human ED produced by CLI neonatal treatment is not mediated by changes in 5-HT1a receptor density in DRN and Hipp.

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1622.M

Periodic Limbs Movements During Sleep in Neuroleptic-Naive Patients with Schizophrenia: A Pilot Study

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Introduction: Like schizophrenia, the physiopathology of periodic limbs movements during sleep (PLMS) is thought to involve abnormal dopaminergic neurotransmission.[1] PLMS are also known to increase with age.[2] A recent report in older patients with schizophrenia surprisingly showed a lower number of patients with PLMS than expected for this age group.[3] We now report on PLMS screening in young neuroleptic-naive patients with schizophrenia.

Methods: Seven acutely-ill neuroleptic-naive schizophrenic patients (mean age = 37.7 ± 7.4) were individually recorded for two consecutive nights in the sleep laboratory of a large psychiatric hospital during the first week of their hospitalization. According to DSM-IV criteria, the patients had first received a diagnosis of schizophreniform disorder at the time of recording and the final diagnosis of schizophrenia was confirmed within six months. These patients were compared to seven healthy participants (age: 23.5 ± 4.7) screened for psychiatric, neurologic and clinical signs of sleep disorders. Anterior tibialis EMG was recorded and PLMS were scored according to standard criteria;[1] periodic leg movements were also scored during waking, both before and after sleep onset. Respiration flow was monitored with thermistors. Results were compared using t-test for independent samples.

Results: Schizophrenic patients showed a difficulty to initiate and maintain sleep, including and increased sleep onset latency, increased waking after sleep onset (WASO) and decreased sleep efficiency when compared to control subjects. None of the participants presented sleep disordered breathing. There were no difference between the two groups for the number of PLMS per hour of sleep (Table 1). There was, however, a tendency for the number of periodic leg movements in waking to be increased.

Table 1

	Schizophrenics	Controls
Sleep latency	32.6 ± 7.9	15.8 ± 5.1
WASO	84.2 ± 10.9	69.5 ± 16.3
Sleep efficiency	77.2 ± 7.8	85.2 ± 3.7
% Stage 1	22.2 ± 4.8	9.2 ± 1.5
PLMS ndx	2.9 ± 1.2	3.4 ± 1.4
PLM wake ndx	35.3 ± 9.3	28.6 ± 12.7
PLMS+wake ndx	14.7 ± 4.5	8.8 ± 3.3
No. PLMS+wake	78.0 ± 23.8	41.9 ± 15.9

ndx = index (number per hour of sleep)

Conclusions: The results of the present study suggest that sleep disorders in acute neuroleptic-naive schizophrenia patients are not due to sleep apnea syndrome or to pathological PLMS. Together with the observation that PLMS is inversely related with symptoms of tardive dyskinesia in neuroleptic-treated patients with schizophrenia,[3] these results also suggest that the abnormal dopaminergic neurotransmission that is thought to exist in untreated and treated patients with schizophrenia does not interact with the physiopathology of PLMS. The issue as to the meaning of increased periodic leg movements during waking in neuroleptic-naive young acute schizophrenic patients deserves to be studied in a larger group of patients.

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1648.M

The Effects of Age and Gender on Waking EEG Power Spectral Density in Depressed and Control Subjects

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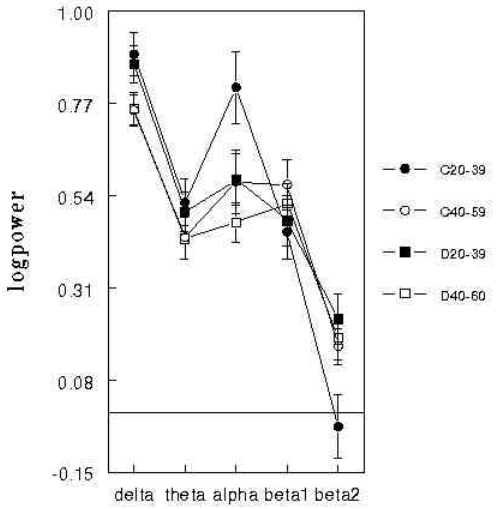
Introduction: Studies have shown differences in quantitative waking EEG between depressed and control subjects.[1] Some authors have also reported age effects on waking EEG power spectral density in normal individuals (Ehlers et al. 1998). It has been suggested that the aging process might affect differentially the sleep EEG of depressed and control subjects. To our knowledge, no study has yet evaluated differential effects of age and gender between depressed and control subjects on quantitative waking EEG.

Methods: Waking EEGs with eyes open for 38 normal (mean age=41.6, 15 women, 23 men) and 38 outpatient depressed subjects (mean age= 39.7, 21 women, 17 men) were compared. Depressed patients met the DSM-IV criteria for major depression. Waking EEGs included in this study were performed on the second evening of a 3-night polysomnography protocol. Waking EEG power spectral densities were calculated (FFTs) on the 128 Hz signals for consecutive 4-sec epochs and 0.25 Hz frequency bands widths. The 0.25 Hz bins were collapsed into 1 Hz frequency ranges. Averages were computed on the first 60 seconds of artifact-free EEG. Main effects and interactions were analyzed with a mixed model regression analysis using fixed-knot regression splines. Post-hoc least squares regression analyses were performed for each 1-Hz frequency bin, using age and group status (control-depressed) as independent variables.

Figure 1



Results: The mixed model analysis showed significant interactions between age and frequency bins ($p<0.0001$) and between group status and frequency bins ($p<0.0001$), showing that the effects of age and group status varied across frequency bins. No interaction was found between age and group status or between gender and group status. Thus, age and gender did not influence control and depressed subjects differently. For illustrative purpose, data were collapsed into the following bands : delta (1-3 Hz), theta (4-7 Hz), alpha (8-12 Hz), Beta1 (13-22 Hz) and Beta2 (23-32 Hz). The figure illustrates mean values (sem) of spectral power when subjects are grouped according to their age and group status (C: controls, D : depressed). Post-hoc analyses showed that spectral power in delta frequency bins (1-2 Hz, 4 Hz) decreased according to age. Depressed subjects had lower power density than control subjects in alpha frequency range (9 Hz, 11Hz) but higher power density in beta2 frequency range (25 Hz, 27-29 Hz, 31 Hz).

Conclusions: Age and gender had no differential influence on the waking EEG of control and depressed subjects in the middle years of life. Depressed subjects did show higher power than controls in beta range. Although the age range did not include elderly, a significant reduction in spectral power in low frequencies was observed as age increased. Interestingly, age effects on spectral power in the low frequencies during sleep have also been reported during the middle years of life (Carrier et al. 1999), suggesting that there might be a common mechanism underlying age effects on sleep and waking EEG.

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1336.M

Polysomnographic Characteristics of Trauma-Related Nightmares

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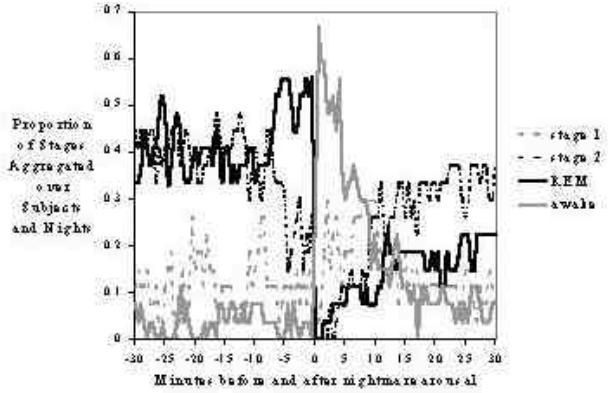
Introduction: Nightmares have been called the "hallmark" of posttraumatic stress disorder (PTSD[1]), yet have proven almost impossible to study in the sleep laboratory. Among 12 laboratory studies of PTSD patients in which nightmare incidence could be estimated, nightmares were observed on only 2% and 4% of nights. In this study, we used ambulatory recording to overcome the laboratory attenuation of episodic parasomnias and obtain psychophysiologic data bearing on the nature of trauma-related nightmares.

Methods: Our sample was composed of Vietnam combat survivors undergoing inpatient treatment and community-residing childhood and domestic abuse survivors recruited through advertisements. All subjects reported current nightmare frequencies of at least one per week. Inpatients slept in their ward rooms and community volunteers slept at home. The recording apparatus included the Oxford Instruments MR95 (for recording of standard polysomnographic parameters) and the AMS44 ambulatory impedance cardiograph. Patients were hooked up between 7:00 PM and 9:00 PM, after which they engaged in normal presleep activity and went to bed when they wished. If they awakened during the night, subjects used a time-stamping cassette recorder to describe any mentation associated with the arousal.

Results: Arousals were scored as being associated with trauma-related nightmares only when the recorded content included violent or fearful narrative features directly related to the traumatic experiences figuring in subjects' PTSD diagnoses. Despite the use of ambulatory methods, the nightmare frequencies observed were strikingly below subjects' estimates of their ambient rates; and many subjects reported no nightmares over six to nine nights of recording. Strict acceptance criteria further reduced the sample to 24 episodes with time-stamped reporting of trauma-related nightmare content concurrent with polysomnographic evidence of an arousal. As indicated in Fig. 1, the probability that subjects were in REM sleep exhibited a sharp rise over the final ten minutes of sleep prior to traumatic-nightmare-associated arousals; however, that

probability did not exceed 57%. The probability that subjects were in stage 2 sleep fell over the last ten minutes prior to nightmares, but did not fall below 27%. The probability of stage 1 sleep prior to nightmares was approximately 10%. The overall percentage of REM sleep in these ambulatory records was only 17%.We compared pre-nightmare sleep to control sleep (nights on which no nightmares were reported) within-subjects, controlling for circadian phase by considering control sleep over same clock-time period as pre-nightmare sleep. Neither sleep continuity nor NREM sleep architecture distinguished pre-nightmare sleep from control sleep. Pre-nightmare sleep was characterized by greater REM time ($p < 0.041$) and reduced REM latency from stabile sleep ($p < 0.08$) compared to control sleep. Pre-nightmare sleep was not associated with increased heart rate or reduced pre-ejection period.

Figure 1



Conclusions: The data suggested that trauma-related nightmares were principally but not exclusively associated with REM sleep. Pre-nightmare sleep was characterized by elevated REM percent appearing against a background of overall low REM percent of sleep (~17%). Considered together with other data,[2,3] these findings suggest that dynamics of REM interruption-suppression and REM rebound may play a causative role in trauma-related nightmare emergence in PTSD.

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1029.M

Spectroscopy Before and After Total Sleep Deprivation in Healthy Adult Men

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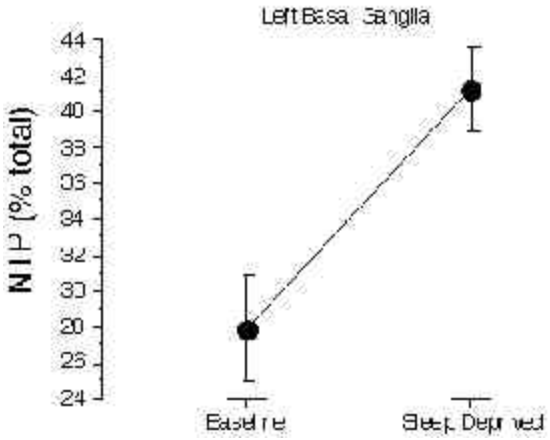
Introduction: It has been reported recently, using phosphorous (31P) magnetic resonance spectroscopy (MRS), that beta nucleotide triphosphate (β-NTP) is significantly lower in the basal ganglia of unmedicated depressed subjects vs. non-depressed subjects.[1] The antidepressant effect of sleep deprivation also has been widely reported (e.g. 2). The effect of sleep deprivation on the brain has not been studied using 31P MRS. 31P MRS identifies region-specific changes in the high energy phosphates α-, β-, and γ-NTP. Therefore, the use of 31P MRS might enable us to detect of chemical changes in the brain that may be related to the antidepressant effect of sleep deprivation. Such chemical changes in the brain are undetectable by more traditional means of assessment which measure only blood flow and glucose metabolism.

Methods: Three healthy, adult men (mean age 30+10 yrs) have participated in this pilot protocol to date. Subjects with a psychiatric, medical, or primary sleep disorder were excluded from the study. The protocol consists of one night of baseline sleep at average bedtime and waketime, followed by a night of total sleep deprivation. A third night of recovery sleep took place for one subject. This subject's sleep was recorded polysomnographically on the baseline and recovery nights. On the baseline night, sleep stage percentages were within normal limits for his age group. Proton decoupled phosphorous spectroscopic images were acquired from subjects at 7 a.m., following the baseline night and after the night of total sleep deprivation, using a GE Signa 1.5T MR scanner (5.4 operating system). Subjects spent 24-25 hours of continuous wakefulness prior to the MRS. Phosphorous-31 spectra were acquired using a short echo time (TE=3ms) proton decoupled phosphorous spectroscopic imaging technique.[3] The regions of interest included the left and right frontal lobe and left and right basal ganglia, including left caudate and putamen nuclei. The nominal voxel size was 4cm x 4cm 5cm (superior/inferior). Spectra were fit using the VARPRO/MRUI time domain technique (Dr. Aad van den Boogaart, Katholieke Universiteit Leuven, Belgium). Mole percent values for inorganic phosphate (%Pi), phosphocreatine (PCr), and α, β, and γ-nucleotide triphosphate (NTP) were calculated. Statistical analyses were performed using ANOVA.

Results: Following a night without sleep, left frontal lobe total NTP values were reduced ($p<.01$) and left basal ganglia total NTP values were increased ($p<.04$), in comparison to baseline values (figure 1).

Figure 1. Mole percent total-NTP in the left basal ganglia following a baseline night of sleep and a night of total sleep deprivation



Conclusions: These pilot data, together with previous findings using 31P MRS, may generate new hypotheses about the effects on the brain of both sleep deprivation and depression and the relationship between the two. Specifically, further study along these lines may provide a better understanding of the beneficial effect of sleep deprivation on depression and reveal new insights into the mechanisms underlying clinical depression.

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1037.M

Suicidality Correlates with Poor Sleep Quality, Nightmares, and PTSD in Sexual Assault Survivors

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Introduction: Suicide is the ninth leading cause of death in the United States. The Surgeon General has called for more research to study this problem, which accounts for 30,000 deaths annually. While known risk factors for suicidality include such factors as comorbid psychiatric disorders, age, and marital status, the relationship between suicidal behavior and sleep has only recently been explored. Previous studies have demonstrated positive correlations between suicidality and poor sleep quality in depressed patients. Patients with chronic posttraumatic stress disorder (PTSD) also may exhibit suicidality, and the current study examined the relationship between suicidality, sleep quality, nightmares, and PTSD symptom severity in PTSD patients.

Methods: A chart review was performed from the intake data of female sexual assault survivors (n=153) who enrolled in a nightmare treatment program. Participants were recruited from the Albuquerque area through local advertisements, private therapists, and the Albuquerque Rape Crisis Center. Inclusion criteria included age 18 or older, female, complaints of nightmares at least once per week for six months, insomnia, and PTSD. Instruments included in the analysis were the Hamilton Depression Rating Scale(Suicide Subscale) conducted through personal interview, and the following self-report questionnaires: Pittsburgh Sleep Quality Index (Component 1: Subjective Sleep Quality); Nightmare Frequency Questionnaire; and Posttraumatic Stress Scale (Total Severity Score). Higher scores reflect greater severity of each measurement. Pearson correlation coefficients were calculated.

Results: The sample suffered from severe nightmare disorders with an average rate of disturbing dreams more than every other night. Insomnia and PTSD were in the moderate to severe range. Significant correlations were obtained for suicidality versus: poor sleep quality ($r = .25$, $p = .002$); nightmares ($r = .26$, $p = .001$); and PTSD ($r = .50$, $p = .000$).

Conclusions: Similar to previous studies, poor sleep quality showed a moderate correlation with suicidality. Nightmares demonstrated a moderate correlation, and PTSD demonstrated a large correlation with suicidality. These findings may be of interest to sleep researchers and specialists because it is well known that suicidal patients often describe the phenomenon of "emotional exhaustion", either in suicide notes (completers) or following non-lethal attempts. The current study raises the possibility that such "exhaustion" may be associated with some aspect of poor sleep quality. Generally, poor sleep quality in PTSD patients would be expected from nightmares, hyperarousal symptoms, anxiety, and ultimately psycho-physiological insomnia. However, new research suggests that sleep-disordered breathing (SDB) may be associated with poor sleep in sexual assault survivors with PTSD. Both SDB and nightmares cause chronic sleep fragmentation, which may deplete essential energy reserves and reduce homeostatic restoration of the central nervous system. This, in turn, hypothetically, may worsen emotional exhaustion, jeopardize coping capacity, and contribute to suicidal behavior. With recent research demonstrating that SDB or nightmare treatment is associated with decreases in nightmares, insomnia and PTSD symptoms, we believe that future treatment research should investigate whether or not such therapeutic interventions also decrease suicidality. Suitable patients for such research investigations could include those suffering from posttraumatic stress, depression, and other psychiatric disorders.

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1385.M

Symptom Severity, Depression, and Sleep/Wake Activity in Post-War Veterans with Post Traumatic Stress Disorder

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Introduction: Sleep disturbance is the most frequent symptom reported by combat with Post Traumatic Stress Disorder (PTSD). The co-morbidity of depression and PTSD is well documented, but relationships between PTSD symptom severity, depression, and sleep/wake activity remain unclear. The purpose of this on-going study is to describe the relationship between PTSD symptom severity, depression, and sleep/wake activity patterns in post-Vietnam War era veterans diagnosed with PTSD.

Methods: Fifteen post-war veterans (60% Caucasian, 13% African American, 27% Hispanic) with a mean age of 53+4 yrs have been studied to date. Sleep/wake activity was monitored at home for 72 hours by wrist actigraphy (Ardsley, NY). The first 24 hrs was an adaptation day. Daytime wake activity was scored from a 2-hr window on each side of the subject's acrophase for days 2 and 3. Sleep variables were automatically scored (Action3 software). Subjects also completed the Impact of Events Scale-Revised (IES-R), Weiss et al., 1997) to assess three components of PTSD symptom severity (avoidance, hyperarousal, and intrusion) and the Beck Depression Index.

Table 1. Actigraphy Estimates of Sleep Continuity (Mean & SD)

	Night #2		Night#3	
Sleep Latency	12.5	±10.9	19	±39.2
Total Sleep Time	422	±90.8	431.2	±89.7
Sleep Maintenance (%)	87.1	±8.7	77.5	±23.8
Mean Wake (daytime, Hz)	106.4	± 23.8	97.8	±17.9
Mean Wake (at night, Hz)	14.5	± 9.9	14.7	±12.3

Results: Actigraph sleep/wake data are presented in Table 1 for both nights. IES-R subscale scores ranged from 0-28 on Avoidance, 3-22 on Hyperarousal, and 1-28 on Intrusion. The BDI scores ranged from 0-43. The BDI was correlated with the IES-R (avoidance r=.78, hyperarousal r=.76, intrusion r=.71). Avoidance was related to mean wake (at night) (r= -.30). Hyperarousal was related to maximum activity during the day (r=.59, p=.002), sleep latency (r=.43), and sleep maintenance (r= -.50).

Intrusion was related to mean wake time during the day (r=.34) and sleep latency (r=.25). BDI was related to mean wake time during the night (r= -.42), sleep latency (r= -.23), sleep maintenance (r= .22), and total sleep time (r=.35).

Conclusions: These preliminary data suggest that both symptoms of depression and symptoms of PTSD are related to objective measures of sleep/wake activity. The more severe the hyperarousal symptoms reported by these veterans, the more wake time was objectively measured during both the day and night.

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1734.M

The Role of REM Sleep Arousal in Major Depression

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Introduction: In this study, we have attempted to replicate our previous findings that corrugator EMG activity during REM sleep is correlated with depressive severity in patients with major depression (MDD).[1,2] Further, we assessed whether 1) subjects with MDD exhibit more motor activity than non-depressed healthy controls, 2) this association is specific to corrugator activity and REM sleep, 3) motor activity in other muscle groups is correlated with severity of depression, and 4) motor activity is associated with other measures of psychological distress (e.g., anxiety).

Methods: 30 subjects have been studied: 20 subjects with MDD and 10 normal controls. Depressed Ss met DSM-IV criteria for MDD and had HRSD scores > 14. Normal control subjects did not report Axis I disorders nor a positive family history of MDD. Control Ss scored < 7 on the HRSD. Subjects spent two nights in the laboratory. Montages for the study included the standard PSG derivations (2 EOGs, F3, F4, C3, C4, O1, O2 and mentalis EMG), three additional pairs of EMGs (right and left corrugator, brachioradialis and tibialis muscles) and one EKG. EOGs and EEGs were acquired according to established criteria.[3]

Results: The mean BDI, BAI and HRSD scores for MDD subjects were: BDI: 14.4 (7.2), BAI:10.4 (5.3), HRSD: 16.8 (4.0). Mean BDI, BAI and HRSD scores for healthy controls were: BDI: 0.6 (1.0), BAI:2.5 (3.8), HRSD: 0 (0.0). Currently, we have analyzed the first night data for 10 Ss with MDD and 9 matched controls. Three levels of analyses were conducted: visual, power spectral (PSA), and correlational. Visual assessment revealed no differences as a function of group. PSA measures (utilizing total power estimates) indicated that Ss with MDD exhibit more EMG activity during Stage 1 (Group x Muscle, $p = 0.05$) and during REM sleep (Group x Muscle, $p = 0.078$). During Stage 1 sleep, MDD Ss exhibited more EMG activity in the right corrugator muscle (8.8 μv2/Hz vs 3.1 μv2/Hz, $p < 0.05$) and the left brachioradialis muscle (62.5 μv2/Hz vs 16.2 μv2/Hz, $p < 0.05$). During REM sleep, MDD Ss exhibited more EMG activity in the right corrugator muscle (3.5 μv2/Hz vs 1.7 μv2/Hz, $p < 0.05$), the left brachioradialis muscle (50.3 μv2/Hz vs 6.1 μv2/Hz, $p < 0.05$) and the left tibialis muscle (27.5 μv2/Hz vs 5.5 μv2/Hz, $p < 0.05$). Correlational analyses revealed that EMG activity (during both REM and Stage 1 sleep) was substantially correlated with BDI and HRSD (r=.48 to .72) and tended to be correlated with the BAI (r= .39 to.56).

Conclusions: We confirmed that MDD patients exhibit motor activity during REM sleep and that this form of somatic arousal is correlated with severity of depression. Further, we found that 1) patients with MDD exhibit more EMG activity than healthy controls, 2) increased activity occurs primarily during Stage 1 and REM sleep, and 3) the pattern of EMG activity suggests right hemisphere abnormalities.

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1751.M

Diurnal Rhythms of Subjective Wakefulness and Anxiety

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Introduction: Both anxiety and wakefulness are forms of arousal modulated by central nervous system and neuroendocrine mechanisms. Anxiety is known to interfere with restful sleep, however, the relationship of daytime sleepiness and anxiety is more complex. Through the waking day, wakefulness varies in a distinctive bimodal rhythm with late morning and afternoon peaks separated by a midafternoon dip, or "siesta".[1] Attempts have been made to establish a circadian or diurnal rhythm for anxiety but results have been equivocal. The present study examines the relationship between the daily rhythm of subjective wakefulness and that of subjective anxiety in a nonclinical sample of students. Specifically, we ask: Does the level of anxious arousal covary with level of wakefulness? It is predicted[1] that a bimodal pattern of wakefulness with a marked siesta effect will be found for anxiety and wakefulness, and[2] that anxiety will vary in a negative relationship to wakefulness.

Methods: 42 undergraduate volunteers were divided into high- (HI-A; STAI-T > 43; N=22) and low-anxiety (LO-A; STAI-T < 34; N=20) groups based on their State-Trait Anxiety Inventory Form Y—Trait Version scores (STAI-T). Subjects filled out questionnaire packets hourly for 2 days. Packets included the Stanford Sleepiness Scale (SSS), a 2-dimensional Affect Grid comprising measures of sleepiness-arousal (Grid-A) and unpleasant-pleasant feelings (Grid-P), and the State-Trait Anxiety Inventory-State Version STAI-S).

Results: When data were adjusted for wake-time, the expected bimodal pattern was visually and statistically evident for alertness on Grid-A for both groups and on SSS for the LO-A group. The LO-A group showed a marked siesta-like dip at hrs 8-9 on both measures. The HI-A group showed its most pronounced dip in alertness (other than bedtime and wake time) at hrs 5-6. Visual inspection of the SSS and STAI-S data show that subjects in both groups experienced drops in anxiety at the hours of lowest wakefulness, roughly the siesta time. This drop in anxiety was more pronounced and statistically reliable for the LO-A. A further finding was the markedly higher sleepiness level experienced by the HI-A group through the day. Not only was the level of anxiety significantly higher for the HI-A group (as was expected) but the levels of wakefulness on both SSS and Grid-A were significantly lower indicating a positive relationship between anxiety and sleepiness.

Conclusions: A bimodal pattern in subjective wakefulness was found,

confirming earlier research.[2] The siesta-related drop in anxiety indicates that, contrary to the original prediction, diurnal anxiety is highest when wakefulness or general arousal is high and lowest during times of sleepiness. The higher level of daytime sleepiness in the high-anxiety group may be related to difficulties sleeping at night.

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1788.M

Sleep Onset Disturbance Discriminates Suicidal Ideation in Patients with Chronic Pain

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Introduction: Sleep disturbance, major depressive disorder, and heightened risk of suicide are among the most clinically significant psychiatric sequelae of chronic pain. While sleep disturbance is associated with suicidality in patients with major depression[1,2] and is a significant predictor of completed suicide in psychiatric patients,[3] it is not known whether sleep disturbance is associated with suicidal behavior in patients with chronic pain. This study evaluates whether subjective sleep disturbance discriminates suicidal ideation in patients with chronic pain.

Methods: 51 outpatients with benign, non-neuropathic, chronic pain (35 females; mean age: 44 ±11.2) were recruited. Patients likely to have substance abuse problems, intrinsic sleep disorders, primary psychiatric disorders and/or other medical problems were excluded. Pain chronicity ranged from .67 to 49 years. Patients completed a pain and sleep survey, the Pittsburgh Sleep Quality Index (PSQI), the Beck Depression Inventory (BDI), and selected subscales of the Multidimensional Inventory (MPI). Subjects were classified as "suicidal ideators" or "non-ideators" based on their responses to BDI-Item 9 (suicide).

Table 1

Comparison of Means for Sleep, Pain, and Depression Severity Variables by Suicidal Ideation Status

Clinical Variables (Higher scores indicate increased severity)	Suicidal Ideators (n=12)	Non-Suicidal ideators (n=39)
PSQI		
Global Severity	13.5 (3.66)	10.97 (4.42)
Sleep Quality	2.2 (.57)	1.72 (.97)
Sleep Latency	2.6 (.52)	1.72 (1.2)***
Sleep Duration	1.33 (.99)	1.46 (1.3)
Sleep Efficiency	1.58 (1.08)	1.49 (1.23)
Sleep Disturbance	2.2 (.39)	2.00 (.56)
Use of sleeping Medication	1.5 (1.57)	1.21 (1.40)
Daytime Dysfunction	2.2 (.72)	1.38 (.88)**
Pain Intensity Rating (0=no pain/5=excruciating)	3.83 (.83)	3.00 (.89)**
Multidimensional Pain Inventory		
Interference of pain (in daily life)	4.98 (.62)	4.23 (1.07)**
Affective distress	4.11 (.98)	3.17 (1.02)**
BDI - Item 9	20.92 (8.61)	14.41 (7.19)*

* p </=.05; p </=.01, p </=.001 (t-tests); Column values = M(SD)

Results: 12 of 51 of patients (24%) endorsed the statement, "I have thoughts of killing myself, but I would not carry them out." (Suicidal Ideators). 39 patients denied suicidal ideation (Non-Ideators). As illustrated in Table 1, subjects with suicidal ideation reported higher levels of sleep onset disturbance, sleep-related daytime dysfunction, increased pain intensity, and more severe pain-related interference, affective distress, and depression (p< .01). Discriminant Function Analysis. Predictors of suicidal ideation status were selected based on the results reported in Table1. The number of predictors were further limited by consolidating the Sleep Latency and Daytime Dysfunction PSQI subscales into one composite score representing Sleep Onset Insomnia Severity. The final predictors (Sleep Onset Insomnia Severity, Pain Intensity, MPI-Interference, MPI Affective Distress, and BDI Total Score Minus Item 9) were entered into a stepwise discriminant function analysis. The only two significant, independent predictors of suicidal ideation status were: Sleep Onset Insomnia Severity (Standardized Canonical Coefficient = .82; F on Step 1 =15.68, p<.001) and Pain Intensity (Standardized Canonical coefficient = .62; F on Step 2 = 12.51, P< .001), respectively. The overall discriminant function equation correctly classified 84.3% of the cases. 10 out of 12 of the ideators were correctly classified by the equation.

Conclusions: The results suggest that chronic pain patients who report severe and frequent initial insomnia (>3x a week) with concomitant daytime dysfunction and high pain intensity are more likely to report suicidal ideation. These results can not be entirely explained by increased depression, affective distress, or pain-related interference.

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1790.M

Longitudinal Measurement of Sleep Complaint Frequency in Patients with Recurrent Major Depression

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Introduction: To our knowledge, no prospective longitudinal studies have documented sleep complaint frequency in either primary or secondary insomnia. In this study, we evaluated the frequency of sleep continuity complaints over a one month interval in patients with secondary insomnia. Our primary goal was to determine how frequently patients reported problems with sleep initiation and maintenance.

Methods: Data for this study were drawn from an ongoing longitudinal study of the clinical course in remitted patients with recurrent MDD (sponsored by the NARSAD Foundation). Data from 16 subjects (10:female, 6:male, mean age = 38.4[11.0]) were included. All subjects were in remission but were selected based on persistent sleep complaints. At intake, the mean Hamilton Rating Scale for Depression (HRSD) was 4.7 (3.6) and the mean Pittsburgh Sleep Quality Index (PSQI) was 8.5 (2.5). The mean age of onset for depression was 22.6 (13.0) and the length of illness was 15.3 (10.3). Four weeks of daily sleep diaries were obtained from each subject. Daily diaries included four sleep continuity measures consisting of sleep latency (SL), time awake after sleep onset (WASO), intermittent awakenings (IWT), and total sleep time (TST). Sleep continuity data were evaluated for frequency of complaints using the following criteria: SL greater than 30 minutes, WASO greater than 30 minutes, IWT greater than 2, and TST less than 6 hours.

Results: The mean Beck Depression Inventory (BDI) score for the monitoring interval (monitored weekly) was 12.1 (10.2). The mean sleep profile (mean of each subject's one month average) was as follows: SL = 32.5 min. (20.0 min.), WASO = 31.2 min. (26.8 min), IWT = 1.6 (1.0), TST = 405.1 min. (64.0 min.). Frequency analyses revealed that problems occurred for sleep latency on 29.5% of the nights, WASO problems on 29.0% of the nights, IWT problems on 23.7% of the nights. Total sleep time problems occurred on 65% of the nights.

Conclusions: Based on these findings, it appears that 1) sleep continuity problems in secondary insomnia do not occur on a nightly basis, 2) that problem frequency is on average equal to about 30% of the time, and 3) that total sleep time deficits sometimes occur as a result of initiation problems and sometimes due to maintenance problems. What might account for this variability across time remains an open question. One can speculate that there may be a rhythm to symptom severity such that several bad nights may be followed by one or more good nights of sleep. Such a pattern might reflect the effects of an increase in sleep pressure over successive nights of poor sleep. Additional analyses on the temporal patterning of sleep disturbances, and the clinical consequences of this pattern are ongoing.

Research supported by NARSAD Foundation

1151.M

The Co-occurrence of Sleep and Paraphilic Sexual Disorder

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Introduction: To date, the two major bedroom activities - sleep and sex, have been studied independently. Typically, sleep is viewed as a completely quiescent behavior while sex is seen as a transient, brief, period of activity preceding sleep. However, recent studies have turned this pattern on its head. Clinical cases of men who sexually assaulted sleeping partners were recently reported.[1] A report of parasomnic sex while sleeping have now been published.[2] The purpose of this study was to investigate sleep abnormalities of patients diagnosed with paraphilic disorder.

Methods: 26 consecutive patients with paraphilia were referred to the Sleep and Alertness clinic for assessment of their sleep disturbances. All patients underwent overnight polysomnographic studies. Standard polysomnographic techniques were used to record the following sleep parameters during the night: electroencephalographic (EEG) activity from the C3-A2 and C4-A1 leads, submental (chin and leg) electromyographic(EMG) activity, bilateral electrooculographic (EOG) activity, thoracoabdominal movements, nasal airflow and oxygen saturation. Sleep Onset Latency (SOL), total sleep time (TST), sleep efficiency (SE), percentage of stage 1, 2, 3, 4 sleep and REM sleep, as well as REM sleep onset were determined. SPSS package for Windows was used for the statistical analysis.

Results: All patients with paraphilic behavior showed a wide spectrum of different sleep disturbance. The most common sleep disorders were obstructive sleep apnea and PLMD (42% and 50% respectively). In some cases the patients had both diagnoses. Out of patients with either apnea or PLMD, 70.5% had the history of criminal activity and had been charged with sexual assault. Polysomnographic features of parasomnia (arousaIs from deep sleep and increased amount of SWS) showed 15% of the patients. Polysomnographic findings suggestive of underlying depression were found in 31% of the patients. Some patients had more than one diagnosis (77%).

Conclusions: There is high prevalence of sleep disorders in paraphilic patients. High percentage of patients suffer from sleep apnea and PLMD that may have significant deliterious effect on the quality of life, health and emotional status. Patients with sleep apnea experience a number of consequences, including sleep fragmentation, excessive daytime somnolence, personality alterations, memory impairment, feeling tired and irritability which in its turn might trigger or exacerbate the paraphilic behavior.

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1492.M

Repetitive Transcranial Magnetic Stimulation (rTMS) in the Treatment of Insomnia Associated with Drug Resistant Major Depression

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Introduction: Repetitive transcranial magnetic stimulation is a new, noninvasive and safe modality with a potential to treat various psychiatric and neurological disorders. It is being used in particular as a new treatment for drug resistant depression. Many patients with depression may in fact present with insomnia. In the context of a study using rTMS to treat drug resistant depression we also assessed its effect on the insomnia suffered by these patients.

Methods: We administered rTMS as an open-label adjunctive treatment to antidepressant medications to 9 patients(all male) with major depression diagnosed on the Structural Clinical Interview for Diagnosis. The rTMS was administered at 90% of motor threshold to left prefrontal lobe at either 1Hz or 5Hz daily for 10 days. 40 stimuli/minute were administered for 15 minutes daily (6000 stimuli per patient). Efficacy was evaluated with an insomnia score calculated as the sum of the three insomnia items on the Hamilton Depression Rating Scale(HDRS). The range of this score is from 0 to 6. The patients were followed on unchanged medications for 2 months following rTMS.

Results: All 9 patients tolerated the rTMS well except for transient headache. Five patients received rTMS at 5Hz and the remaining four patients at 1Hz. The mean(± S.D.) baseline insomnia score was 3.667(± 1.323). The mean insomnia score at 4 weeks and 8 weeks were 1.889(± 1.3) and 1.77(± 1.9) respectively. The improvement was statistically significant at 4 and 8 weeks ($P<.05$, paired t-test)

Conclusions: rTMS is effective in treating insomnia associated with drug resistant major depression. Further studies are needed to explore rTMS role in the treatment of other types of insomnia e.g. psychophsiological insomnia etc.

1524.M

Sleep Problems in Autistic Spectrum Disorders

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Introduction: Several reports showed that autistic spectrum disorders had a high prevalence of sleep disorders, often associated with mental retardation; the most frequent disturbances were disorders of initiating and maintaning sleep (extreme sleep latencies; long night wakings, shortened night sleep and early morning waking) and circadian rhythm. Few studies about prevalence of parasomnias have been carried out, often with contradictory results. To better address the occurrence of sleep problems in children with autistic spectrum disorders, we conducted a questionnaire based study on these children.

Methods: Twenty-four consecutive children (22M, 2F; mean age 6 years, 4 months) were evaluated at the Sleep Center of our Department. Diagnosis was made according to DSM-IV criteria. Subjects showed different grades of mental retardation and were compared to an age-matched control group of 270 children (134M, 136F; mean age 7 years, 2 months). Evaluation included a complete medical and physical examination, laboratory and neurophysiological investigations and neuroimaging to evaluate the presence of CNS diseases. The questionnaire consisted of two sections: the first one used to obtain demographic, behavioural and clinical data, the second made up of 24 items in a Likert-type scale; sleep disorders were considered if the episodes were present at least two nights per week.

Results: Mean sleep onset time was 9.43 pm and mean awakening time 7.20 am. Daytime naps were present in 50% of cases. All children maintained a regular sleep schedule. Autistic children showed a higher prevalence of cosleeping (58.8% vs. 5.18%; X2=53.25; $p < 0.0001$); few children had sleep disorders during infancy (10.5%) and mothers reported them as good sleepers. The main problem reported was the difficulty to fall asleep at night (58.8% vs. 8.89%; X2=33.55; $p<0.00005$); a high percentage of subjects showed a sleep latency > 30' (50% vs. 7.04%; X2=19.94; $p <0.0001$). The prevalence of night wakings (more than two awakenings per night at least 2 times per week), higher than controls (25% vs. 7.04%), failed to reach statistical significance (Yates corrected X2 = 2.69; p=0.10). Parasomnias were more frequent in autistic children: hypnic Jerks (41.18% vs. 4.81%, X2=27.25; $p<0.00005$), rhythmic movement disorders (20% vs. 1.85%; X2=11.15, $p<0.001$), nocturnal hyperhydrosis (50% vs. 34.45%; X2=8.67, $p<0.005$), sleepwalking (18.75% vs. 1.85%; X2=10.26, $p<0.005$), snoring (43.75% vs. 14.81%; X2=7.22, $p<0.01$), nocturnal hyperkinesia (68.75% vs. 25.93%, X2=11.62, $p<0.001$), nightmares (20% vs. 1.85%, X2=8.78, $p<0.005$), sleep terrors (12.5% vs. 1.48%, X2=3.68, $p<0.05$). No differences have been found regarding sleeptalking (12.5% vs. 10.74%), breathing difficulties (18.75% vs. 8.89%), bruxism (13.3% vs. 10.37%) and restless sleep (13.3% vs. 18.52%).

Conclusions: These preliminary results contradicted the common reports about high prevalence of disorders of maintaining sleep in pervasive developmental disorders. Due to the limitation of the sample we could not make any inference on these results that could be also affected by the high frequency of cosleeping.. However, we confirmed the elevated frequency of parasomnias, even if the literature showed conflicting results.

1526.M

Limb Movements During Sleep in Combat-Related Posttraumatic Stress Disorder

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Introduction: One of the core diagnostic clusters of posttraumatic stress disorder or PTSD in the DSM-IV is defined by persisting symptoms of heightened arousal. Among the symptoms listed are difficulty initiating and maintaining sleep. We have previously suggested that sleep aspects of heightened arousal in PTSD include anxious awakenings, micro-awakenings and motor activity intruding into sleep (Mellman et al., 1995). Relevant findings included recurring limb movements during sleep (LMS) in close to a third of the subjects. Brown and Boudewyns (1996) reported diagnosing periodic LMS in the majority of a group of PTSD cases assessed by polysomnography (PSG). The goal of the present study was to evaluate characteristics of LMS in subjects with combat-related PTSD in greater detail and to preliminarily explore their relationship to characteristics of LMS occurring in a group diagnosed with periodic limb movement disorder (PLMD).

Methods: Available PSG records of the previously studied subjects with combat-related PTSD with an average of at least 4 LMS per hour of sleep (PTSDLM group) were reviewed (n=6 men). Records for 6 men who presented to the sleep laboratory and did not carry a diagnosis of PTSD and ended up being diagnosed with PLMD were reviewed for comparison. None of the subjects were taking medications affecting the CNS at the time of the study. In addition to standard sleep measures records from the PTSDLM and PLM D groups were reviewed for LM characteristics (e.g. association with sleep stage; amplitude, duration, and intervals separating LMS, which were obtained by sampling across the night when LMS were numerous).

Results: The PLM group was older than the PTSDLM group (65.5+ 11.6 versus 44.7+ 2.9, $p<.01$) and had more frequent LMS overall (33.5+20.4SD, LMS per hour versus 10.7+7.3 , $t=2.6$, $p<.03$). None of the PLMD had in excess of 10% of LMS during REM sleep where 27% of one and 59% of another PTSD subject's LMS occurred during REM sleep. There were trends for LMS in the PTSDLM group to be of longer duration (2.0+.5 seconds versus 1.5+.5, $t=1.9$, $p<.08$) and to be separated by longer intervals (346.3+329.2 seconds versus 66.7+62.5, $t=2.0$, $p<.07$).

Conclusions: While preliminary, and limited by inherent differences between the small sized groups, our data suggest that LMS in PTSD may be distinct from LMS occurring in PLMD. Mechanisms of motor disinhibition during sleep could be relevant to broader issues of disturbed arousal regulation in PTSD.

References:
(1) Mellman TA, Kulick-Bell R, Ashlock LE, Nolan B: Sleep events in combat-related post-traumatic stress disorder. Am J Psychiatry 152:110-115, 1995.
(2) Brown TM, Boudewyns PA: Periodic limb movements of sleep in combat veterans with postraumatic stress disorder. J Traumatic Stress 9:129-136, 1996.

POSTER PRESENTATIONS

1838.E

Abnormal Circadian Rhythm of Sleep Propensity in Chronic Schizophrenia

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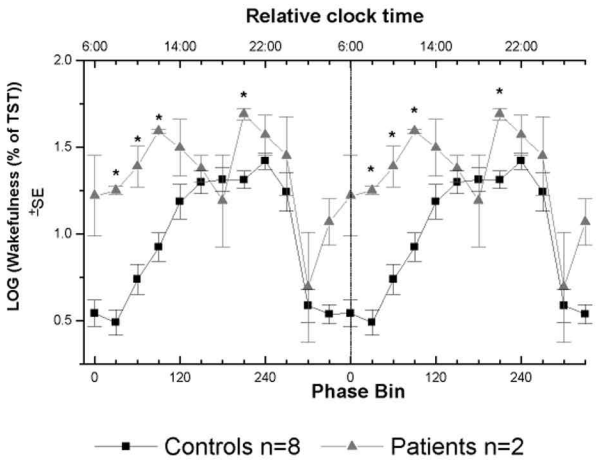
Introduction: It is well established that sleep propensity varies with circadian phase in humans.[1] However, very few studies have attempted to clarify the circadian variation of sleep disturbances in schizophrenia. The aim of the present study is to adequately quantify the circadian variation of sleep propensity in chronic schizophrenia by using a protocol that partials out the masking effect of the rest-activity cycle.

Methods: A 34 y.o man and a 39 y.o woman suffering from paranoid schizophrenia based on the DSM-IV criteria and the concurrence of two independent psychiatrists were enrolled. Both patients were naive to neuroleptic medications. A 31 y.o. healthy young man with no medical or psychiatric condition was also enrolled. All subjects had extensive laboratory tests including a dosage of TSH and a toxicological screening. Subjects maintained regular 8-hour sleep periods for at least 3 weeks before entering the laboratory. They were scheduled to live individually in a time-isolation unit on "30-h days" for 10-15 solar days. Core body temperature was measured continuously by use of a rectal sensor. Very dim levels of light (less than 10 lux) were maintained throughout all waking episodes. Nonparametric spectral analysis of core body temperature data was used to assess the intrinsic phase and period of the endogenous circadian pacemaker. Sleep data were folded at the endogenous circadian period by computing the circadian phase for all 20-sec epochs. The amount of wakefulness was educed by assigning data to 30° bins for each subject. Data were then averaged across the two schizophrenic patients. The results were compared with normative data published for healthy young subjects[1] using two-sample Student's tests.

Results: The endogenous intrinsic period was estimated at 24h04, 23h29, and 24h19 for the schizophrenic man, the schizophrenic woman, and the healthy control, respectively. The variation of wakefulness within sleep presented a robust variation with circadian phase. When compared with normative data for this age group, the percentage of wakefulness within sleep was significantly higher in schizophrenic patients for the circadian bins 15°-45°, 45°-75°, 75°-105°, and 135°-165° ($p<0.05$). In contrast, the circadian variation of wakefulness within sleep of our control subject was not statistically different from the normative data published for young healthy controls.

Figure 1



Conclusions: These results suggest that sleep efficiency is reduced over 30% of the circadian cycle in patients with chronic schizophrenia compared to healthy subjects. The present study also revealed that the "window of opportunity" for consolidated sleep appears more restricted in schizophrenia. Similar observations have been reported in healthy elderly individuals.[2] Further analyses of slow wave activity are underway to clarify the mechanisms involved in the pathogenesis of sleep disturbances in chronic schizophrenia.

References:
(1) Dijk DJ, Czeisler CA. Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves and sleep spindle activity in humans. J Neurosci 1995;15:3526-3538.
(2) Dijk DJ, Duffy JF, Riel E, Shanahan TL, Czeisler CA:Ageing and the circadian and homeostatic regulation of human sleep during forced desynchrony of rest, melatonin and temperature rhythms. J Physiol (London) 1999;516:611-27.

Supported by the National Alliance for Research on Schizophrenia and Depression. DBB is supported by a Scholarship from the Medical Research Council of Canada.

1842.M

Persistent 48-Hour Periodicity with Alternating Nighttime Sleep Duration: A Case Study

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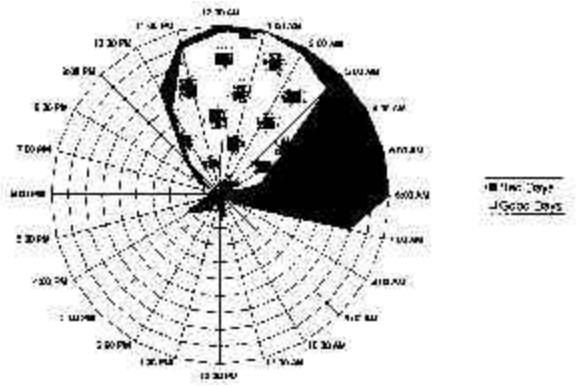
Introduction: Over the past 200 years less than 20 cases of individuals with persistent 48-hour periods of alternating mood (e.g., depressed one day, manic the next) have been described. In some of these cases there has been a clear pattern of alternating sleep duration. These alternating mood patients are best appreciated as extreme examples of rapid cycling bipolar disorder. This abstract presents the case of a man with persistent alternating sleep duration in the absence of significant mood symptoms.

Methods: The history was obtained from a 60 year old married Caucasian business executive. There was no known family history of sleep disturbance or psychiatric disorders. He had no psychiatric history. He has been treated with Synthroid for hypothyroidism for about 10 years. He regarded his previous nighttime sleep and daytime functioning as normal. His previous sleep hours had been approximately 10:30 p.m. until 6:30 a.m., and napping was extremely rare. Beginning in 1995, and without obvious precipitants, he began to experience alternating short and normal sleep durations that have persisted with high predictability until the present. These are associated with what he describes as "good" and "bad" days, respectively. He denies any associated sense of mood fluctuation. *Good day*: Having fallen asleep about 9:30 p.m., he awakens spontaneously about 3:00 a.m. feeling alert and energetic. He will read, write, or manage finances until his 5:00 a.m. breakfast, which is followed by a vigorous three-mile walk. He goes to work early, and he has a long productive day with meetings well into the evening. He never naps on these days. Other than the earlier awakening, he describes this as a previously normal day. *Bad day*: Having fallen asleep about 9:30 p.m., he is awakened by his wife's alarm at 6:00 am. He remains in bed until 7:00 am. He feels rather sluggish as he prepares to get to work. Some days he will drive to his parking place and nap in his car before going in. He feels fatigued throughout the day. Most days he will nap again later in the morning and/or in the afternoon. Occasionally he will feel somewhat more energetic by late afternoon or evening.

Results: The patient maintained a log of his sleep-wake cycle for 56 days (28 good and bad days). The log data was consolidated into a radial plot (see figure) showing the probability of his being asleep during each hour of the day and night. This graphical representation demon-

strates the markedly reduced sleep duration preceding the good days. The bad days have relatively normal sleep duration and a greater tendency for daytime napping.

Figure 1



Conclusions: This persistent 48-hour pattern may represent a variant of the rapid cycling bipolar disorder with very low amplitude in mood fluctuation. It also raises the question of whether an underlying 48-hour sleep-wake oscillation can be dissociated from mood changes.

References:
(1) Richter CP: Two day cycles of alternating good and bad behavior in psychotic patients. Archivives of Neurology and Psychiatry 1938;39:587-598.
(2) Bunny WE, Hartmann EL: Study of a patient with 48-hour manic-depressive cycles. Archives of General Psychiatry 1965;12:611-625.

1844.M

EEG Sleep Spindle Activity and NonREM Sleep in Neuroleptic-Naive Acute Schizophrenics

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Introduction: EEG sleep spindles (SS) are thought to represent a sleep protective process by which access of inputs to the brain are diminished through deactivation of thalamo-cortical loops. SS are markedly reduced in normal and demented old age as well as in various neurological and psychiatric disorders. An abnormally high SS density (i.e., no./min. sleep) was reported in the first nonREM period of chronic, neuroleptic-withdrawn schizophrenic patients.' To better address the spindling features of schizophrenia, we recorded the sleep of 10 schizophrenic patients never treated by neuroleptics.

Methods: Ten acute schizophrenic patients (6 males, 4 females; age: 29.7±16.1 years) never treated with neuroleptics were compared to ten healthy controls (7 males, 3 females; age: 22.0±4.5 years) screened for psychiatric, neurologic and clinical sleep disorders. All participants spend two consecutive nights in the sleep laboratory. Sleep stages were determined for night 2 according to Rechtschaffen and Kales (1968) using 20 sec. epochs. Stage 2 SS were visually identified on C3 (C4 for 2 patients). Results were compared using Mann-Whitney U-test for independent samples.

Results: No difference was found between patients and controls for the density of SS. However, patients showed significantly less minutes of stage 2 nonREM sleep in the total and last third of night (U=21.0, p<.03 and U=12.5, p<.005, respectively) as well as a non-significantly decreased number of SS in the total (552.0±83.1 Vs 709.1±132.9) and last third (145.0±22.8 Vs 189.4±49.9) of night. Patients also showed less minutes of stages 3+4 nonREM sleep in the total and first third of night (U=25.0, p<.05 and U= 19.0, p<.02, respectively).

Figure 1. Distribution of stage 2 sleep across the night in control participants and patients with schizophrenia.

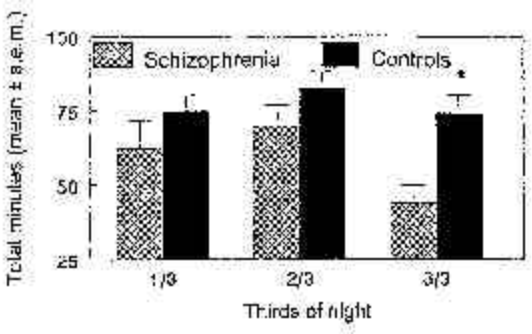
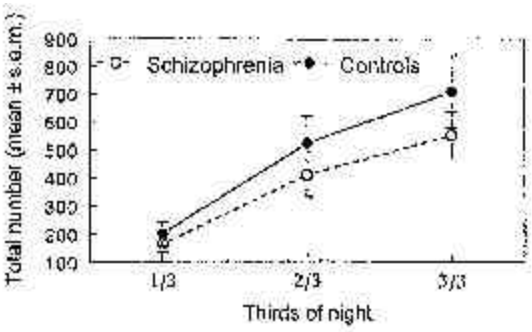


Figure 2. Accumulation of stage 2 sleep spindles across the night in control participants and patients with schizophrenia.



Conclusions: We have not observed a decreased SS density in neuroleptic-naive patients but we still cannot exclude the possibility that thalamo-cortical gating mechanism are impaired in schizophrenia since the absolute number of SS was decreased non significantly; a greater number of participants should resolve this issue. It could be argued that the decreased absolute number of SS may have led to underscoring of stage 2 but the fact that SWS was also reduced favors the alternative proposition that a weakening of nonREM sleep maintenance mechanisms is present in schizophrenia. This should be discussed in view of the recent description in healthy controls of a relation between nonREM seep and procedural memory. Since some patients with schizophrenia present impairments in procedural performance, both phenomena could be associated in schizophrenia.

References:
(1) Hiatt JF, Floyd TC, Katz PH, Feinberg L Further evidence of abnormal non-rapid-eye-movement sleep in schizophrenia. Arch Gen Psychiatry 1985;42:787-802.
(2) Smith C, MacNeill C. Impaired motor memory for a pursuit rotor task following stage 2 sleep loss in college students. J Sleep Res 1994;3:206-13.
(3) Schroder J, Tittel A, Stockert A, Karr M. Memory deficits in subsyndromes of chronic schizophrenia. Schizophrenia Res 1996;2:19-26.

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1855.M

Use of the SCID as an Objective Measure for Evaluating the Prevalence of Depression in Patients with OSAS

Maczaj M, Kapuria S, Pieczalski M, Relja M, Goel V, Slintak C, Chopra A, Gujavarty K

Introduction: An association between OSAS and depression has been described in the literature, however, the exact incidence and prevalence of depression in this patient population has not been established. To the best of our knowledge, the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) has not been administered to patients with OSAS to evaluate for depression. The goal of our study is to define the prevalence of depression in patients with polysomnographically diagnosed OSAS by utilizing the SCID.

Methods: We administered the SCID to every consecutive adult patient who presented to the Center for a polysomnographic evaluation of OSAS during a one month period. Twenty-two patients were administered the SCID and diagnosed with OSAS. SCID findings, and sleep study results including sleep architecture, AHI, RAI and arterial oxygen desaturations were evaluated. There were 12 men and 10 women in the study sample. The ages ranged between 21 and 82 years old. The median age was 58 years.

Results: SCID revealed that 46% (10/22) of the OSAS patients were normal. The total percent of depression (any type; including both past and current) identified by SCID was 41% (9/22). Gender subdivision revealed that 40% (4/10) of the women and 42% (5/12) of the men had been depressed. Twenty-three percent (5/22) of the patients with OSAS had an active depression at the time of testing and were on antidepressant medication. Of this 23% with active depression, 20% (2/10) were women and 25% (3/12) were men.The SCID depression findings were as follows:Major Depression: 18% (4/22); Minor Depression: 14% (3/22); Depression NOS: 9% (2/22).Other findings were as follows:Anxiety disorders: 9% (2/22); Substance abuse: 14% (3/22); Bipolar disorder: 0.05% (1/22); Schizoaffective disorder: 0.05% (1/22); Schizophrenia: 9% (2/22); Eating disorder: 0.05% (1/22).

Conclusions: The lifetime prevalence of depressive disorders in the general population ranges between 10-25% for women and 5-12% for men.[1] The 40% prevalence of depression in our OSAS population of women is statistically significant up to a general prevalence of 15% ($p<.0270$). The 42% prevalence of depression in our men is statistically significant at both the upper and lower estimates of the general population ($p<.0014$; $p<.0000$ respectively). The point prevalence of depression ranges between 5-9% in the general female population and between 2-3% in the male population. The 20% point prevalence in our OSAS women is statistically significant at a general point prevalence of 5% ($p<.0299$). The 25% point prevalence for our OSAS men is statistically significant for the upper and lower estimates of the general population ($p<.0038$; and $p<.0000$ respectively). We recognize that the number of patients in our current sample is small. We are continuing to collect SCID information on all of our OSAS patients to further clarify the prevalence of depression in OSAS patients.

References:

(1) Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition, 1996; Washington, DC: American Psychiatric Association.

1858.M

REM Sleep EEG Spectral Analysis in Neuroleptic-Naive Patients with Schizophrenia: Increased Prefrontal and Anterior Right Hemisphere Beta Activity

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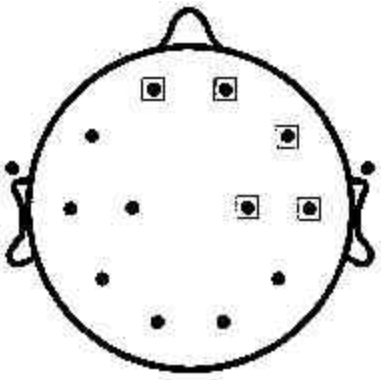
Introduction: There have been numerous published reports on functional brain abnormalities in schizophrenia, yielding an important number of apparent contradictions due to treatment status of the patients and brain activation methods used. Since REM sleep is a state of spontaneous and endogenous activation of the CNS, we decided to perform quantified analysis of the EEG during this state in neuroleptic-naive patients.

Methods: Six acute patients never exposed to neurolepties (4 M, 2 F, mean age = 37.7 ± 7.4) were individually recorded for two consecutive nights in the sleep laboratory of a large psychiatric hospital during the first week of their hospitalization. According to DSM-IV criteria, the six patients had first received a diagnosis of schizophreniform disorder at the time of recording and the final diagnosis of schizophrenia was confirmed within six months. These patients were compared to six healthy participants (4 M, 2 F; 23,5 ± 4.7 years-old) screened for psychiatric, neurologic, and sleep disorders. All participants had a 12-electrodes EEG montage (C3, C4, Fpl, Fp2, F7, F8, T3, T4, T5, T6, O1 and O2) referenced to linked-earlobes. Night two was scored according to Rechtschaffen and Kales (1968). For each of the first three REM sleep periods, five four-second epochs of artefact-free EEG were selected, totaling 60 seconds of EEG. This was then submitted to Fast Fourier Transform with a resolution of 0.25 Hz and a cosine window smoothing; power amplitude was extracted. Spectral analysis generated four frequency band windows: Delta (0.75-3.75 Hz), Theta (4.00-7.75 Hz), Alpha (8.00-12.75 Hz), and Beta (13.00-20.25 Hz). Mann-Whitney U-test was used for between-group comparisons on absolute and relative activities for each frequency band.

Results: Compared to controls, patients had significantly more relative Beta activity on Fp1 ($U=5.5$, $p<.05$), Fp2 ($U=3.5$, $p<.02$), F8 ($U=3$, $p<.02$), C4 ($U=5$, $p<.04$), and T4 ($U=2.5$, $p<.01$). A non-significant decrease was observed on Delta, Theta, and Alpha relative power amplitudes on all these electrodes. No significant between-group difference was observed on absolute frequency bands activities.

Figure 1. Sites of increased REM sleep Beta EEG activity in neuroleptic-naive schizophrenic patients are the bilateral prefrontal area and the anterior right hemisphere.



Conclusions: These results are compatible with PET and MRI observations showing a reduced metabolic rate in the right thalamus and abnor-

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malities in the frontal cortex and right hemisphere of drug-naive schizophrenic patients.[1] They support the notion that brain circuits involving thalamus, prefrontal, and temporo-limbic cortices contribute to the basic biology of schizophrenia and yield deficits in sensory filtering in this disease.[2] It has been proposed that REM sleep EEG Beta activity reflects REM-on neurons activity.[3] This would support the notion that REM-on mechanisms are over-active in schizophrenia.

References:
(1) Buchsbaum MS, Someya T, Teng CY, Abel L, Chin S, Najafi A et al. PET and MRI of the thalamus in never-medicated patients. Am. J. Psychiatry 1996; 153:191-199.
(2) Weinberger DR. On localizing schizophrenic neuropathology. Schizophrenia Bull 1997;23:537-540.
(3) Merica H, Blois R. Relationship between the time curses of power in the frequency bands of human sleep EEG. Neurophysiol. Clin. 1997;27:116-128.

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1859.K6

A Case of Periodic Hyper/Hyposomnia - Sleep Lab Evaluation

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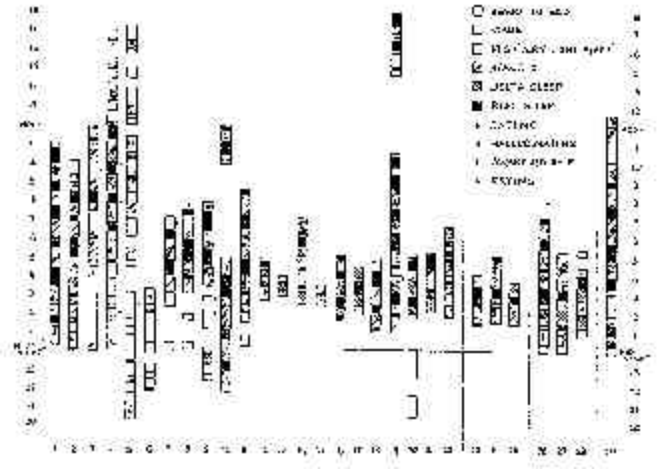
Mayo Clinic

Introduction: In a companion abstract, the case of a 36-year-old professional woman with periodic hypersomnia/hyposomnia is discussed. Reported here are 29 laboratory nights from this patient. Initially she slept in the lab for 22 consecutive nights, chronicling the end of a hypersomnia episode leading into a phase of hyposomnia. During this phase, she practically lived in the sleep laboratory except for work. Three subsequent nights each were recorded two weeks later (23-25) and three months later (26-28) when she was in a period of normal sleep. One night (29) was recorded at the beginning of another episode of long sleep, 4.5 months after the initial 22 nights.

Figure 1



Results: Nights I through 4 show long sleep (about 12 hours in bed, no delta sleep). Except for night 2, long nights contain "very light sleep" (VLS), described below. Nights 5 and 6 seemed to be "crisis nights": waking hallucinations, over 50 percent wake and mainly stages I and 2. In those 48 hours, there were only 5 minutes of REM sleep! Nights 12 through 22 show short sleep, except on night 19. There was considerable delta sleep during short nights and almost no VLS sleep."Very light sleep" (VLS) is a sleep stage not previously described. It is similar to alpha/delta. It is characterized by over 50% alpha waves interspersed with 5-10% delta waves and absolutely no sleep spindles. Our patient never entered VLS from wakefulness or stage 1, always through stage 2. During the periods of VLS, normal REM/NREM sleep cycling seems cancelled. Using 3 nights, we tried to determine the depth of VLS by the method of ascending stimuli and found that VLS has an arousal threshold that is higher than wakefulness, about the same as stage 1, and lower than that of REM sleep or stage 2 sleep.

Conclusions: The composition of sleep varied markedly between long and short nights. Whether VLS is idiosynchratic to this patient or a characteristic of this sleep pathology remains unclear.

1865.N

Impact of Scoring 2%Desaturations on Respiratory Disturbance Incex Severity Level

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Introduction: The severity of sleep apnea/hypopnea syndrome is estimated by the number of apneas and hypopneas scored. Techniques of measurement of airflow and effort can be imprecise. Therefore, arousals and desaturations corroborating identification of hypopneas are useful. A recent task force has recommended that the desaturation should be >3%.[1] However desaturations of >2% may also be significant. Certainly, a 2% desaturation occurring on a flat portion of the oxyhemoglobin dissociation curve indicates a greater drop in blood oxygen tension than a 3% desaturation on a steep part of the curve. In order to assess the effect of 2% desaturation on scoring hypopneas, we double scored studies.

Methods: Fifty consecutive polysonmograms on adults were scored manually. Apneas were scored by standard criteria- Hypopneas were scored when there was a clear reduction in amplitude of respiratory signal >5001o, or when there was lesser reduction in amplitude associated with arousals or desaturations. Studies were scored twice using desaturation criteria of >2% and >3%, and respiratory disturbance indexes (RDIs) were compared- Acquisitions were made with the Ahce-3 System, Version 1.20. Airflow was determined by Thermistor and effort by Piezo Sensor. Saturation was recorded with Healthdyne Model 930 Oximeter, with oximeter averaging time of 4. Saturation was digitally displayed on the polysomnogram. Studies were scored by a registered polysomnographic technologist. Severity level for RDI was slightly modified to avoid ambiguity of high and low limits at each level.

Table 1 - RDI Severity Levels - 50 Cases

RDI	Severity Level	# Studies RDI >3%
0-4.9	0 (normal)	5
5-14.9	1 (mild)	20
15-29.9	2 (moderate)	12
>30	3 (severe)	13

Table 2 - Change in Severity Level Using >3% vs.> 2% Desaturation

Degree of Change	# Cases
0	19
1+	30
2+	1

Results: Table I compares severity levels of studies scored. Four of the 5 cases scored as normal with >3% desaturations were determined to be

abnormal (mild), using >2% desaturation. Furthermore, only 13 studies were in the severe category using >3% desaturation versus 20 using >2% desaturation. Table 2 shows the impact of different scoring criteria on severity level. With r/o desaturation, 31 of 50 studies (62%) were graded at a higher severity level. Also, the mean difference in RDI by different scoring criteria was 12.1 (5.4 SD).

Conclusions: Sleep apnea/hypopnea severity as determined by the RDI, is significantly greater when 21/6 desaturation is used in hypopnea recognition compared to 3% desaturation. Many studies, otherwise scored with normal RDI, became abnormal. Also, studies that were scored with moderate RDL became severe. These results could have significant impact in patient management and reimbursement. For example, the Health Policy Committee Working to Improve Medicare's CPAP Policy has recommended initiation of CPAP for RDI of at least 30, regardless of the patient's symptoms (AASM Bulletin, Fall 1999). Recognition of these more subtle hypopneas would also help in assessing the effects of therapy such as during CPAP titration and treatment. Also, diagnostic ambiguity might be clarified in sonic cases where idiopathic hypersomnia or UARS arc considered in the differential diagnosis.If >2% desturation is used in scoring hypopneas, a change in the recommended severity scale may be warranted.

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1234.N

Pupillary Unrest and EEG Sleepiness

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Introduction: As people become sleepy, large amplitude, spontaneous oscillations in pupil size (i.e., fatigue waves) have been described. The pupillary unrest index (PUI) numerically quantifies cumulative changes in pupil size (Ludtke et al., 1998) during 15 minutes of alertness level pupillography testing (ALT). The mean±SD PUI for 140 normal subjects recorded between 8 AM and 12 N has been reported as 4.94±1.99 mm/minute (Wilhelm et al., 1999). The PUI has been found to be correlated with the Stanford Sleepiness Scale in normal subjects, and the Epworth Sleepiness Scale in OSA subjects. Increases in slow wave EEG (theta) activity have been associated with fluctuations in level of alertness in awake, active individuals. The purpose of this study was to determine if objective sleepiness reflected by changes in theta EEG activity increased with rises in the PUI in untreated narcoleptics (8 F & 8 M, mean age = 30.3±8.1) and untreated OSA (7 F & 9M, mean age = 36.9±7.5) subjects diagnosed with PSG and MSLT, and normal control subjects (8 F & 8 M, mean age = 30.4±7.4) without any clinical evidence of a sleep disorder.

Methods: Subjects participated in the pupillographic ALT during which pupil diameter (Mayo Clinic pupillometer) and EEG (Grass Model 7) recordings were conducted about 12 hours after the midsleep period. During the ALT subjects were seated quietly in a comfortable chair located in a quiet, dark environment, and were instructed to stare straight ahead at a red dot while trying to stay awake. Pupil diameter (R & L eye) and polysomnography (C3/A2, P3/A2, O1/A2, ROC/A1, LOC/A2 & bilateral mentalis EMG) were collected concurrently at 256 Hz for 15 minutes. After pupil data cleaning, pupil diameter data were downsampled to 8 Hz, and C3/A2 EEG data to 64 Hz. Power spectral density functions (FFT) were calculated on 6 sec epochs for minutes 5-11 of the EEG recordings, and standardized for each subject by dividing each 6 sec epoch by the mean theta power obtained for the first minute of dark recording. The PUI for each 6 sec EEG window was calculated, and, using the Wilhelm et al. (1999) normal finding, classified into four stages (Stage 1 PUI = 0 - 4.99 mm/min to Stage 4 PUI = 15-20 mm/min). The 6 sec theta values for each PUI stage were aggregated for each subject regardless of when they occurred during the 5-11 minute time period.

Results: ANOVA revealed that there were significant differences in standardized theta power ratios by condition (narcoleptic, OSA or control) and PUI pupil stage (Stage 1- Stage 4) forming 12 groups for analyses [F(11) = 14.01, p .000]. Post Hoc Least Significant Difference (LSD) testing revealed that there were significant differences (p .05 or <) both within and between subject groups by PUI stage. Within groups, statistically significant differences in theta power ratios were found as follows: narcoleptics - Stages 1 and 2 were < Stage 3, Stage 3 < Stage 4; OSA - Stages 2 and 3 were less than Stage 4. Between groups the theta power ratios were significantly greater for narcoleptics and OSA subjects across Stages 1-4 compared to controls. At Stages 3 and 4 the theta ratios were greater for narcoleptics compared to OSA subjects.

Conclusions: Together with our earlier findings regarding pupil miosis and theta power increases (Merritt, et al., 1999), the increases in theta ratios by PUI stage, and the differences between subject groups provide substantial evidence that the pupillographic ALT is a measure of increasing sleepiness in awake individuals. Since the pupillographic ALT is a convenient, easily repeatable objective measure that can be used in a wide variety of settings, further research comparing the ALT to MSLT and more comprehensive PSG findings is warranted.

References:
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1880.N

Heart Rate Variability (HRV) in Conjunction with NPSG Testing May not Provide a Reliable Indicator of Arousals From Sleep but can Enhance the Identification of Cardiac Disease.

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Introduction: Many groups claim that Heart Rate Variability (HRV) can be used as an indicator of arousal. Medications that reduce autonomic function (ex. beta-blockers) or diseases that cause autonomic dysfunction (ex. Diabetes) may decrease the reliability of this indicator of arousal. True HRV analysis, as it pertains to arousal, requires removal of ectopic beats, such as PVCs and PACs, to provide a true R-R variability. HRV in this sense is characterized in the time domain by the standard deviation of all normal R-R intervals (SDNN and SDANN) and in the frequency domain by the FFT analysis of the heart rate signal data (excluding the ectopy) and the ratio of the low frequency to high frequency data (LF/HF). This type of HRV analysis cannot be determined by the heart rate signal from a Pulse Oximeter, but requires elaborate computerized systems dedicated to this type of procedure. We propose that Heart Rate Variability (HRV) analysis is a useful augmentation to routine polysomnograms, particularly in conjunction with arrhythmia

analysis, BUT it is NOT a reliable indicator of arousal in a significant percentage of patients routinely presenting for diagnostic sleep testing.

Methods: HRV and arrhythmia analysis was performed on 127 patients undergoing polysomnography for OSA. Polysomnograms were staged and scored in a routine fashion. Cardiac data was obtained using 3 channel recorders simultaneously with the NPSG studies. Data was screened for cardiac abnormalities and all of the ectopy was removed from the data prior to performing HRV analysis.

Results: Of the 127 subjects studied, 37 (31%) demonstrated abnormally low HRV with decreases in both time and frequency domain HRV parameters. Of these 37 patients the AHI ranged from 7.4/hr to 112/hr with an avg. of 28/hr (± 22/hr), and the SaO2 nadir ranged from 56% to 95.6% (avg. 82.8 ± 9.6). Seven patients (18.9%) were diagnosed with Diabetes and twelve (32%) were on medications known to inhibit autonomic function. All patients had some degree of arrhythmia but the range varied widely. Ventricular ectopic beats occurred on an average of 437 per study (ranging from 7705 to 0) and supraventricular ectopic beats averaged at 471 per study (ranging from 6998 to 0). Ventricular tachycardia runs were identified for at least one episode in seven patients.

Conclusions: With 31% of OSA cases demonstrating reduced HRV, it is clear that HRV is not a reliable measure of repetitive arousals, which is in contradiction to previous reports by other groups. Causes for this, range from medication effect such as beta-blockers to conditions causing autonomic neuropathy such as Diabetes. Furthermore, accurate assessment of HRV may not have been performed by other groups in that ectopic beats were not excluded from the data in some reports. However we find HRV to be very useful in detecting early autonomic neuropathies and congestive heart failure, identified by the decreased HRV pattern. Furthermore, by performing extensive three channel arrhythmia analysis (which is required for the removal of all ectopic beats) many cardiac abnormalities can be identified which provide additional utility to the diagnostic evaluation.

1590.N

A Neural Network for Rejecting Artifacts From the Eyes-Open Awake EEG

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Introduction: Quantitative analysis of waking EEG can reveal homeostatic and circadian aspects of sleep drive. However, the waking EEG can be corrupted by a variety of physiological and non-physiological artifacts that can significantly affect quantitative analysis. Visually rejecting artifacts is labor-intensive. The aim of this project was to employ an artificial neural network (ANN) to reject artifacts from the waking EEG, and to compare the ANN's performance to visual artifact rejection.

Methods: A database of waking EEG studies from 76 adult subjects was used for training and testing the ANN. Subjects were instructed to focus on a fixed object and to minimize eye and body movements for five minutes, during which one EEG, two EOGs and a bipolar EMG were digitized at 128Hz. A human EXPERT1 categorized each 1-second epoch in the recording as either "artifact" or " artifact-free". The selected studies had at least 15 artifact-free 4-second intervals, each consisting of four consecutive 1-second epochs. To assess the reliability of visual artifact rejection, a second human EXPERT2 independently evaluated 30 of the 76 studies. The behavior of each 1-second epoch was characterized by a 10th-order autoregressive (AR) model for the EEG, right EOG, and EMG signals. The coefficients of the three AR models were normalized to Z-scores and concatenated into a single feature vector for each 1-second epoch. A three-layer feedforward ANN was trained to model the relationship between the input feature vectors and their corresponding output labels ("artifact" or " artifact-free") from EXPERT1. The 76 awake EEG studies contained a total of 25814 1-second epochs; 4048 artifact epochs and 4048 artifact-free epochs were randomly selected to train the ANN, and those remaining were used to test the ANN. Spectral analysis was performed to validate each artifact rejection method. Mean 4-second log power spectral densities of the waking EEG were computed for these conditions: no artifact rejection (NO-REJECT), and artifact rejection by EXPERT1, EXPERT2 and ANN. Paired T-tests were performed on each 1Hz-wide frequency band to compare NO-REJECT vs. EXPERT1, EXPERT1 vs. EXPERT2 and EXPERT1 vs. ANN. Significance was set at a Bonferroni-corrected level of p<.002. Kappa statistics were used to assess chance-corrected agreement between artifact rejection methods.

Results: For epochs from the 30 studies classified by both human experts, EXPERT2 agreed with EXPERT1 at a rate of 90.7% (Kappa = 0.797). The ANN classified the test epochs at a rate of 91.2% agreement with EXPERT1 (Kappa = 0.77). Every frequency band showed significantly higher power spectral density in the NO-REJECT condition than in the EXPERT1 condition ($p < 0.001$ for each; Figure 1). No significant differences were found between the ANN and EXPERT1 spectra ($p > 0.002$ for each frequency band; Figure 2). The EXPERT1 and EXPERT2 spectra did not differ significantly in any band.

Figure 1

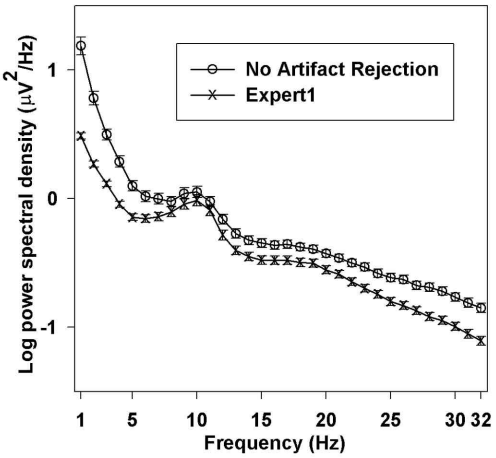
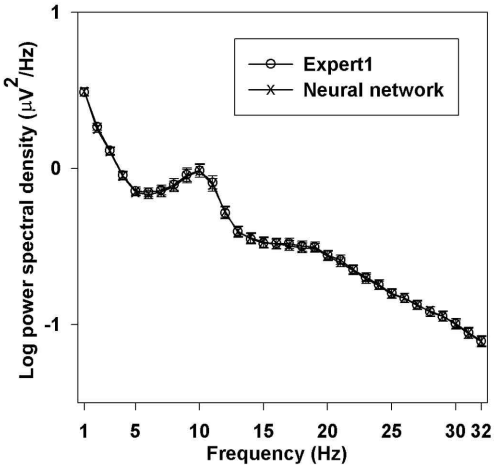


Figure 2



Conclusions: The ANN performs to the standard set by the two human experts, as indicated by both kappa statistics and power spectral analysis. This project demonstrates the feasibility of applying an ANN to automate the rejection of artifacts from the eyes-open awake EEG.

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1593.N

Evaluation of an Unattended Monitoring System for Automated Detection of Sleep Apnea

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Introduction: There are currently a number of portable recording systems available which are specifically designed for the screening and diagnosis of Sleep Disordered Breathing (SDB) events in the patient's home environment, ranging from full, multi-channel, polysomnography (PSG) systems to simpler units with only a few recording channels. However, all of these models share several common features which are less than optimum for home recording. First, while they are portable, they are not designed for use with an ambulatory patient. Second, they are not designed for unattended use; a trained technician must come to the patient's home to aid in setting up and disconnecting the system and in retrieving the data. In addition, the patients must be outfitted with an array of tethered electrode wires and sensors which are then connected to rather bulky body-worn monitors or table-top consoles. Finally, most require computerized or subjective analysis of the data by trained professionals; none provide for objective, automatic identification of apnea events. The ApneaCheck system (IM Systems, Baltimore, MD) was designed to overcome these limitations by allowing for data to be collected in miniature, self-contained, tetherless, synchronized recorders, which can be easily placed and removed by the patient. The data is automatically scored for identification of SDB events. The purpose of the current study was to evaluate the capability of the ApneaCheck system to detect SDB events in patients with a range of sleep apnea rates and, more specifically, to evaluate the system's ability to capture, identify and count apneic events.

Methods: 7 subjects who had previously displayed symptoms of SDB (ranging from minimal to severe apnea) were each admitted for a standard, overnight, PSG evaluation and were simultaneously outfitted with the ApneaCheck recorder system, which included thoracic and abdominal respiration belts, a chest-mounted activity monitor, a wrist activity monitor for determination of sleep-wake state, and a recorder for nasal and oral airflow data. The PSG data was independently scored for number and duration of SDB events, which were defined as any cessation or reduction by 50% or more in airflow lasting at least 10 seconds, or any reduced airflow lasting 10 or more seconds and associated with either an oxygen desaturation greater than 3% or a movement arousal at the end of the event. The PSG and ApneaCheck data were then analyzed for point by point agreement for airflow, and thoracic and abdominal respiratory effort. In addition, overall agreement across subjects for SDB rates from the PSG and ApneaCheck data were compared for airflow alone and for thoracic effort combined with airflow.

Results: The point to point correlation between the PSG and ApneaCheck output showed an excellent agreement, with an overall average correlation of 0.97 (r for: airflow = 0.97, thoracic effort = 0.98, abdominal effort = 0.97). SDB rates from the PSG and ApneaCheck were also observed to correlate well with one another; the correlation for airflow alone was 0.94, and for the combination of airflow and thoracic effort was 0.90. Automated detection of SDB events by the ApneaCheck system, as compared to the visually read PSG data, was observed to be 83.7% (with a 1.6% false detection rate) for obstructive apnea events and, for central apneas, the detection rate was 100% with a 5.5% false detection rate. In addition, all 7 subjects reported excellent acceptance of the ApneaCheck system, returning high scores on measures of comfort, ease of use and lack of sleep disturbance.

Conclusions: The results of this pilot study are encouraging. The current findings indicate that the ApneaCheck system provides an accurate means of identifying and recording SDB events associated with sleep apnea without the use of traditional PSG monitoring. ApneaCheck's automated detection routines correlate quite highly with the standard method of SDB detection with very few false detections. The next stage of research with the ApneaCheck system will be to conduct larger scale, more in-depth studies with this equipment and to evaluate multiple-evening recordings in the home environment.

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1594.N

A New Artificial Neural Network For Sleep Stage Scoring

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Introduction: We have extended our work[1] on automated sleep stage scoring. Artificial Neural Networks (ANN's) were developed, trained, and validated on 275 full night polysomnograms. The performance of the algorithm was assessed by comparison with the scores of three technologists in the validation set.

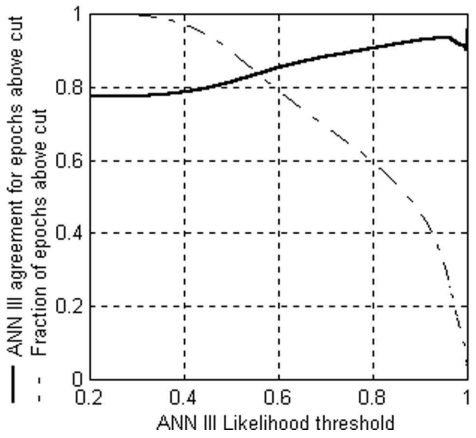
Methods: Of the 275 records, 225 were consecutive PSG studies, representing an unbiased sample of records of two sleep centers. Of the 225 records, 153 were diagnostic studies for sleep-disordered breathing, 6 for narcolepsy, and 66 for CPAP titration. Three technologists representing 3 different centers scored each 30-second epoch by the Rechtschaffen and Kales standard[2] as wake, 1, 2, 3, 4, REM, or unscorable. Each record was scored once, twice, or three times, by each technologist (an average of 5.5 scores per record), with at least 3 months between re-scores of the same record. The scorers were blind to all other scores, including their previous scores. ALGORITHM: The target likelihood for a stage is the fraction of scorers assigning that stage to the epoch, with each scorer given equal weight. Stage likelihoods are used as targets for ANN training and performance evaluation. The data is divided into training, test, and validation sets so that the fractions in each diagnostic group are preserved and the number of records in the validation set is about twice of the combined training and test sets. The training and test sets are alternating halves of 88 records, the validation set has 187 records. ANN ARCHITECTURE: Processing is done in a sequence of three ANN's, trained and tested in sequence. The architectures for ANN-I, II and III are 17-12-7, 33-20-7 and 33-20-7 nodes per layer, respectively. ANN-I has 17 input variables corresponding to waveforms within the epoch. The inputs to ANN-II include the ANN-I input variables, 14 context variables derived from the ANN-I output in a neighborhood of (6 epochs, patient age and time within the recording. Thus ANN-II adds "context" sensitivity. ANN-III has the same architecture as ANN-II, but uses context variables derived from the output of ANN-II. The outputs of all networks are estimates of stage likelihoods. PERFORMANCE: All ANN's are optimized using only the training set. Performance is evaluated on the test and validation sets. For each epoch, the stage scored with highest likelihood by ANN-III is compared to the highest likelihood manual stage.

Results: The table lists algorithm to manual and corresponding manual inter-scorer agreements for the training, test, and validation sets. The output likelihoods can be used to quantify confidence in the algorithm stage score for any epoch. In high confidence epochs (ANN-III stage likelihood >80%) the ANN-III to manual agreement is 90% in the validation set. The figure shows the fraction of validation set epochs above a given ANN-III likelihood threshold and the corresponding ANN-III to manual agreement for these epochs.

Table 1

	#Epochs	inter-scorer agreement	ANN-III manual
Training set	36,795	77.9%	85.1%
Test set	36,793	76.1%	77.3%
Full validation set	156,927	77.8%	77.4%
Validation set - high confidence	93,509	86.5%	90.6%

Figure 1



Conclusions: In this large data set scored by multiple scorers, the algorithm to manual agreement compares favorably to the average inter-scorer agreement. ANN to manual agreement is highest in epochs with high ANN output likelihood.

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1605.N

The Value of the Epworth Sleepiness Scale in Predicting the Severity of Obstructive Sleep Apnea

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Introduction: Daytime sleepiness is a cardinal symptom of several different sleeping and waking disorders including obstructive sleep apnea (OSA). The Epworth Sleepiness Scale (ESS) is a self administered questionnaire which has been used to estimate the degree of sleepiness in a patient, and to help predict who needs a sleep study to investigate possible sleeping/waking disorders such as obstructive sleep apnea.(Johns et al 1991; Johns, M 1993) We have previously reported that when the ESS is completed by a significant other, it is associated with the scores of the Multiple Sleep Latency Test. (Van Ert et al 1999) We hypothesized that the ESS, as scored by the patient or their spouse, may be useful in predicting the severity of OSA.

Methods: The ESS was prospectively and consecutively administered to 211 patients referred to our facility, prior to any type of sleep study. When possible, the significant other completed an ESS regarding the patient's sleepiness without knowledge by the patient. Patients who underwent a nighttime polysomnogram were classified by severity based on their respiratory disturbance index (RDI), which was defined as the sum of apneas, hypopneas, and respiratory effort related arousals. Physicians interpreting the studies were blinded to the result of the ESS scores. Linear regression models were constructed with age, sex,and the patient's ESS as independent variables and the RDI as the dependent variable.

Results: The clinical diagnosis of sleep apnea was present in 74% of all sleep studies in our center. Patients were excluded from this analysis if they had any other condition which might contribute to complaints of sleepiness. Neither the age nor the gender of the patient correlated with RDI. Interaction terms were also not significant. The patient's ESS (n=110) failed to show an association with the RDI (p=.55). The significant other's ESS score (n=67) was more closely associated with the RDI but not significantly so (p=.17).

Conclusions: The ESS score of both patients and their significant others were not associated with the severity of obstructive sleep apnea. Patient's estimates of sleepiness do not provide useful information in the diagnosis of OSA.

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Research supported by Saint Vincent Hospital, Green Bay, Wisconsin.

1893.N

Human Electroencephalogram (EEG) Induces Transient Coherence in a Spatially Extended Chaotic Model: Implications for Online Sleep/Wake EEG Pattern Recognition

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Introduction: We report on a technique of EEG pattern recognition that may have relevance to measurement methods in sleep/wake behavior and physiology. It involves a novel numerical simulation in which EEG is applied as a perturbation to a system of differential equations. These equations are a model of a hyperchaotic system (Baier et al., 1999). We have demonstrated that within narrow windows of frequency and amplitude criteria the model can be "tuned" to detect different short segments from a relatively homogenous section of EEG.

Methods: The model we used consists of a linear array of 100 cells each governed by the equations in Table 1. Each cell is diffusively coupled to two neighbors such that activity in one cell can propagate to the next cell and so on. Solving equations 1 and 2 results in the chaotic pattern seen on the left side of the spatio-temporal plot in fig. 1a. We used plots like fig. 1a to observe the overall results of our simulations. The vertical axis is the spatial array of 100 cells and the horizontal axis is model simulation time (about 50 s of real time in this case). We used a 45 s segment of EEG (C3/A2) from a noncomplaining male volunteer in stage 2 sleep. The EEG segment was purposely selected to have little periodic activity such as sleep spindles. The EEG was recorded with the EMBLA system (Flaga Medical, Reykjavik, Iceland), sampled at 100 sps, bandpass filtered 0.5 to 45 Hz, and scaled by 10000 for this simulation.

Results: Fig. 1a shows a simulation with EEG signal added to only cell #1 of the 100-cell array. We observe a background of excitable chaos and one section where the coherent behavior extends completely across the field of 100 cells. ON indicates when EEG starts. Fig. 1b shows the 10.5 s segment of EEG responsible for extended coherence. We created an artificial sequence of repeated sections of this "detected" EEG segment and obtained global coherence shown in fig. 1c. Fig. 1d shows the switch to a high-amplitude periodic oscillation in the time series of the 100th cell of the array. We were able to change the frequency of the model relative to the EEG such that a different segment of the EEG was similarly detected. Visual appearance and Fourier spectra of nondetected EEG was quite similar to that of detected EEG. As a control, Gaussian white noise alone, in place of the EEG was not detected and did not induce extended coherence in the model.

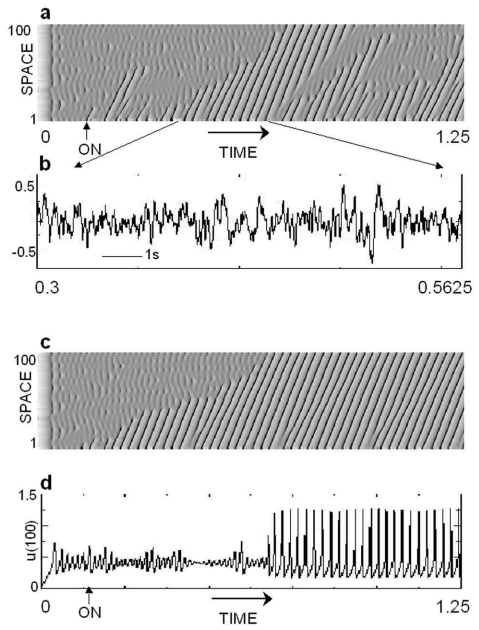
Table 1. System of equations for the hyperchaotic system

$$\frac{1}{w}\frac{du}{dt} = -f(U,V) + V - 0.8U + \alpha(1 - e\Omega) \quad (1) \qquad \text{where} \quad f(U,V) = \frac{m_2 U}{(1+U)} + \frac{m_3 U^2 V}{((0.81+U^2)(0.8+V))}$$

$$\frac{1}{w}\frac{dv}{dt} = f(U,V) - V \quad (2)$$

e is the coupling constant, and Ω is the EEG signal.

Figure 1



Conclusions: These are preliminary results in the sense that we used a small sample of EEG from a single source. "Tuning" is accomplished by adjusting the match of frequency and amplitude between the EEG and the model. There may be practical interest in developing a system like this as a tunable detector of EEG sequences to help measure sleep/wake physiology and behavior. It remains to learn more about how an irregular signal like EEG can combine with a chaotic system to produce a coherent pattern and to learn more about the significance of the detected EEG segments.

References:

(1) Baier, G., et al. Local stimulation induces long range order in spatio-temporal disorder. J. Chem. Phys. 110, 3251 (1999).

1611.N

The Apneagraph: A New Screening Device for Sleep Apnea

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Introduction: Treatment of obstructive sleep apnea (OSA) and related disorders depends in part on disease severity. One measure of severity is the frequency of abnormal respiratory events (respiratory disturbance index [RDI]). RDI is most accurately determined by all-night polysomnography (PSG), but for economically feasible large scale disease detection a screening device is required. The device should be easy for non-specialist personnel and patients to use. It should be inexpensive and capable of detecting all clinically significant cases, even if some specificity in detection is lost.

Figure 1. The Apneagraph: A New Screening Device for Sleep Apnea

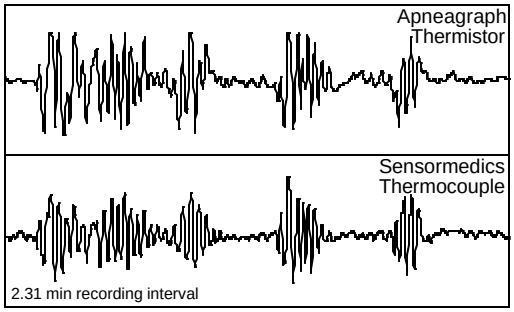

Table 1

PSG Standard→	All Respiratory Channels				Airflow Only	
Apneagraph Scored by→	Eye (n=9)		Machine (n=18)		Machine (n=18)	
	PPV	NPV	PPV	NPV	PPV	NPV
≥5 apneas/hr	83.3	100	100	58.3	100	91.7
≥10 apneas/hr	66.7	83.3	100	91.7	100	92.3

Methods: The Apneagraph (CSA Inc.) is an ambulatory airflow recorder. It measures 5cm x 4cm x 1.5cm and uses a standard oronasal thermistor to detect airflow. Its 64 Kbyte memory can store airflow sampled at 2 Hz for up to 9 hrs. In this institutionally approved study, subjects were 27 consecutive consenting sleep disorders center patients who were undergoing diagnostic PSG (Sensormedics 4200) for suspected sleep apnea. Subjects wore the Apneagraph simultaneously with the standard PSG airflow thermocouple. For the clinical gold standard, RDI was measured for the 27 patients manually (experienced scorers) in combination with the Sensormedics PSG auto-scoring algorithm using

all respiratory channels. The Apneagraph waveforms from nine subjects were printed and scored manually to estimate RDI. Data from the 18 remaining subjects were auto-scored by the Sensormedics algorithm using the PSG airflow channel only and then using the Apneagraph airflow channel. The Apneagraph data were used to calculate the number of respiratory events per hour of recording, which was used as the estimate of RDI (events/hr of sleep). Positive predictive values (PPV) and negative predictive values (NPV) were calculated for cases (subjects with ≥ 5 or ≥ 10 events/hr) and non-cases (remaining subjects) by comparing the Apneagraph data to the clinical gold standard as well as to the auto-scored data from the PSG airflow channel.

Results: Airflow waveforms obtained by the Apneagraph and PSG were remarkably similar (Figure). Respiratory event frequency ranged from 0 to 100.4 events/hr. The Apneagraph correctly predicted all cases and most non-cases when its data were machine scored (Table).

Conclusions: Interim analysis of these initial 27 subjects suggests that the Apneagraph is an effective means of detecting sleep apnea cases, whether defined by standard clinical methods or by purely algorithmic procedures. A limitation of the Apneagraph is that it does not distinguish obstructive from non-obstructive apneas. A more serious limitation is the absence of sleep-stage data, especially total sleep time, for which the RDI, but not the Apneagraph events/hr, is adjusted. Thus, severity will be underestimated by the Apneagraph when sleep efficiency is low.

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1256.N

Movement-Related Variability of Heart Activity During Sleep

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Introduction: Measurement of heart rate (HR) variability is used in clinical routine as a marker of the autonomic nervous system (ANS) activity. Most commonly HR is altered by having the subject do deep breathing at a constant rate. However subjects can have difficulty in performing and keeping a deep breath. Tests not requiring active participation of the subject could be more reliable. Movements during sleep have been reported to be associated with autonomic nervous reflexes. The aim of the study was to 1) Characterise the autonomic nervous responses to sleep movements through variability of the R-R interval, 2) Recognise the type and the proportion of movements producing the optimal effect, 3) Obtain normative values of HR response following sleep movement, 4) Determine whether this response precedes or follows a movement, 5) Study the response in patients with autonomic dysfunction.

Methods: We investigated 13 healthy professionally active subjects, without known sleep disorders (7 men and 6 women, mean age 34 years, range 25-49) and 2 patients (56 and 72 years) with well documented dysfunction of the sympathetic and parasympathetic systems. Night sleep recordings were done at home using a paperless recording system ("SleepBox", Biosys AB, Sweden). The subjects reported sleep quality in a simple questionnaire. Body and respiratory movements were recorded using a piezo-electric pad placed under the subject's mattress. One intercostal ECG derivation was also recorded. Data were unloaded on a PC, movements automatically detected and duration calculated. The movements were grouped according to their duration (< 1s, 1-4s, 5-9s). The results were controlled by visually checking the recordings. Epochs containing movements preceded by 40 s and followed by 20 s movements-free periods and without respiratory disturbances were analysed. For each movement selected, the R-R intervals were calculated 20 s prior to and 20 s following the onset of the movement. The R-R interval surrounding the beginning of a movement was included in the pre-movement interval. The accuracy of positioning the interval surrounding a movement was 1 s ± 0.5 R-R interval. We defined the R-R baseline as the mean R-R interval in a 5 s epoch 20 s prior to the occurrence of the movement. Mean R-R values for all movements were calculated for each subject, together with their variability (SD). From these mean values, a grand mean (and SD) was calculated for the whole group. Acceleration A was defined as the minimal value of the R-R interval (5 % or more below the baseline) within 5 s following the occurrence of a movement. The time of occurrence was noted. Slowdown or "deceleration" D was measured as the time necessary for returning to baseline. A rebound effect was defined as the maximum value (> 5 %) above baseline of the R-R interval within 10 s following the minimal value. Time of occurrence was noted. Finally the time for recovery and final return to baseline was reported.

Results: All control subjects presented a complex autonomic response to sleep movements with a HR acceleration, already within the 5 s epoch preceding onset of movement (p=0.005, paired t-test), followed by a sudden slowdown often to lower values than the initial HR, hence a rebound effect. This bradycardia could end rapidly or persist a longer time. Although other types of movements presented this response, we report the results of the 1-4 s movement group, with totally 172 movements analysed, (mean 13 SD 8 per subject). Movements <1 s were few and the marked movement artefact of the longer 5-9 s group could mask the initial R-R response. Initial mean (SD) R-R interval (baseline):1.03 (± 0.15) s. Mean value at onset of movement: 0.93 (± 0.10) s. Mean minimal A value of R-R interval: 0.83 (± 0.09) s occurring 2.2 (± 0.5) s after the onset of movement. Mean time for zero-crossing of the baseline following A:5.11 (± 0.83) s. Mean maximal value D of R-R interval: 1.22 (± 0.20) s occurring 8.9 (± 1.5) s after the movement. Mean time for final return to baseline (if occurring): 13.5 (± 1.8) s. While 74 % (127) of all the movements were followed by a clear A and D response, 90 % were followed by either A-D or only D. We did not find a correlation between the subjective evaluation of sleep quality or the sleep latency and the intensity of the HR response to movements. There were no significant sex differences. The two patients with ANS dysfunction did not show HR variability following sleep movements (< 4% of all movements).

Conclusions: That D is observed more often than A might be due to the positioning of the R-R interval in relation to the occurrence of the movement. The variability observed of the HR response can be related to the state of activity of the ANS known to change during sleep; the response can be strongest during REM and arousals, when the ANS is the most active. A might reflect a sympathetic response, and D its deactivation and/or activation of the parasympathetic system. The significance of A preceding movement onset is not fully clear. Analysis of the HR-movement reflex during sleep might give information about the state of these systems and, when quantified with normal age-related ranges of responses, might be used as a non-invasive heart-rate test.

1258.N

The Transition From Awakeness to Drowsiness and Sleep - A Microscoring Method to Study Hypnagogic EEG

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Introduction: Under conditions of monotony regular oscillations between wakefulness and sleepiness occur, a major concern e.g. for vehicle's drivers. Many systems are under development for early detection of drowsiness. They all have to be validated against the golden standard, EEG. However EEG patterns covering drowsiness, a progressive process, are poorly documented. Conventional sleep staging system, with only one score for wakefulness and another one for sleep, cannot

describe this process, and analysis of 30 or 20 s epochs is too long to describe the rapid changes related to drowsiness. The aim of this study was to develop an analysis method of EEG specifically intended for study of drowsiness and the gradual transition from wakefulness to sleep. It could ultimately be used to test drowsiness detection systems based on parameters others than the EEG.

Methods: Eighteen healthy subjects, 11 men and 7 women participated in this investigation, totalling more than 60 investigations. Some of the subjects were also investigated following partial sleep deprivation. Conventional polysomnography was done using a 14-channel Nihon-Kohden paper polygraph. In most of the cases the subjects were continuously video filmed. Subjective level of sleepiness and awakeness were assessed using analogue visual scale and the Karolinska Sleepiness Scale.We used 2 tests: the Multiple Sleep Latency Test (MSLT), measuring the subject's ability to fall asleep when given naps opportunities and the Maintenance of Wakefulness Test (MWT), used to study the ability to maintain alertness during daytime. For both tests 5 recording sessions of about 25-30 min. and 45-50 min apart, were performed, throughout the day, in a silent semi-dark room. For the MSLT the subjects were asked to lie down on a bed, to relax and not resist against sleep. For MWT, comfortably installed in a chair, they were asked to try to remain awake and to look at a point fixed under a TV camera. Each MSLT-MWT recording was visually scored for each 20 and 10 second period using the standard Rechtshaffen and Kales sleep stage criteria. Epochs with 2 s duration were also analysed. Each 1 s was scored according to a scale of 0 to 5, based on the background activity and the occurrence of events:Score 0: Flat signal; beta activity; continuous alpha activityScore 1: Alpha less than 50 % of 1 s epoch; decreased frequency and/or amplitude of alpha; rhythmic alpha activity in the central leads.Score 2: Intermittent occurrence of theta activity temporo-occipitalScore 3: Rhythmic theta activity temporo-occipitalScore 4: In the central leads: Progressive amplitude development of theta activity; rhythmic 2-4 Hz waves; evoked potentials; ripples, low voltage alpha or theta waves alternating with flattening or "suppression"; bursts of sharp theta; POSTS (occipital); slow eye movementsScore 5: Isolated or rhythmic vertex sharp waves, high amplitude low-frequency waves, K-complex or spindle.The values of the two 1 s periods were added to get the final score of the epoch. The sum of the points should however not exceed 10 for each 2 sec-epoch, the rank order of the scores determining the final EEG stage for the 2 s epoch. The results of the micro-analysis were plotted against time and compared to the conventional scoring.

Results: Sleep was almost always reached after a certain time. We plotted the time course from wakefulness to true sleep as defined by conventional sleep staging using 20 or 10 s epochs. Sleep Onset (SO) was defined as the first occurrence of epochs with unambiguous sleep. Plotting the score values of the micro analysis for each consecutive 2 or 6 s epoch produced EEG profiles characterised by great fluctuations without any distinctive pattern. However, filtering the data by averaging values of 3 consecutive epochs - hence a mean score for a 6 s episode - improved significantly the profile. Smoothing were further obtained by averaging many consecutive 6 s episodes. The optimal widths of the filter window, for best sensitivity and noise reduction, were found to be 60-120 s. In order to obtain a dynamic profile we used a "moving" averaging, incrementing with steps of 2 or 6 s, these values representing the final temporal resolution of the method. The procedure yielded to trends with progressive and smooth increase from a low value to a higher one, the highest point reached when SO was established according to the conventional EEG staging method. This high value was maintained as long as sleep was maintained.

Conclusions: Description of drowsiness requires higher temporal resolution than what is provided by standard sleep staging system. EEG microstaging and profiles developed using "filtering" and moving averaging technique reflected adequately the progressive transition from awakeness to sleepiness. The method was sensitive and reproducible.

1266.N

Night-to-Night Variability of Apnea Severity

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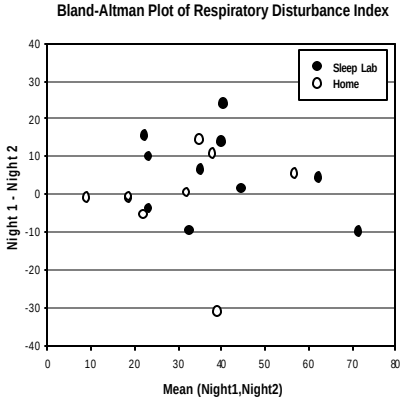
Introduction: Previous studies have revealed conflicting results regarding night-to-night variability in the respiratory disturbance index (RDI) in patients evaluated for obstructive sleep apnea (OSA). While there are inconclusive data regarding in-lab night-to-night variability, there are no data regarding night-to-night variability in diagnostic studies conducted in the home.

Methods: We prospectively studied 10 patients referred to the sleep laboratory with suspected OSA on 4 nights (2 nights in the sleep lab and 2 nights in the home) over 6 to 22 days (mean=12±5 days). Patients had 5 recordings (PSG on lab nights 1 and 2 with ambulatory recordings on lab night 2 as well as 2 nights in the home). The order of the studies (lab vs. home) was randomized. PSGs included EEG, EOG, EMG-Chin, EMG-Anterior Tibialis, ECG, nasal-oral thermistor and nasal pressure for airflow, thoracic & abdominal motion, body position, oximetry, and pharyngeal sound. The ambulatory recordings consisted of actigraphy, pulse rate, nasal pressure, thoracic & abdominal motion, body position, oximetry, and pharyngeal sound. OSA severity was classified as mild (RDI >= 5 and < 20), moderate (RDI >= 20 and < 40), or severe (RDI >= 40). Studies were analyzed blindly.

Table 1

Pt	Sleep Laboratory			Home	
	Night1	Night2		Night3	Night4
	PSG	PSG	Amb	Amb	Amb
1	39	32	32	43	33
2	65	60	50	18	19
3	28	18	12	18	19
4	30	15	14	-	15
5	52	29	32	24	55
6	67	77	73	59	54
7	21	25	27	8	9
8	47	33	30	42	28
9	45	44	45	32	32
10	28	38	39	20	25

Figure 1



Results: We observed considerable night-to-night variability in the RDI between the 2 nights in the lab (see Graph). The delta RDI for the lab studies was 10 or greater in 50% of the patients. When night 2 was compared to night 1 in the lab, OSA severity was misclassified in 40% of the

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patients (2 went from moderate to mild, 2 went from severe to moderate). We observed less night-to-night variability in the RDI between the 2 nights in the home. The delta RDI between studies was 10 or greater in 33% of the patients. When night 2 was compared to night 1 in the home, OSA severity was misclassified in 22% of the patients (1 went from moderate to severe, 1 went from severe to moderate). There was excellent agreement in the RDI on lab night 2 between the ambulatory recording equipment and the full PSG ($r=0.975$, $p<0.001$; see Table). The RDI in the home tended to be lower than in the sleep lab (mean RDI home=28±14, mean RDI lab=40±17,NS).

Conclusions: Based on this small sample, there is considerable night-to-night variability in the RDI. However, the differences observed are not likely to commonly affect clinical care.

1273.N

A Confirmatory Principal Components Analysis of the Stanford Sleepiness Scale

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Introduction: Analysis of a modified version (MSS) of the Stanford Sleepiness Scale (SSS[1]) suggests the presence of two underlying factors.[2] The present study uses a confirmatory principal components analysis of the MSS items to substantiate these findings. Further, the stability of the proposed two-factor solution over time, under conditions of increasing sleep loss, is examined.

Methods: Data were obtained from 140 normal, healthy males (mean age = 21.1 years) who each participated in one of ten separate studies investigating the effects of prolonged wakefulness on performance. Although the specific protocols for each study differed, common design features included: four testing sessions evenly spaced between approximately 2400 and 0730; and the use of the SSS and MSS. In each test session, performance testing, MSLTs, or MWTs, - depending on the aim of the individual study - followed administration of the subjective measures. The results obtained from these additional measures will not be considered in the present abstract.

Table 1

	Time of Testing			
	2430 Hrs.		0230 Hrs.	
	r_{cc}	r_{α}	r_{cc}	r_{α}
Component 1	.87*	.89	.91*	.89
Component 2	.80*	.85	.85*	.86
	Time of Testing			
	0430 Hrs.		0630 Hrs.	
	r_{cc}	r_{α}	r_{cc}	r_{α}
Component 1	.88*	.85	.91*	.91
Component 2	.86*	.86	.82*	.84

Note. r_{cc} = congruence coefficient; r_{α} = coefficient alpha;
* p = .00001

Results: The present data were compared to previous findings[2] at each test time by extracting two components and using an orthogonal Procrustes technique to rotate these to a target matrix based on the original MSS structure.[2] Similarity was assessed using congruence coefficients (see Table). There was a good fit for the two-component model at each of the four test sessions. The appropriate number of underlying dimensions was further assessed using the minimum average partial rule and parallel analysis:[3] the existence of two components was again confirmed. Finally, scale scores were calculated using simple unit weights for items loading on each of the two components. As seen in the table below, both Component 1 scale scores and Component 2 scale scores displayed admirable internal consistencies across testing sessions.

Conclusions: The findings of the present study provide further support for the existence of two underlying dimensions on the SSS. Their exact nature is still largely unknown although it has been speculated that the first dimension may reflect a state of activation whereas the other may assess the propensity for sleep. The notion of sleepiness as a multidimensional construct suggests that it is critical for measurement instruments to reflect its complex nature. Item analyses and validity studies examining the relationship of the component scores to physiological and performance tests and the effects of prolonged wakefulness should help to elucidate this intriguing question.

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1641.N

Hourly and 30-Minute Sampling: Similar Phase, Duration and Amplitude Estimates for Plasma Melatonin

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Introduction: Reducing the sampling rate for plasma melatonin while maintaining acceptable estimations of phase, duration and amplitude presents many advantages. Less frequent sampling is less costly and less demanding on subjects and technicians. To address this issue, we compared hourly (Q60) and 30-minute (Q30) sampling rates during a 9-10 day in-laboratory circadian study protocol.

Methods: Thirty-five young (25.5 ± 6.6 y), healthy subjects were studied. Subjects maintained a regular schedule for at least 2 weeks prior to entry into the laboratory. Subjects then underwent 3 baseline days (16 h at ~80-150 lux, 8 h at ~0 lux) before participating in a 27-49 h pre-stimulus constant routine (CR). During CRs subjects were kept awake in dim light (~10-15 lux). Potential masking effects were kept constant or distributed evenly across circadian phases throughout the CRs. After an 8 h sleep episode, subjects were exposed to a 16-h stimulus day containing either a dim (~10-15 lux) or bright (~10,000 lux) stimulus. Following an 8-h sleep episode, subjects underwent a 30-65 h post-stimulus CR. Sampling for plasma melatonin began on the third baseline day and continued every 30 minutes throughout the study. Plasma melatonin was assayed using I-IRA (DiagnosTech International, Osceola, WI). We analyzed the Q30 melatonin data collected under four different conditions: third baseline night, pre-stimulus CR, post-dim stimulus CR, and post-bright stimulus CR. Phase was estimated by linearly interpolating between samples and then calculating the midpoint, dim light melatonin onset (DLMO) and offset (DLMOff). The midpoint was calculated by taking the midpoint of the upward and downward mean crossings (Shanahan, 1995). DLMO 15 pg/ml and DLMOff 15 pg/ml were defined as the times the melatonin reached a threshold value of 15 pg/ml (Lewy et al 1985). The DLMO 25% and DLMOff 25% were defined as the times the melatonin reached 25% of the peak value of the pulse. The durations were defined as the length of time spent above either 15 pg/ml or 25% of the peak. Amplitude was defined to be the area under the curve (AUC) between the DLMO and DLMOff at 15pg/ml, calculated using the trapezoidal rule. Every other sample was then deleted from the

original Q30 data set, and the analysis was repeated using this new Q60 data set. For each method, the difference between Q60 and Q30 estimates were then calculated for the first melatonin pulse in each condition. A general linear model was used to compare the four conditions for each estimation method. Paired t-tests were then used to compare Q60 and Q30 sampling rates for each estimation method.

Table 1

# pulses	Estimation Method	p-value	mean (s.d.) for Q60-Q30
99	Midpoint	n.s.	0.90 (5.2) min
97	DLMO 15pg/ml	<0.008	-1.9 (9.1) min
97	DLMOFF 15 pg/ml	<0.001	2.4 (9.7) min
96	DLMO 25%	<0.0001	-4.7 (12.3) min
96	DLMOFF 25%	<0.0001	6.5 (17.6) min
96	Duration, 15mg	<0.0001	4.3 (14.4) min
96	Duration, 25%	<0.0001	11.1 (27.4) min
31	AUC, Baseline	<0.0009	-10.4(12.7) h/pg/ml
65	AUC, CRs	n.s.	2.6 (15.1) h/pg/ml

Results: The general linear model showed no significant differences among the four conditions for all estimation methods of phase and duration. Therefore, all further analyses grouped these conditions together. For the AUC, the baseline condition was significantly different from the post-bright CR and the post-dim CR condition ($p<0.003$). Therefore, in all further analyses of AUC, the CR conditions were grouped together, and the baseline condition was analyzed separately.

Conclusions: Hourly sampling of plasma melatonin provided equivalent phase estimates (using the midpoint method) to 30-min sampling under both baseline and CR conditions, and equivalent amplitude estimates (using AUC) under CR conditions. Other estimation methods of melatonin phase, amplitude and duration were significantly different when Q60 sampling was used rather than Q30, but the average differences were small with narrow standard deviations. Choice of sampling frequency should thus depend on the required level of precision for these measures.

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1647.N

Respiratory Effort Related Arousals (RERA) - UARS - Another Method of Diagnosis.

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Introduction: Validated criteria for respiratory effort related arousal (RERA) (upper airway resistance syndrome), diagnosis are currently unavailable. In the recent recommendations by the task force of the American Academy of Sleep Medicine use of esophageal manometry was felt essential for the diagnosis of RERA.[1] With the inherent limitation of using esophageal manometry in routine testing, we evaluated the possibility of modifying conventional pattern of interpreting computerized polygraphic data combined with use of CPAP (continuous positive airway pressure) to identify patients with RERA.

Methods: Thirty-eight patients with a combination of apnea/hypopnea syndrome and significant cyclical unexplained electrographic arousals with increasing respiratory effort were identified between January 1998 to October 1999. Twenty-six patients were excluded either because of an apnea/hypopnea index over 6 or inability to tolerate a trial of CPAP. The remaining 12 patients who met the following criteria proposed for diagnosis of RERA were assessed. 1. Increasing respiratory effort on conventional thoracic and abdominal strain gauge terminated by an electrographic arousal or arousal to full wakefulness was used as a primary criteria for identifying patients. 2. All studies were read as 90 second epochs as opposed to the conventional 30 second epochs as this clearly identified the increasing effort. 3. Oxyhemoglobin desaturation of any degree above 1% occurring just prior or concurrent with the increasing effort with return to pre desaturation level immediately with arousal. 4. Increase in the heart rate accompanying the arousal. 5. A crescendo pattern of snoring prior to the arousal if present. 6. Resolution of the cyclical arousals with an appropriately arrived at continuous positive airway pressure (CPAP). Additional factors taken into consideration included occurrence of the events of subtle hypopneas in relation to the supine position and exclusion of all other possible causes for the cyclical arousals such as apnea/hypopneas confirming the standard ASDA criteria, periodic limb movements of sleep, seizures, lower extremity flexor spasms and bruxism. Eight patients had a whole night PSG using Biologic Sleep Scan 17 channel Montage, following which they returned for a CPAP titration, 4 patients underwent a split night evaluation with an initial diagnostic part followed by use of CPAP in the second half of the night.

Results: Nine patients were males and 3 females, age range was between 27-59 years. All patient presented with a complaint of nocturnal snoring, sleep fragmentation and varying degrees of daytime sleepiness. The PSG data in pre and post CPAP group in the 12 patients studies is shown in Table 1. A trend towards improvement in the sleep efficiency, slow wave and REM sleep was observed in the post CPAP group (stastically not significant), however, more importantly, the episodes of cyclical electrographic arousals, subtle desaturations and increased effort resolved with the arrival to an appropriate CPAP pressure in each patient. The data regarding post CPAP change in the quality of life in terms of degree of daytime sleepiness is being collected, however, all the above patients are currently using CPAP with ongoing efficacy in terms of sleep continuity and resolution of degree of daytime sleepiness.

Table 1

POLYSOMNOGRAPHIC DATA

			WHOLE NIGHT GROUP PRE CPAP SLEEP STAGE %							POST CPAP SLEEP STAGE %					
PT#	SEX	AGE	TST *	I	II	III IV	R	A/H **	S.E. ^	TST*	I	II	III IV	R	S.E. ^
RTN '															
1	M	27	438	17.2	55.6	12.8	14.5	2.2	90	350	8.7	61.2	13.6	16.6	84
2	M	44	327	17.3	45.7	19.9	17.4	0.7	68	345	8.3	38.3	32.0	21.5	87
3	M	48	425	23.7	42.0	15.6	18.8	3.5	87	450	12.7	57.5	12.8	17.2	92
4	M	55	389	25.3	50.1	16.3	8.4	6.0	87	386	9.8	54.7	26.4	9.2	94
5	M	37	401	5.5	77.5	4.9	12.3	4.8	92	428	16.0	66.3	8.1	9.7	88
6	M	46	348	16.7	58.2	12.8	12.4	5.9	79	385	15.8	60.3	11.7	12.2	82
7	F	45	374	18.7	60.4	9.4	11.5	0.9	78	387	17.7	57.6	5.9	18.7	80
8	M	51	424	11.8	62.6	10.6	15.1	2.0	86	298	12.2	55.3	24.1	8.4	86
ME#			390	17.0	56.5	12.8	13.8	3.3	83	379	12.7	56.4	16.8	14.2	87
SPLT#															
9	F	53	110	34.4	62.4	3.6	-	6.0	73	184	52.7	29.6	17.7	-	72
10	F	49	176	31.4	50.4	13.0	5.1	4.1	79	137	9.5	21.8	31.6	37.1	82
11	M	59	173	72.8	15.9	11.6	-	5.9	80	136	11.7	42.1	19.4	26.7	70
12	M	55	196	19.4	69.6	8.4	2.8	4.3	93	137	11.3	58.6	18.6	11.6	75
ME#			164	39.5	49.6	9.2	2.0	5.1	81	149	21.3	38	21.8	18.9	75

*=total sleep time in minutes ** apnea/hypopnea index # split night study
^ sleep efficiency ' group with whole night study with and without CPAP

Conclusions: Modifying the interpretation of standard computerized polygraphic data to using a 90 second analysis epoch, assessing the effect of CPAP on resolution of cyclical arousals accompanied with

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increased respiratory effort, subtle desaturations and increased heart rate can be an effective method to diagnose RERA. Evaluation of the above mentioned criteria in a larger sample of patients with comprehensive analysis of the degree of daytime sleepiness pre and post study may help establish the value of the above protocol and may prove to be a practical alternative to using esophageal manometry for diagnosis of RERA (subtle hypopneas).

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1317.N

The Sleep Problem Inventory (SPI): Towards the development of a Multidimensional Self-Report Instrument

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Introduction: The use of a nocturnal polysomnogram in the assessment and diagnosis of sleep disorders is a costly procedure, and often not covered by health insurance. Moreover, referral to a sleep clinic is often delayed because of limited bed-space and clinic availability. Given these and other practical concerns, there is a growing need for a self-report instrument that can be used to screen for individuals who may be experiencing a sleep disorder. Existing self-report instruments tend to focus on symptoms related to a single sleep disorder, or measure subjective variables like sleep quality and satisfaction. In addition, many researchers have developed unstandardized 'in-house' instruments for use in their sleep laboratories to screen for sleep disorders, sleep affecting habits, or sleep hygiene. With few exceptions, most existing instruments have unknown psychometric properties. The present study is the first phase of a program of research aimed at developing a valid and reliable self-report instrument for assessing the core symptoms of common sleep disorders.

Methods: The first stage in development of the new instrument was to create a list of items related to sleep-disorder symptoms. The core symptoms for the various sleep disorders were taken from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and the International Classification of Sleep Disorders (ICSD). The initial item-pool consisted of several hundred items, although the research team shortened the pool to 117 items by eliminating redundant items or those that seemed biased towards a very narrow range of individuals. The final pool of items included symptoms associated with insomnia, breathing related sleep disorder, hypersomnia, circadian rhythm sleep disorder, narcolepsy, nightmare disorder, sleep terror disorder, sleepwalking disorder, and REM behavior disorder. The item-pool also contained a set of questions that assess sleep habits and behaviors associated with poor sleep hygiene. The new questionnaire (called the Sleep Problems Inventory; SPI) was administered to 425 non-clinical adults. For each item, participants responded to a 4-point intensity Likert scale (ranging from "not true of me", 1 to "very true of me", 4). Respondents were asked to answer the questions with respect to sleep behavior and sleep problems they "may have experienced in the last few months".

Results: A series of exploratory factor analyses were conducted to examine the multidimensionality of the SPI. Separate dimensions were found for insomnia, breathing related sleep disorder, hypersomnia, circadian rhythm sleep disorder, narcolepsy, nightmare disorder/sleep terror disorder, sleepwalking disorder, and REM behavior disorder. The results from the exploratory factor analyses were used to develop various subscales for the SPI. Preliminary psychometric analyses suggest that the subscales on the SPI have adequate internal reliabilities.

Conclusions: A new self-report scale has been developed that measures symptoms associated with a cross-section of common sleep disorders. The scale appears to have sufficient psychometric properties to warrant additional research. In particular, the factor structure for the SPI needs to be cross-validated in other samples. Future research needs to examine the scale's convergent and divergent validity using individuals with sleep disorders.

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1677.N

Measurement of Sleep: A Fuzzy Approach

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Introduction: There is a long history of attempts to measure sleep through both objective (e.g. PSG) and subjective (e.g. sleep diary) methods. Subjective methods have been criticized because of the high level of disagreement with objective criteria. This can partly be accounted for by the very nature of sleep as a state in which we are almost wholly unaware of our physiological state. Another source of error involves the manner in which people are asked about their sleep. Traditionally, questions have been phrased so as to require a point estimate response, which assumes that people are capable of generating a representative numeric value. Fuzzy set models use distributions of possible estimates rather than single values. The aim of this study was to examine the use of fuzzy vs. point estimates of sleep. These data are part of a larger study investigating fuzzy approaches to the measurement of health behaviors.

Methods: Data from 93 subjects are included in these analyses (45 men, 48 women; mean age=29.3 years; SD=10.5, range 18-62). Subjects completed an initial interview consisting of questions about various health-related behaviors. These questions were phrased in both point estimate and fuzzy set formats. For example, subjects were asked to give a point estimate for total sleep time (TST); "During the past 30 days, approximately how many hours did you usually sleep per night?" In the fuzzy condition, this question included the sentence, "I usually sleep between __ and __ hours per night" in order to capture the range of normal values. In addition, they were asked to estimate the most and least they slept on any night in order to obtain upper and lower boundaries. The same procedure was used in order to obtain estimates for sleep latency (SL).

Table 1

	TST (hours)	SL (minutes)
Lower boundary	3.9	9.6
Minimum	6.1	25.1
Point estimate	7.2	29.1
Maximum	8.1	41.9
Upper boundary	10.4	86.0

Results: Mean values obtained for each estimate are given in the table below. For TST, the range of the fuzzy estimates spans 2 hours, suggesting that there is considerable variability across nights. The point estimate falls approximately at the midpoint of this range. The range for SL is much smaller (16.8 minutes). The point estimate falls at the lower end of the range, suggesting that it underestimates the true average. TST and SL both have wide ranges of boundary values, indicating that even the estimated typical range does not capture information about total sleep variability.

Conclusions: Sleeping patterns are highly variable and traditional subjective point estimates do not adequately characterize this complexity. Point estimates also do not necessarily represent a true average of sleep patterns across time, suggesting that people are not always capable of generating an accurate point estimate. Fuzzy set approaches to measurement capture important information about the typical variability in sleep patterns without requiring a specific numeric value that may be difficult to estimate. More research is needed to better understand the fuzzy nature of internal representations of sleep in order to obtain accurate self-reports.

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1340.N

Validation of the Epworth Sleepiness Scale (ESS) and Sleep Quality Profile (SQP) in Hepatitis C Patients

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Introduction: Efficacy and safety studies of interferon α-2b (INFα-2b) and INFα-2b plus ribavirin for chronic hepatitis C (HCV) report insomnia as a side effect of this therapy in 20 to 39% of those subjects. Insomnia may involve a variety of noctural sleep disturbances and is often associated with variety of daytime symptoms, including daytime sleepiness. However, no tool for assessing daytime sleepiness or nocturnal sleep disturbances has been tested for reliability or validity in this population. This study's aims were to estimate the reliability and validity of the Epworth Sleepiness Scale (ESS) and Sleep Quality Profile (SQP) in an outpatient hepatitis C patient population.

Methods: Psychometric testing was preformed on the ESS and the SQP questionnaires. The ESS is composed of an 8 item 4 point Likert scale (response range 0-3) designed to measure daytime sleepiness. Ranges of total scores is 0 to 24 with scores > 10 indicating significant daytime sleepiness, and scores > 16 indicating extreme daytime sleepiness. The SQP is composed of a 10 item dichotomous scale designed to identify symptoms of noctural sleep distrubance. Internal consistency was tested using Cronbach's alpha and Kudor-Richardson alpha, respectively. Construct validity was tested through principle component factoring with varimax rotation to examine the underlying dimensions of the ESS and the SQP.

Results: Fifty-three (53) chronic HCV patients with compensated liver disease and no uncontrolled concomitant illnesses, currently receiving INFα-2b plus ribavirin, were evaluated using the ESS and SQP questionaires. The sample was obtained at The Texas Liver Center, a university affiliated outpatient facility. The questionaires were administered to participants in a private room in the clinic prior to the clinic visit. For the ESS, two factors with eigen values > 1.0 emerged: daytime sleepiness and excessive daytime sleepiness. This is not the same result obtained in studies using other populations. Items which loaded above 0.40, and distinctly loaded on a single factor, were included in the reliability analysis. Theoretically, the ESS measures a single concept of daytime sleepiness without subscales. The internal consistency, estimated by Cronbach's alpha for 8 items was 0.83. For the SQP, three factors with eigen value > 1 emerged: sleep-associated limb movements, sleep-disordered breathing, and insomnia. Items which loaded above 0.40, and distinctly loaded on a single factor, were included in the reliability analysis. All of the items were distinctive in their loadings. Theoretically, the instrument is measuring a single concept of disturbed sleep. The internal consistency, estimated by Kudor-Richardson, for the 8 items was 0.80.

Conclusions: The ESS and SQP are reliable and valid instruments in screening for daytime sleepiness and noctural sleep disorders in the hepatitis C population receiving INFα-2b plus ribavirin. Future research should investigate the construct validity, sensitivity and specificity of these questionnaires.

1352.N

Relative Importance of Position, Location, and Activity Interest Level on Self-reported Sleepiness

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Introduction: Epworth Sleepiness Scale (ESS) is currently the most widely used questionnaire for evaluating self-reported sleepiness. However, ESS does not differentially evaluate effect of activity interest level (interesting vs. boring), position (standing, sitting, laying down), or location (public vs. private place) on self-reported sleepiness. It is generally thought that such factors should make a difference with respect to whether a person might inadvertently doze. To our knowledge, systematic data are not available; therefore, we conducted a survey to assess effect of these factors on sleepiness.

Methods: We constructed a questionnaire (Daytime Sleepiness Questionnaire-DSQ) to assess sleepiness. Respondents are asked to estimate the probability of falling sleep in different situations, to indicate if they have fallen asleep in such situations, and how often such events occur. Each situation presents an activity differing with respect to interest level, position, and location. A total of 42 situations were presented. For the present analysis, we considered only data from Epworth-like questions ["how likely are you to doze off while…?"] for a select number of activities. 53 control subjects from the general population and 53 patients with sleep-disordered breathing completed the DSQ and ESS.

Results: The table below shows the relative importance of position, location, and activity interest level on self-reported sleepiness in normal controls and patients with OSA. The following notation was used: (positions) L- Lying down, S- Sitting, St- Standing; (location) Pr- Private, Pu- Public; (activity interest level) B- Boring, I- Interesting; * Significantly different (P<0.05); # Marginally different (P<0.1).

Table 1

Activity	Normal	OSA
Watching	BL*>BS*>IL*>IS	BL#>BS*>IL>IS
Reading	BL*>BSPr*>IL*>ISPr*>BSPu>ISPu	LB>BSPr*>IL>ISPr#>BSPu*>ISPu
Thinking	L*>SPr*>SPu	L#>SPr*>Spu
Listening	BL*>BSPr*>BSPu>IL>ISPr*>ISPu	BL>BSPr*> IL*>ISPr> BSPu*>ISPu
Eating	Pr*>Pu	Pr*>Pu
Waiting	Pr*>Pu*>PuI	Pr*>Pu*>PuI
Doing nothing	S*>St	S*>St

Conclusions: This data indicate that activity interest level, position, and location differentially affect self-reported sleepiness. Interestingly, patients with OSA had less consistent results; however, the same general profiles were found. Thus, subtle differences that under normal circumstances affect self-reported sleepiness are less relevant to the sleepy individual. Activity interest level was consistently the primary factor, while position and location show weaker influences. It is likely that these effects are mediated through change in sympathetic nervous system activity. Postural change, internal stimuli, and external stimuli are known to alter autonomic balance; thereby, changing the estimated probability of dozing.

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1354.N

A Comparison of Wrist Actigraphy with Polysomnography as an Instrument of Sleep Detection in Elderly Persons

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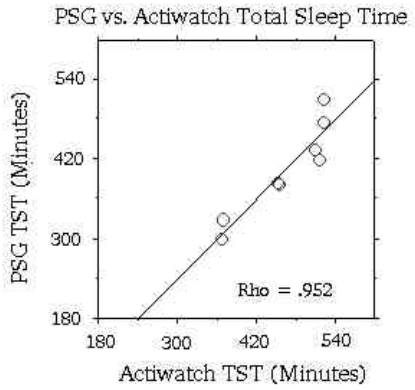
Introduction: Methods for detecting and recording the sleep/wake cycle in humans are limited. Polysomnography (PSG)-long considered the gold standard-provides detailed information on sleep, but is not suitable for nightly long-term studies. Wrist actigraphy is a low cost, non-invasive, and unobtrusive alternative to PSG, but its accuracy has not been extensively validated in healthy seniors and those with neurodegenerative diseases. We report initial results of a study comparing actigraphy with PSG for determining sleep times in eight healthy elderly subjects (mean age = 74.5).

Methods: Data were collected over a three-night period using the MiniMitter Actiwatch (AW64 series) employing a digital integration method and Sandman Dos version 2.4 for PSG.[1] The two measures were performed simultaneously for 11-hours over three separate nights in the Clinical Research Center at OHSU. An experienced sleep technician, utilizing a 12-channel montage, performed PSG. PSG was scored using the standard R&K scoring criteria. The sleep technician was blind to actigraphy scored sleep. Actiwatches and PSG equipment were synchronized prior to data collection to maximize epoch-by-epoch analyses. Two Actiwatches were placed on the subjects non-dominant wrist. Agreement rates and Spearman's rank correlation coefficients were determined for total sleep time (TST), wake after sleep onset (WASO), and sleep onset latency (SOL) employing three different sensitivity settings provided by the Actiware-Sleep application.

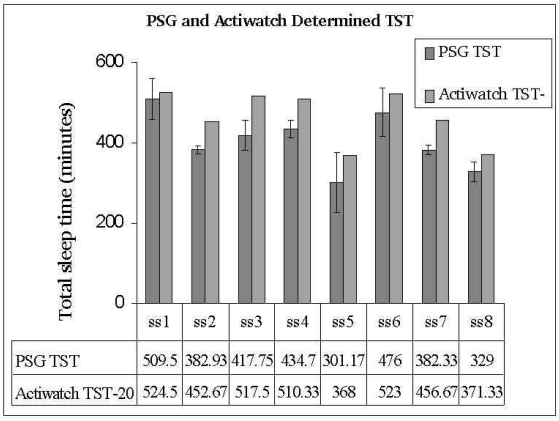
Results: At the "high sensitivity" setting we found an agreement rate of .84 for all nights, and a Spearman's rank correlation coefficient of .952, ($p<.0117$) comparing the means of 3 nights (Fig.1.) The average overestimation of TST by actigraphy was 61.32 minutes (Fig.2.).

Figure 1



Conclusions: This study found PSG/actigraphy correlations similar to those found in previous studies[2]. Actigraphy determined sleep consistently demonstrated good correlation with PSG determined sleep, and fair correlation when comparing PSG wake determination to actigraphic wake determination. Actigraphic overestimation of sleep occurred in all subjects. The Actiware-Sleep application defaults to a "medium sensitivity" setting, which defines the threshold for sleep/wake determination. In our sampling, a higher sensitivity, i.e. lower activity-count threshold for the determination of wakefulness, resulted in greater accuracy and no significant change in Spearman's rank correlation.

Figure 2



	ss1	ss2	ss3	ss4	ss5	ss6	ss7	ss8
PSG TST	509.5	382.93	417.75	434.7	301.17	476	382.33	329
Actiwatch TST-20	524.5	452.67	517.5	510.33	368	523	456.67	371.33

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1365.N

Very High Frequency Energy (Kappa) in Human Surface EEG: Correlation with Behavioral State

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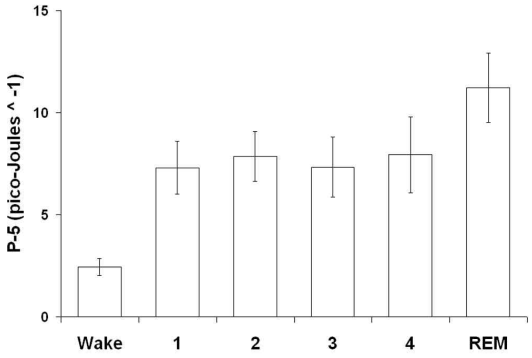
Introduction: While traditional approaches to EEG frequency analysis have excluded the domain above 50 Hz, recent data suggest these frequencies contain important physiologic information. First, EEG from implanted grids in seizure patients showed that a signal in the 100-150Hz range presaged the onset of seizures.[1] Second, Nakata et al demonstrated a correlation between sleep state and the parameters of a double Lorentzian fit of the EEG spectrum above 100 Hz.[2] Finally, two of us (RFK, KAL) demonstrated that specific components of the high frequency EEG signal (80-1kHz; "kappa" band) showed consistent changes that correlated with transient sleep episodes in normal subjects.[3] The current work is intended to extend the latter finding to evaluate 1) the relationship between frequency bands within kappa and normal sleep states; 2) the anatomic dependence of signal content in the kappa band; and 3) the relationship between kappa and traditional EEG frequency bands.

Methods: Eight normal subjects, aged 18-40, were recorded overnight using standard polysomnographic techniques. Six EEG derivations were recorded (F3,F4,C3,C4,O1,O2) along with EOG and EMG (Heritage PSG and Model 15; Grass Instrument Div., Astro-Med. Inc., W. Warwick, RI). The EEG signals were also recorded in parallel using wide-band amplification (20-50KX, LF=0.3Hz, HF=1kHz) and 3kHz/channel sampling frequency for calculation of the P-5 algorithm (3) and the conventional EEG bands. P-5 tracks the changes in energy for sub-bands of kappa empirically identified by their sensitivity to changes in behavioral state (3). P-5 was computed with 6561 data points

and a 50% data overlap (1.09-sec. steps). Conventional EEG spectral bands examined were: delta (0.5-2.0), delta2 (0.5-4.0), theta (5.0-7.0), alpha (8.0-12.0), sigma (12.0-14.0), total (0.5-30.0).

Results: P-5 correlates with sleep state, with lowest levels during wakefulness and a sharp increase that reliably correlates with polysomnographic sleep onset (Fig.1). Average levels were stable within all stages of NREM sleep. A second sharp increase in P-5 occurs with REM. Transient arousals seen in the polysomnogram were reliably associated with corresponding decreases in P-5. There was no statistically significant dependence of P-5 on EEG derivation. Small differences were seen among specific derivations and between left and right hemispheres, but the amplitude and direction of these varied with subject and between successive sleep cycles in the same recording. There were no significant correlations between P-5 and conventional frequency bands.

Figure 1. P-5 as a function of sleep state in normals (N=8)



Conclusions: These data demonstrate that high frequency EEG correlates with neurophysiologic changes associated with behavioral state. While the origins of this component of the EEG spectrum are not known, some possibilities can be excluded. The previous recording of high frequency activity from depth electrodes is inconsistent with an EMG origin. Further, P-5 is distinct from the traditional frequency bands. Finally, the absence of anatomic localization suggests that the source of kappa is either centrally located in the neuroaxis, or diffuse in origin. Studies examining the origin of kappa activity in animals are currently underway.

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1367.N

Transient Arousal: Frequency and Duration in All Sleep Stages

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Introduction: Arousals, induced by endogenous or exogenous stimuli, are among the many events that are observed in polysomnograms. Although many of these arousals are associated with respiratory events and body movements, some appear to be spontaneous, that is, a normal physiological feature of sleep. Characteristics of transient EEG arousals have been examined and definitions proposed (Atlas Task Force, 1992). The purpose of this study was to describe specific parameters for transient arousal identification, to examine the distribution of the arousals among sleep stages in adults, and to introduce another variable, the arousal fraction (AF), that could add to a more complete explanation of the impact of arousals on sleep quality and continuity.

Methods: EEG (C4-A1) and submental EMG recordings were obtained from 20 adults (13 males, 7 females) between 25 and 46 years of age. Subjects had been referred to a sleep disorders center, but after all night polysomnography, were without significant sleep apnea (AHI <=5.0) or periodic limb movements in sleep (PLMS index <=0.2). All had a total sleep time (TST) of >300 minutes. Subjects were free from medical conditions and medications that could alter EEG characteristics. Both EEG and EMG were sampled at 100 Hz using a SensorMedics 4100 computer-assisted data acquisition and analysis system interfaced with Grass amplifiers. The Atlas Task Force (1992) transient arousal criteria were adopted with the modification that arousals of >15 seconds duration were excluded. To maximize the visualization of the EEG frequency changes on the computer monitor, only C4-A1 and EMG were displayed for scoring within each 30 second sleep epoch. Sleep stages had been scored previously and arousals were not scored if they began in an epoch scored as awake. After a joint training period, two scorers independently identified arousal presence by epoch number, start time from the beginning of the epoch in seconds and duration in seconds. Inter-rater reliability was calculated (kappa), butonly those arousals identified by both scorers were included in subsequent analyses. A transient arousal index (TAI) was calculated as the number of arousals divided by total sleep time (TST) x 60. In addition, the AF was computed as the sum of arousal durations in minutesdivided by TST. The total arousal duration was averaged over subjects and normalized to the average TST x 100. The TAI and AF also were computed for each sleep stage. Finally, these two variables were normalized over all subjects, that is, the average amount of arousal time in each sleep stage was divided by the total time in each sleep stage x 100.

Results: Inter-rater reliability was 0.48 which falls within the moderate range of kappa. The average arousal frequency was 19 (range= 3 to 30) and the average TAI was 3 per hour of TST (range= 0.6 to 4.8). By sleep stage, the average arousal frequencies were: Stage 1 (4.1), Stage 2 (13.0), Stage 3/4 (3.0) and Stage REM (4.8). The average arousal duration was 7.5 seconds (range= 5.5 to 10.4). Average durations (in seconds)for each sleep stage were : Stage 1 (7.5), Stage 2 (7.8), Stage3/4 (6.0), and Stage REM (7.6). The highest percentage of arousal time was observed in Stage 2 sleep (55%), followed by Stage REM (20%) and Stage 1 (20%), then Stages 3/4 (5%). After normalization, the largest AF shifted to Stage 1 (35%), followed by Stage REM (24%), Stage 2 (23%) and lastly, Stages 3/4 (18%).

Conclusions: Visual scoring that incorporated a maximum duration and restricted arousals analyzed to those identified by both scorers yielded an average that was lower than arousal indexes reported in previous studies. This difference may be accounted for by (a) the exclusion from this study of scorable respiratory events and PLMS which are known to evoke arousals, (b) limiting the duration of the arousal to 15 seconds and (c) events selected from data with a reliability (kappa) in the moderate range. Average arousal durations were consistently close to 7.5 sec except for Stages 3/4. As with the number of arousals the average duration is shorter than that reported by others. A larger sample should be examined to determine if these findings are an artifact of the methodology or reflections of real physiologic phenomenon. The use of a normalization technique and incorporation of arousals in epochs scored as Stage 1, provided a new distribution of AF that appears physiologically reasonable. The clinical significance of this finding compared to disruptions of other sleep stages requires confirmation. AF is proposed as a

measure of sleep time displaced by transient arousals. Further analyses are needed to determine if total arousal time (AF), and the duration of arousal in specific sleep stages, correlate more highly with complaints of sleep fragmentation and sleepiness than the frequency of occurrence alone.

1071.N

A Comparison of Two Screening Methods for Obstructive Sleep Apnea: EdenTrace vs Pulsox-M24

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Introduction: Polysomnography (PSG) is considered to be the gold standard for the diagnosis of obstructive sleep apnea (OSA). However, it is expensive, and its availability is still limited in Japan. There is a need for a simple and low cost screening method. Two methods of screening for OSA are available at our hospital: limited-data PSG and pulse oximetry. We assessed the validity of these screening methods when compared against PSG.

Methods: We retrospectively reviewed the records of patients in whom both limited-data PSG and standard PSG were performed or both pulse oximetry and standard PSG were performed. One hundred forty-three patients underwent standard PSG between September 1998 and September 1999. Of these, 52 were also examined with limited-data PSG (Mallinckrodt Inc., St. Louis, MO) and 35 with pulse oximetry (Pulsox-M24, Teijin Ltd., Tokyo, Japan). We utilized these data to calculate the correlation coefficient, sensitivity and specificity against standard PSG. PSG data were collected on an Alice 3 system (Respironics Inc., Pittsburgh, PA) and scored manually by a single PSG technician. Sleep apnea was diagnosed for respiratory disturbance index (RDI)>5. The EdenTrace data was automatically processed with EdenTrace Analysis Software to obtain the RDI. Using the data from the Pulsox-M24, oxygen desaturation index for 2% of threshold (ODI2) was automatically computed with DS-M software. RDI from the EdenTrace (hereafter RDIe) and ODI2 from the Pulsox-M24 were utilized for further analysis.

Table 1. Patient Characteristics

	EdenTrace	Pulsox-M24	P-value
No. of patients	52	35	
Male/female ratio	40 : 12	28 : 7	0.73
Age (mean±SD) [yrs]	61.1±10.1	60.9±13.0	0.94
Apneic/normal ratio	46 : 6	32 : 3	0.66
RDI (mean±SD)[#/h]	23.6±18.8	20.2±17.1	0.40

Table 2. Diagnostic Accuracy

Method	Cut-off	TP/FN	FP/TN	Sens.(%)	Spec.(%)
EdenTrace	5	43/3	4/2	93.4	33.4
(RDIe)	10	41/5	1/5	89.1	83.4
	15	32/14	1/5	69.6	83.4
Pulsox-M24	5	28/4	0/3	87.5	100
(ODI2)	10	26/6	0/3	81.2	100
	15	21/11	0/3	65.7	100

Sens.: sensitivity, Spec.: specificity, TP: true positive,
FN: false negative, FP: false positive, TN: true negative

Results: Table 1 shows patient characteristics. Statistical analysis showed no significant difference in age, gender, severity of OSA, and proportion of PSG diagnosed apneics between the groups. Regression analysis achieved a correlation coefficient of 0.654 ($p<0.0001$) between RDIe and RDI, and 0.762 ($p<0.0001$) between ODI2 and RDI. Table 2 shows the diagnostic sensitivity and specificity of each method using three different cut-off values.

Conclusions: The results of our study suggest that both methods have nearly equal sensitivity around 90% and that the Pulsox-M24 can provide higher specificity than the EdenTrace. Furthermore, the Pulsox-M24 has several merits. It is as small as a watch, low cost (under $2,000), is easily used at home by oneself, can collect data for up to 24 hours. The Pulsox-M24 could be a convenient screening tool for OSA and especially useful in the primary care or general practice setting.

1405.N

Evaluation of a Vestibular In-line Pressure System (VIPS) Using Magnetic Resonance Imaging.

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Introduction: We have been investigating applying CPAP orally to treat OSAS and felt that it might be useful to confirm beneficial effects on upper airway dimensions. This study reports an analysis on awake patients with OSAS comparing different breathing routes with and without CPAP using magnetic resonance imaging (MRI).

Methods: The upper airways of four patients with OSAS (with RDI's > 15) were scanned using a Siemens Vision 1.5T MRI in the awake state, supine, during four different breathing methods: nasal breathing, nCPAP (using the patients' choice of nasal mask), oral breathing and oCPAP with VIPS. CPAP pressure in both cases was 10cm H20. 2DFLASH imaging (30 second scan acquisition) was used in the axial plane. The minimum airway diameter (MAD) was measured by two experienced technicians blinded to the method of breathing each on two occasions and the inter-observer variability recorded. The oCPAP VIPS system used is described elsewhere.[1]

Results: MAD was much larger using the oral versus nasal routes with and without positive airway pressure. Comparing oCPAP with nCPAP each patient achieved the following increases in MAD: 329%, 414%, 580% and 680%. Inter-observer variability was low $p = 0.23$ (two-tail t test

Conclusions: Our initial experience suggests that oCPAP with VIPS enlarges the MAD in awake patients with OSAS. MRI of the upper airway offers great utility in assessing the impact of different airway systems with reliable results.

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1414.N

Dysfunctional Beliefs and Attitudes about Sleep Questionnaire: Preliminary Factor Analysis

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Introduction: Insomniacs tend to hold catastrophising and dysfunctional beliefs about the adverse effects of insomnia on daytime functioning.[1] Morin et al[2] believe that many people with insomnia hold faulty beliefs, unrealistic expectations, and misattributions about sleep, and may catastrophise and exaggerate the negative consequences of sleep loss on daytime functioning. These dysfunctional beliefs may exacerbate sleeping difficulties by heightening emotional pre-sleep arousal. The Dysfunctional Beliefs about Sleep Questionnaire (DBAS)[3] was designed to examine the beliefs and attitudes about sleep of insomniacs. The present questionnaire has 30 items which Morin suggests cover five themes:[2] 1. Consequences of insomnia; 2. Control and predictability of sleep; 3. Sleep requirement expectations; 4.Causal attributions of insomnia; and 5. Sleep-promoting practices. However, as yet, no factor analysis of the questionnaire has been undertaken. The present paper is a report of an exploratory factor analysis.

Methods: The DBAS was administered to 543 poor sleepers at three sites: 257 insomniacs participating in a research project or attending an insomnia clinic (Wright & Lack; Adelaide, Australia); 153 clients attending an insomnia clinic (Morin; Richmond,Virginia); 133 insomniacs participating in a research project (Edinger; Durham, North Carolina). The mean age was 44.8 yrs (range 14 to 88 yrs).

Results: The 30 items of the DBAS were subjected to a principal component analysis and a varimax rotation. Five principal components (factors) were extracted, each with eigenvalues greater than 1.0, and together accounted for 42.4% of the variance. The first factor (20.1% variance accounted) comprised eight loaded (>.50) items related to the adverse consequences of poor sleep on daytime functioning. The second factor (6.9%) comprised nine items but only two high loadings (>.50) relating to unpredictability of sleep. Factor 3 (6.3%) comprised five items with four high loadings relating to poor sleep practices. Factor 4 (4.7%) comprised six items with only two high loadings relating to the need for medication as the only solution to insomnia. Factor 5 (4.4%) had only two items both with low loadings (<.50) and could not be characterised.

Conclusions: Factor 1 corresponds closely with Morin's[2] Theme 1. The highest loaded items of Factor 2 correspond to Morin's Theme 2. Factor 3 corresponds to Theme 5. Factor 4 also appears to be included in Theme 5. The two items of Factor 5 were included in Themes 2 and 5. These results suggest the need for a confirmatory factor analysis to test these apparent relationships more precisely. In any case, this initial factor analysis seems to be a promising first step for the development of a revised DBAS.

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1095.N

The Sensitivity and Specificity of the Sleep Assessment Questionnaire© (SAQ©) in the Identification of Patients with Insomnia, Restless Legs Syndrome/Periodic Limb Movement Disorder, and Narcolepsy/Idiopathic Hypersomnia

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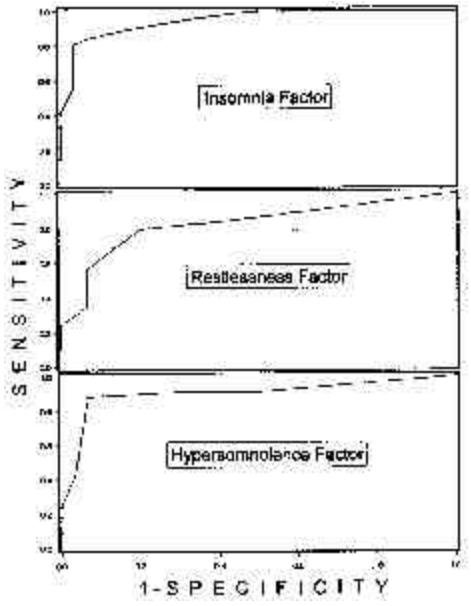
Introduction: The 17 item Sleep Assessment Questionnaire (SAQ©) has been shown to have favourable sensitivity and specificity in differentiating patients with sleep apnea,[1] and fibromayalgia/chronic fatigue[2] from healthy controls. The purpose of this study was to assess the utility of three additional SAQ© factors, i.e. "insomnia", "restlessness", and "hypersomnolence", in identifying respective patient groups with psychophysiological/ idiopathic insomnia, restless legs/sleep-related periodic limb movement disorder, and narcolepsy/idiopathic hypersomnia.

Methods: From a database of 3000 patients with sleep/wake related disorders who completed the SAQ©, and were diagnosed clinically and by polysomnography, 46 patients had psychophysiological or idiopathic insomnia (30 females, 16 males, mean age = 40.5 ± 11.8), 48 patients had periodic limb movement disorder or restless legs syndrome RLS/PLMS (24 females, 24 males, mean age = 52.3 ± 13.2), and 33 patients had narcolepsy or idiopathic hypersomnolence (20 females, 13 males, mean age = 31.36 ± 16.31). None of these patient groups had any other identifiable sleep-related disorder according to ICSD (revised 1997). The sensitivity and specificity of the "insomnia", "restlessness", and "hypersomnia" factors were calculated by comparing the SAQ© "insomnia" "restlessness"and "hypersomnia" factor scores of the respective patient groups to those of 30 healthy controls who had no sleep-related disorder (10 females, 20 males, mean age = 31.9 ± 9.6). The sensitivities and specificities of each of the factors were plotted in receiver operating characteristic curves (ROCs).

Results: The three ROC curves are displayed in Figure 1. The ROC curve of the SAQ© Insomnia Factor shows optimal sensitivity of 82.6% and specificity of 93.3%. The ROC curve of the Restlessness Factor shows optimal sensitivity of 80% and specificity of 79.2%. The ROC curve of the Hypersomnia Factor shows optimal sensitivity of 87.9% and specificity of 93.3%.

Figure 1



POSTER PRESENTATIONS

Conclusions: The Sleep Assessment Questionnaire© differentiates psychophysiologic/idiopathic insomnia patients, RLS/PLMS patients, and narcoleptic/idiopathic hypersomnia patients from healthy individuals. These results suggest that the SAQ© is a useful instrument for screening not only individuals with sleep apnea, fibromyalgia/chronic fatigue syndrome, but also those with psychophysiologic/idiopathic insomnia, RLS/PLMS, and narcoleptic/idiopathic hypersomnia.

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1430.N

Accuracy of a Nasal Cannula/Pressure Transducer System Versus Nasal Thermistor for the Detection of Respiratory Events During Overnight Polysomnography

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Introduction: The measurement of airflow during polysomnography is essential for the diagnosis of sleep related breathing disorders. The most prevalent technology utilizes a nasal thermistor to detect changes in airflow. More recently, pressure transducers attached to nasal cannulae have been used to detect respiratory events during sleep. The potential advantages of this latter system include possible lower cost, hygiene, and enhanced ability to detect the presence of upper airway resistance syndrome (UARS). We conducted a prospective trial to assess the accuracy of the nasal cannula/transducer system in detecting respiratory events compared to the nasal thermistor.

Methods: Seven patients (5 male, 2 female) with a mean age of 49 (range 30-71) were randomly assigned to have their airflows simultaneously measured by a nasal thermistor and the cannula/pressure transducer system during overnight polysomnography. All polysomnograms were manually scored. The data from the thermistors and the cannula/pressure transducer were evaluated separately. Hypopneas were defined as a; 50% < 90% reduction in airflow signal amplitude lasting > ten seconds. Apneas were defined as a; 90% reduction in airflow signal amplitude lasting > ten seconds.

Results: There were no significant differences between the Apnea-Hypopnea Indices, Apnea Indices, Hypopnea Indices, and the total number of respiratory events measured by the two systems. The data were analyzed using the mean difference (± SD) between the two systems for each measured variable. The mean difference (± SD) between the Apnea-Hypopnea Indices was 1.52(± 7.74) p= 0.3.* The mean difference (± SD) between the Apnea Indices was 0.9 (± 25.5) p= 0.9 # The mean difference (± SD) between the Hypopnea Indices was 0.59 (± 19.4) p= 0.9.# The mean difference (± SD) between the total number of recorded respiratory events (apneas plus hypopneas) was 3.57(± 31.2) p=0.30.* *p values based on Wilcoxon's signed rank test. #p values based on paired t-test.

Conclusions: There were no significant differences between the Apnea-Hypopnea Indices, Apnea Indices, Hypopnea Indices, or the total number of respiratory events measured by the nasal cannula/pressure transducer system compared to the more standard nasal thermistor. These results suggest that the nasal cannula/pressure transducer system is as accurate as the nasal thermistor at detecting respiratory events during sleep. This study is limited by the small sample size. We are planning to enroll additional patients in the study.

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1765.N

Actigraphic Assessment of Sleep in Depressed Patients

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Introduction: Although actigraphy has been used to measure sleep patterns of depressed patients, its validity has not been systematically tested against polysomnography (PSG) in individuals with major depression. This study assessed the validity of scoring criteria of the Actigraph Data Analysis Software (ADAS), in estimating sleep from wrist-activity data of depressed patients. In addition, we examined whether new criteria could be developed to characterize optimally sleep and wakefulness patterns of those patients.

Methods: Twenty-four patients (mean age = 45, SD = 9, men = 17, women = 7) were recruited from on-going polysomnographic sleep studies of individuals who met diagnostic criteria for a current Major Depressive Episode. Individuals were scheduled for two consecutive nocturnal PSG recordings performed at the sleep laboratory, San Diego Veteran Administration Medical Center. PSG recordings were performed using standard recording montage including two electroencephalographic channels (C3-A2, C4-A1), two electrooculographic channels (ROC-A1, LOC-A2), and one electromyographic channel (Submentalis). PSG records were scored manually by trained technicians according to standard criteria. Volunteers also wore a wrist actigraph concomitantly to measure wrist activity. Activity data from these monitors represented wrist movement translated into an electric signal through a piezoelectric sensor. Supra-threshold accelerations (> 0.1 g) were band-pass filtered (i.e., 0.25-3.00 Hz) over 60-second epochs and were stored into memory until downloaded into a computer.

Results: Actigraphic data were scored with ADAS, providing general actigraphic variables including total sleep time (TST) and sleep efficiency (SE). Actigraphic data for all volunteers were first scored with the normative criteria (i.e., actigraphic sleep threshold [AST] = 10 counts and wake interval post arousal [WIPA] = 3 minutes) along with an initial sleep onset criterion of 15 minutes of consecutive activity counts below the AST. Application of those criteria to the present sample grossly overestimated sleep, mostly noted among patients with severe sleep disturbances. We then examined whether optimal criteria could be developed to score actigraphic data of depressed patients. In that analysis, the sample was subdivided and cases were randomly assigned to a calibration sample (n = 12) or a validation sample (n = 12). Analysis indicated that optimal criteria for depressed patients were AST =1 count and WIPA = 3 minutes. Application of the previous algorithm yielded a correlation coefficient of 0.85 and an error of 35 min, whereas the optimized algorithm for this sample yielded a correlation coefficient of 0.81 and an average error of 6 minutes.

Conclusions: Our results suggest that different scoring criteria may be optimal for different samples or wrist-activity monitors of different design characteristics. It is plausible that the sensitivity of the monitors used in our study may not be optimal for detecting subtle movement that might indicate nocturnal arousals in depressives who lie still in bed while awake. It is of interest to examine whether a different sampling rate or activity summation interval (e.g., second-by-second) might yield a more representative activity profile.

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1119.N

Comparison of the Maintenance of Wakefulness Test to a behavioral test - the Oxford Sleep Resistance (OSLER) Test in the evaluation of wakefulness.

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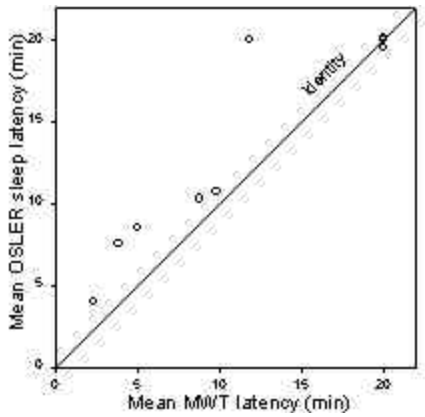
Introduction: The Maintenance of Wakefulness Test (MWT) quantifies the ability to remain awake during soporific circumstances. Because of continuous EEG monitoring this test is labor intensive and costly. The OSLER test,[1] which is based on computerized monitoring of patients' behavioral response to a flashing light, has been proposed as a replacement for the MWT. The present study compares the OSLER test to the standard MWT. We also compared the onset of sleep defined by non-response in the OSLER to onset of sleep based on simultaneous EEG.

Methods: Thirteen patients (11 OSAS, 2 Narcolepsy) were studied during the day following nocturnal polysomnography. The testing protocol consisted of three sessions two hours apart beginning 2 hours after awakening. During each session (patient recumbent in a dimly lit room), a standard MWT nap and an OSLER test were performed in alternating order. Tests were separated by 5 minutes and had maximum duration of 20 minutes each. EEG sleep onset was defined by the appearance of 15 consecutive seconds of unequivocal sleep, irrespective of epoch placement. During the OSLER test simultaneous EEG monitoring allowed the onset of sleep to be determined as during the MWT. The task in the OSLER test consisted of responding to a light stimulus every 3 seconds (removing the dominant-hand index finger from a switch). OSLER test sleep onset was defined as occurring after 7 consecutive missed responses. Both MWT and OSLER test were terminated after EEG defined sleep onset. Time from lights out to sleep onset was measured to determine the latency to sleep in each test

Results: Three comparisons were made between EEG sleep latency and the behavioral test. Although trending to be slightly longer, mean OSLER sleep latency (non-EEG) was not significantly different from mean MWT EEG sleep latency (bias=1.7 min, 95%CI=-0.01to 3.46, r=0.94, see Figure). Within sessions, measurements of sleep latency showed a slightly longer sleep latency during OSLER than during MWT (bias=1.71 min, 95%CI=0.43 to 2.99 r= 0.88). Agreement of sleep latency by OSLER and simultaneous measurement of EEG sleep latency was also good for each nap (bias=-0.97 min, 95%CI= -2.62 to 0.22 r= 0.91). During sequential naps there was no obvious systematic adaptation or learning effect seen in the OSLER performance.

Figure 1



Conclusions: Our data suggest that the OSLER test is a useful surrogate for direct EEG measurement of sleep latency, and could be used in place of the MWT to evaluate daytime wakefulness. The tendency of the OSLER test to measure a slightly longer sleep latency may be secondary to the associated cognitive and motor activity, but a minor modification of cut-off values for normal may compensate for this.

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1127.N

Movement Artifact in Oximetry Recordings During Sleep/Wake States in Neonates

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Introduction: In a previous study (Montgomery-Downs et al 1998), we found that slower Quiet Sleep respiratory rates through the first six postnatal months were related to higher mental development scores assessed at six months and one year. As a follow-up study, we are using pulse oximetry to investigate the relationship between blood oxygenation (SpO2) and respiration rate. However, the use of pulse oximetry for the study of neonates has been challenged as producing an unacceptably high proportion of movement artifact (Fletcher et al 1998). For this preliminary report, we recorded the sleep states and wakefulness in infants simultaneously with oximetry recording and analyzed the proportion of SpO2 data with movement artifact in each state.

Methods: Twelve healthy, fullterm infants born at a local community hospital participated in the study. Synchronized sleep/wake state and SpO2 recordings were made during the nighttime in the hospital on the second postnatal day and then in the home at 2 weeks and 6 weeks. Sleep was recorded using the Motility Monitoring System (MMS) (Thoman et al 1987). Oxygenation was measured using Mallinckrodt's NPB-295 pulse oximeter averaging over 2-seconds and recorded in real time on a laptop computer. Each 2-second epoch during which movement interfered with the pulse waveform was marked by the oximeter. One Day 2 recording was lost due to equipment failure. The average recording duration was 7.4 (SD±1.4) hours during Day 2, 5.6 (SD±3.0) hours during Week 2, and 7.2 (SD±1.8) hours during Week 6. The states of

Sleep/Wake Transition, Active/Quiet Sleep Transition, Arousals in Active Sleep and Arousals in Quiet Sleep were combined as Indeterminate Sleep for comparison purposes.

Results: The percentage of data obstructed by movement in each state was 58.7% in Wake (W), 15.4% in Active Sleep (AS), 9.9% in Quiet Sleep (QS), and 37.1% in Indeterminate Sleep (IS) for Day 2; 54.3% in W, 8.1% in AS, 2.2% in QS, and 28.2% in IS for Week 2; 47.9% in W, 6.3% in AS, 0.8% in QS, and 15.4% in IS for Week 6.

Conclusions: Using the MMS and an oximeter that signals artifact, subject movement obliterates markedly less SpO2 data than previously reported for healthy, fullterm neonates. Thus, pulse oximetry is appropriate for use in our study that will address hypotheses about baseline SpO2 differences in healthy, fullterm infants and their implications for mental development.

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1148.N

Impact of Alpha EEG Activity on Various Sleep Parameters

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Introduction: Alpha rhythm is a normal EEG finding in adults who are in a state of quiet alertness, with their eyes closed. This 8-13 Hz activity is synchronous, uniform and symmetrical in regard to hemispheric distribution. Notwithstanding, intrusions of alpha activity into different sleep stages, and into slow-wave sleep in particular, are indicative of poor sleep quality, and related to a number of musculo-skeletal syndromes, including fibromyalgia. In this group of disorders alpha EEG activity "over-rides" normal sleep EEG. Most of the studies report associated increase in amount of stage 1 in total sleep time and a decrease in total amount of SWS – the later is still somewhat controversial. The purpose of our study was to determine at what point the alpha EEG activity becomes "increased" or "raised". Normally, the level of alpha EEG activity is scored visually, using a simple five-point scale, where score of "1" describes 0-20% intrusion of alpha rhythm into NREM sleep, score of "2" 20-40% intrusion, and so on. The recommendation1 was that alpha EEG activity should be reported, without establishing whether it is increased or not. Indeed, it is more difficult to establish where is a point when amount of alpha EEG activity becomes excessive, or disruptive in regard to sleep quality.

Methods: Using the premise that clinically significant increase in alpha activity manifests itself through decrease of restorative phase of sleep (SWS) and increase of non-restorative phase of sleep (stage 1), we tried to correlate various sleep parameters and amount of alpha EEG intrusion. We analyzed 254 randomly chosen sleep records; alpha EEG was visually scored using half-point system (1.5, 2, 2.5 etc.) to ensure higher level of accuracy. Sleep parameters analyzed were sleep efficiency, percentages of sleep stages in TST, percentage of intervening wakefulness, sleep latency and REM latency.

Results: Our results show that score of "2" presents a clear cut-off value for (clinically) significant increase in alpha EEG activity. Alpha intrusion of >40% should be considered as abnormal. At that point there is a significant increase in non-restorative phase of sleep, and significant decrease in restorative phase of sleep. Conversely, the alpha activity of 0-40% (score 2*) should be considered as normal. There was a trend towards decreased amount of SWS (stage 3) in patients who had alpha score higher than 2. Further efforts to establish clinically relevant cut-off value for raised alpha EEG activity should include analysis of more of the relevant sleep parameters (i.e. arousal index, stage shift index, sleep quality questionnaires). The essence of the study is presented in Table 1.

Table 1. Variability of stages 1 and 3 percentage in different alpha EEG subgroups

Sleep variable	Normal	Abnormal	p
Alpha1/stage1	6.07± 3.13	7.73±3.96	0.022*
Alpha1/stage3	8.0±6.64	5.84±3.12	0.12
Alpha1.5/stage1	5.88±2.84	8.03±4.03	0.000002*
Alpha1.5/stage3	7.16±5.10	5.74±3.10	0.06
Alpha2/stage1	6.99±3.28	8.3±5.49	0.01*
Alpha2/stage3	6.48±4.12	5.5±2.86	0.026*
Alpha2.5/stage1	7.52±3.83	7.68±4.1	0.676
Alpha2.5/stage3	6.19±3.91	5.74±2.96	0.318
Alpha3/stage1	7.35±3.69	8.83±4.86	0.083
Alpha3/stage3	6.14±3.69	5.5±3.4	0.296

* statistically significant differences

Conclusions: Using the commonly measured sleep parameters we were able to determine that the cut-off value for raised alpha EEG activity is score of "2" or 40% of alpha EEG intrusion.

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1813.N

"Polysomnographic Assay": A New Technique Detects Commonly Missed Cheyne-Stokes Respiration, Central Apneas, and even "Central" Hypopneas.

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Introduction: Cheyne-Stokes respiration (CSR) is characterized by periodic, gradual rises and falls in tidal volume and respiratory frequency every 30 to 120 sec with central apneas. It occurs normally in stages 1 & 2 sleep, and in many diseases, e.g. congestive heart failure. It may cause frequent arousals, hypoxemia, and EDS. CSR is often overlooked during routine scoring of PSG at customary display of 30 sec/screen because the slow periodicity (>30 sec/cycle) makes it difficult to appreciate. Central apneas are often misscored as obstructive or mixed. Hypopneas are often mistakenly assumed to be obstructive. We have developed a new display format — "Polysomnographic Assay (PSGA)" — to facilitate detection of events with slow periodicity while still allowing identification of shorter events (e.g. apneas).

Methods: The PSGA was developed at Cleveland Clinic by collaboration between specialists in biomedical engineering and medicine. It is

designed to represent the PSG record with 1-sec resolution in a compressed format (up to 15 min/screen, i.e. up to 30 epochs of 30 sec each into one screen) while retaining the important information in each channel. It is extracted automatically by computer from the scored digital PSG record. Features of the PSGA include (Figure): 1) Bright contrasting colors to mark various events, including sleep stage, apneas, hypopneas, arousals, leg jerks and arrhythmias; 2) A time-frequency image and intensity plot to represent the relative frequency content and intensity of the EEG channels; 3) Traces to represent EMG power/intensity following elimination of the EKG artifact; 4) Plots of eye and leg movements, SaO2, snor intensity, heart rate and respiratory rate; and 5) An 'envelope' representing airflow peaks and troughs. We describe PSGA of a patient with CSR and one with central apneas, and compare them to the regular PSG record (30s/screen).

Figure 1

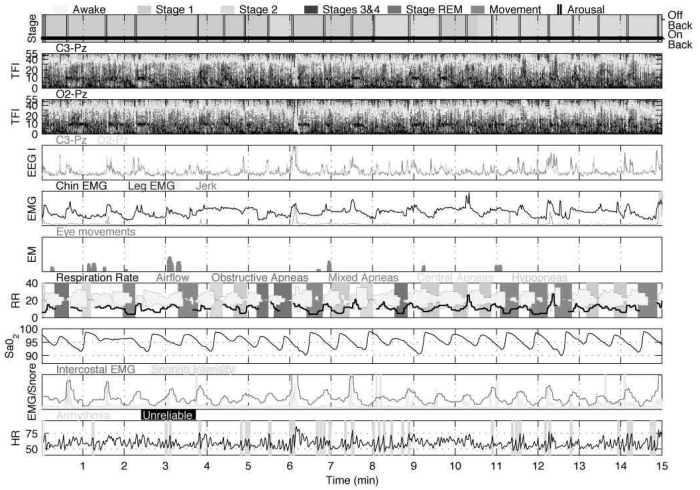

Table 1

PSG and PSGA scoring results*:

Patient #	1	2
SE	61%	64%
Arousals	177	73
Arousal Index	48	17
Apneas	111	25
Central	109	13 (23)
Obstructive	2	12 (2)
Hypopneas	44	24
Central	- (40)	- (22)
AHI	42	12
Mean SaO_2	91.5%	94%
Snoring	Light	Heavy

*Numbers in ( ) = PSGA scoring.

Results: Patient 1 (CSR): An 82 year old male with EDS, witnessed periodic breathing with apneic episodes without snoring noted by his wife, BMI 21 kg/m2 and ESS 15. Patient 2 (Central Apnea): A 44-year-old male with EDS, loud snoring, and BMI 51 kg/m2. Results of the standard PSG and PSGA scoring are shown in Table. Application of PSGA resulted in the following advantages. 1) The time-aligned plots allowed temporal correlations of events in different channels, e.g. arousal, airflow changes, SaO2, and intercostal (ic) EMG. 2) The intuitive, color-coded display made it much straightforward to identify and interpret important events. 3) The modified icEMG signal provided a clear representation of respiratory effort, and correlated well with snoring and airflow events. For patient 1, the PSGA showed that the changes in airflow, SaO2, arousals, icEMG and snoring were synchronous and very regular in frequency and amplitude, with minimum variation in peaks and troughs for each cycle. This is typical of CSR and unusual in OSA and UARS. For both patients, the timing of changes in airflow amplitude and icEMG intensity revealed the respiratory events to be of central origin, as was confirmed on retrospective review of the PSG record. In contrast, during routine PSG scoring, multiple central apneas and "central" hypopneas were misscored as obstructive or mixed, due to difficulty in differentiation on respiratory or icEMG channels.

Conclusions: Generation and review of PSGA from a scored digitized PSG record requires little human effort. It facilitates and expedites the diagnosis of CSR, central apnea, and many other events. Its routine use may thus improve the interpretation of PSG studies for patients with sleep disorders.

1534.I

Drowsiness and Behavior in Response to PERCLOS Feedback During Simulated Nighttime Drives

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Introduction: Recent technological advances in miniaturized drowsiness detection monitors have accelerated the development of on-line, human-centered, objective monitoring technologies for tracking alertness-drowsiness in the transportation industry. In a laboratory-based, independent validation study, we experimentally tested the scientific validity of six alertness-drowsiness on-line technologies to predict a dynamic range of performance lapses and found that only PERCLOS,[1] a video-based human-scored measurement of the proportion of time subjects had slow eye closures, was highly accurate in detection of drowsiness-induced performance lapses.[2] Based on these results, investigators at Carnegie Mellon Research Institute developed an objective PERCLOS monitor using infrared retinal reflectance, which formed the basis of the current study. An experiment was then performed to determine the alertness and driving behaviors of truck drivers who received visual and auditory feedback from the objective PERCLOS monitor during simulated nighttime drives.

Methods: In a within-subjects design, n=16 truck drivers (Commercial Drivers License holders) drove a high-fidelity truck simulator (TruckSim", ref. 3) to establish the effects of PERCLOS feedback while driving on 1) driver alertness-drowsiness; 2) driving performance; 3) driver-initiated behaviors; 4) drivers' subjective sleepiness; and 5) drivers' perceptions. Subjects served as their own controls, driving one simulated 4-hr night drive without PERCLOS feedback (control condition), and one simulated 4-hr night drive with PERCLOS feedback (experimental condition). In the experimental condition PERCLOS feedback of drowsiness level consisted of a visual gauge. If drowsiness persisted, a tonal warning was issued, and if drowsiness continued, one of two types of alerts were issued (i.e., a voice alert that drowsiness was present and corrective action was needed, or a peppermint odor coupled with a buzzer alert). Order of drive and type of warning alert within drives were counterbalanced across subjects. To ensure a dynamic range of alertness-drowsiness, drivers completed the 2 nighttime simulated drives between 5-10a.m. after a normal night drive for their company, and naps and caffeine were not permitted. Results were analyzed by mixed model ANOVA accounting for variation among subjects in intervention effects.

Results: There were consistent effects of PERCLOS feedback on five domains of outcome variables. Relative to the no-feedback (control) condition, during the second-half (i.e., drowsier portion) of the simulated drive, PERCLOS feedback 1) reduced the number of drowsiness alerts drivers received ($p = 0.024$); 2) reduced driving lane departures

per minute (p = 0.036); 3) had no effect on drivers' decisions to stop driving, but increased drivers' postural changes while driving (p = 0.038); 4) decreased drivers' ratings of sleepiness after the drive (p = 0.038); and 5) was perceived by the majority of drivers as having improved their alertness levels.

Conclusions: The consistency of PERCLOS feedback effects across drowsiness indices, driving performance metrics, behavioral variables, and drivers' perceptions of benefit, suggests that an automated PERCLOS drowsy-driving system may promote driver alertness and safety during the drowsiest portions of night driving. However, the automated PERCLOS feedback system used in this study needs to be validated to the same standards used to identify the original potential of a PERCLOS measure.[1] In addition, studies are needed to determine whether drivers will utilize this PERCLOS monitor in a responsible manner. Finally, other technologies for acquiring PERCLOS information may be needed, if drowsiness monitoring includes daytime driving (higher ambient light)

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1536.N

Comparison of C3 to C4 Leads in Determination of Sleep Onset in Multiple Sleep Latency Testing

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Introduction: Multiple sleep latency testing (MSLT) is an important tool for accurately quantifying daytime sleepiness. Electroencephalographic recordings have previously demonstrated higher amplitude of the posterior dominant rhythm over the nondominant hemisphere. This difference may also extend to the persistence of alpha frequency rhythms in drowsiness.

Methods: To investigate the potential of lateralized differences in loss of alpha rhythms influencing sleep latency estimations, we compared left to right central leads (C3, C4) to contralateral mastoid leads (A2, A1) in ten patients undergoing MSLT. All subjects had at least four naps performed at two-hour intervals and studies were selected for a clearly defined alpha frequency, posterior dominant rhythm. MSLT montages showing left and right electrooculogram, occipital electroencephalogram and one channel of central electroencephalogram to contralateral mastoid were shown. Each nap was reviewed and scored independently by two physicians who are board certified in sleep disorders medicine. Each montage was reviewed separately and the scorer was blind to the patient identification, and montage. Sleep latencies were calculated as the time between lights out and first 30 second epoch scored as stage 1 sleep. Sleep latencies and mean sleep latencies were compared from side to side and between readers. Statistical significance was determined using a student t-test ($p<0.05$).

Results: A total of 7 of the 41 naps demonstrated, as interpreted by at least one reader, at least two minutes or greater difference in sleep latency between left to right montage recordings. One subject had three naps showing a two minute or greater difference in left to right sleep latency. One subject had two naps with lateralized difference of two minutes or greater, and two subjects had one nap each with a lateralized difference. The differences were not consistently lateralized to one side. The mean sleep latencies for the patients ranged from 1 to 7 minutes. There was no consistent difference of left compared to right mean sleep latencies. Only one subject had a one minute left to right difference in mean sleep latency, and the remaining 9 subjects had mean sleep latency lateralized differences of 30 seconds or less. In three of the subjects, both scorers commented on difficulty interpreting at least one nap because of artifact in a single channel. However, estimation of sleep latencies were consistent between both readers.

Conclusions: This study shows, that for the majority of patients, mean sleep latencies are consistent between left central and right central recordings. We found no significant lateralized differences in these subjects. Further study of a larger set of subjects may demonstrate other trends in lateralized findings. Considering the drive to minimize recording hardware, this study would support the ability to record sleep latency data utilizing one central lead. However, for some patients, artifact may interfere with interpretation of the electroencephalographic data. The ability to compare the left central to right central leads aids in determining the sleep latency.

1556.N

The accuracy of Mini-Motionlogger and Actiwatch in the Identification of Sleep as Compared to Sleep EEG.

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Introduction: Actigraphy has for many years been used in the measurement of sleep/wake, however, whilst some literature exists for the accuracy of the Mini-Motionlogger (Ambulatory Monitoring Inc. Ardsley, New York) as compared to EEG (E.g Sadeh et al 1995), little if any exists for the Actiwatch (Cambridge Neurotechnology Cambridge U.K/Mini-Mitter, Sunriver, Oregon). A recent clinical trial investigating the effects of 3 hypnotics in 16 young healthy volunteers, with a subjective complaint of poor sleep, allowed us to simultaneously compare both devices against sleep EEG. Because actigraphy is increasingly being used in many fields of research to measure sleep, it is important to have data concerning the accuracy of the technique using the proprietary software.

Methods: All volunteers had their sleep EEG recorded on to the Nicolet Ultrasom system using a conventional montage with a fixed time in bed of 480 minutes. Recordings were then staged according to Rechtschaffen and Kales by an experienced scorer. All volunteers additionally wore both an AMI 32-C Mini-Motionlogger and a CNT Actiwatch on the same non-dominant wrist. Each device was set to record in 1 minute epochs. Actigraphy records were synchronised with the EEG, and sleep/wake analysis was performed using the proprietary software, (AMI ACTION3 v.3.15, CNT Sleepwatch 98 v.4.08). Statistical analysis was performed using SAS. Initially, data for Total Sleep Time (TST), Sleep Efficiency (SE%) and Sleep onset Latency (SOL) were analysed. The clinical trial involved the recording of a total of 448 nights, however, only those nights for which there were complete data for all three records were used in the analysis (n=382). Correlations were performed using Spearman's rho. Median disagreement between the actigraph and EEG and the range of the disagreement were calculated.

Results: There were quite strong, positive and significant (all $p>0.0001$)

correlations between the Mini-Motionlogger (AMI), Actiwatch (CNT) and EEG in the identification of the three variables. TST (minutes) - EEG mean 440.8, s.d. 25.7, median 448.75. AMI - rho=0.548, mean 440.0, s.d. 45.0, median 457.0, median disagreement +8.25, range -215 to +89. CNT - rho=0.513, mean 430.9, s.d. 25.5, median 434.5, median disagreement -14.25, range -136 to +86. SE% - EEG, mean 93.96, s.d. 4.74, median 95.3. AMI - rho=0.413, mean 91.63, s.d. 9.36, median 95.21, median disagreement +0.09, range -45.27 to +13.9. CNT - rho=0.398, mean 89.74, s.d. 5.31, median 90.5, median disagreement -4.8, range -28.75 to +15.71. SOL (minutes) - EEG mean 11.56, s.d. 13.04, median 7.00. AMI - rho=0.528, mean 9.57, s.d. 10.42, median 8.00, median disagreement +1, range - 109 to +90. CNT - rho =0.617, mean 7.03, s.d. 10.51, median 3.00, median disagreement -4, range -92 to +69.5.

Conclusions: This study found that the correlations between Mini-Motionlogger, Actiwatch and EEG were significant, but in the case of the Mini-Motionlogger weaker than those obtained by other researchers. There was a wide degree of variation in how the volunteers slept during the study e.g minimum SE was 65.5% with a maximum of 99.2%, this may explain some of the weakness of the correlations, however, further analysis is required in order to investigate the relative strengths\weaknesses of each type of actigraph. The results suggest that both devices, when used in a routine manner with data analysed by the proprietary software, are able to relatively accurately measure sleep\wake and allow useful data to be collected when the performance of sleep EEG is not an option.

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1567.N

Accuracy of Two Ambulatory Devices for Automated Detection of Restless Leg Activity

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Introduction: Two major contributors to inadequate, nighttime sleep include periodic limb movements (PLM) during sleep and the Restless Legs Syndrome (RLS). Clinical and research work on these conditions has been limited in the past due to the expensive nature of polysomnographic (PSG) evaluations, the difficulty involved in multiple night assessment and the inherent subjectivity in the scoring of such events. Two tetherless devices, the PAM-RL and the Kick Counter (IM Systems, Baltimore, MD) were developed to overcome these limitations by allowing for the characteristic leg movements associated with these disorders to be automatically and objectively identified and recorded outside of the sleep lab environment over multiple evenings. The PAM-RL monitor assesses the PLM/hour rate for patients, while the Kick Counter provides a measure of the total PLM/per night rate during a sleep period. A primary difference between the units is that the data from the PAM-RL must be downloaded to a computer for offline analysis while the Kick Counter displays a final tally of the PLM/night rate directly on a built-in LCD display, requiring no offline scoring. Previous pilot data has shown the PAM-RL monitor to be an accurate means of assessing PLM and RLS activity; the purpose of the present study was to conduct a larger-scale evaluation of the PAM-RL and to provide a preliminary assessment of the Kick Counter.

Methods: 17 RLS patients (6 with mild symptoms, 5 moderate, 6 severe), 7 insomnia patients and 11 normal controls were observed during a nighttime sleep period during which they wore both a PAM-RL recorder and a Kick Counter on the ankle of one leg and were monitored using standard polysomnographic methods, which included the EMG signal for the anterior tibialis on the same leg on which the monitors were placed. A trained scorer read each PSG tracing to determine the PLM/hour rate for each subject. The PAM-RL/hr rates during sleep, as determined automatically from the PAM-RL data were compared to the PSG data for each hour of the sleep period. The Kick Counter data was compared to the total PLM counts for the evening from the PSG data. The subjects also wore both monitors at home for a period of two evenings in order to assess their ease of use by the subjects in the home environment.

Results: Analyses revealed that the PAM-RL provided an excellent degree of agreement with the PSG data for identification of the PLM/hour rate (r2 = 0.92) across all subjects. Similarly, the Kick Counter was also observed to exhibit a high degree of agreement with the PSG data for identification of the PLM/night rate (r2 = 0.80). Furthermore, the subjects reported that the monitors were very easy to use with a nominal amount of instruction and did not provide any significant discomfort during sleep.

Conclusions: The current findings support the existing pilot data which indicates that the PAM-RL system can be accurately used as a means of assessing PLM and RLS activity without the use of traditional PSG equipment. Furthermore, the Kick Counter also provides an accurate means of assessing this activity as well. While the Kick Counter did not correlate as highly with the PSG data as did the PAM-RL, it appears that this device would provide a useful measure of PLM and RLS activity for multiple evenings outside of the traditional, sleep laboratory setting.

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1265.O

From Diagnostic Centre to Online Educator: The Internet Can Augment the Role of a Sleep Lab, a Descriptive Study

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Introduction: The demand for online services is growing at a rapid rate. To meet this demand, our clinical laboratory developed a comprehensive sleep disorders web-site (www.rohcg.on.ca/sleep.html, winner of a "Links2Go Key Resource Award", 1999). The site is interactive and provides the opportunity to submit questions, post testimonials, and search for topics of interest. The purpose of the site is two-fold: (1) to enhance public education, and (2) to identify subject areas of greatest public interest. These areas are then redesigned accordingly in order to fulfil the public's educational needs.

Methods: Two sets of data were summarized: 1) web-site traffic and 2) email contacts. Web-site traffic on the site was monitored using Webtrends Web Log Analyzer software. This software monitored the hits for each section of the site over a 9 month period (January 1/1999-September 30, 1999). The sections with the most hits were deemed the most requested. Email contacts submitted via the site (n=287) were divided into 23 content categories consisting of 22 sleep disorder categories (eg. insomnia) and 1 polysomnography category (ie. sleep architecture questions and comments). Percentage values were calculated for each of these email contact categories to determine areas of greatest public interest.

Results: An examination of the web-site traffic revealed that there were 7, 770 successful hits to the entire site in the 9 month period (864 suc-

cessful hits/month or 28/day). The average user session length was 31 minutes. The five most requested web-site pages addressed sleep apnea (172 hits), insomnia (151 hits), sleep terrors (55 hits), REM behaviour disorder (53 hits) and sleep paralysis (48 hits). Interestingly, questions and comments regarding sleep paralysis were submitted most frequently (15% of all emails), followed by insomnia (9.7%), sleep terrors (8.9%), sleepwalking (8.7%) and sleep apnea (3.5%).

Conclusions: This study demonstrates that the public is now actively searching the internet for information on sleep disorders. In addition, our email contact provides personalized answers to the public's questions and can therefore increase the educational role of a sleep lab. Future directions point toward a growing need for sleep disorder centres to provide information on-line through web-site communication. The most requested topics can be identified and catered to accordingly. A sleep laboratory can utilize traffic feedback to identify important topics and then create its own niche on the information superhighway. Thus, the internet is a useful tool in sleep disorders awareness and can help sleep labs identify areas of greatest interest for their web-site visitors. Based on our results, we conclude that there is a specific need for additional web-site public education on sleep apnea, insomnia, parasomnias, and sleep paralysis.

1268.O

A Survey of Subjective Sleep Length of Shiftworkers Based on Time of Day of Sleep Onset

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Introduction: For years it has been known that sleep taken during the day is shorter than sleep which occurs during the night (Czeisler, Weitzman, Moore-Ede, Zimmerman, and Knauer, 1980). The same circadian mechanism which increases daytime alertness is responsible for shortening daytime sleep, and it is clear that there is a time-of-day effect in that sleep episodes are increasingly shorter the later in the morning sleep begins (Akerstedt and Gillberg, 1982). Because of this, substantial efforts have been made throughout the industrial and military communities toward minimizing work schedules which necessitate daytime sleep, particularly daytime sleep which begins late in the morning. To determine the extent to which these efforts have been successful in the Army aviation community, a survey of work and sleep hours among U.S. Army pilots recently was conducted.

Methods: A total of 157 Army aviators and support staff from Fort Rucker, Alabama; Fort Campbell, Kentucky; and Fort Benning, Georgia, were administered a one-page questionnaire which contained questions about work and sleep times of personnel on night shift. The main purpose of the questionnaire was to describe the work and sleep cycles of aviation units in order to determine what countermeasures should be evaluated in upcoming studies designed to help soldiers adapt to rotating shifts. Of the 157 surveys collected, 12 of the responders were not included for various reasons, leaving a total of 145 questionnaires included in the data analysis.

Results: The responses indicated that 96.9% of the aviation staff worked between 3 and 10 nights per month, with 35.2% indicating more than 10 nights per month. The most common work hours, reported by 40.7% of responders, indicated a beginning time for duty around 1300 with a return home of some time before 0600; however, the times of duty hours varied greatly among the responders. Of those people who reported going to bed before 0400, 24.4% said they slept more than 7 hours per day, with the same percentage (24.4%) reporting 5 hours or less of sleep per day. Of those people who reported going to bed after 0400, only 11.6% reported sleeping more than 7 hours, while 44.4% reported sleeping 5 hours or less per day. When subjective quality of sleep was calculated based on bedtime, 4.9% of those who reported bedtimes before 0400 indicated poor sleep all the time while on night shift, while 9.3% of those who reported bedtimes after 0400 indicated poor sleep all the time while on night shift.

Conclusions: Night operations remain a critical element of U.S. Army aviation's combat role, requiring deviations from the natural circadian cycles. These data indicate that it is impossible for Army aviators to completely avoid work schedules that disrupt sleep schedules, and that the educational message regarding the impact of daytime sleep on sleep quality is not reaching this target audience. In U.S. Army aviation, it appears that the amount of sleep obtained by aviators on night shift is not adequate to prevent the occurrence of significant sleep debt. As indicated in this survey, reported sleep length for night workers was at least 3 hours shorter than the recommended 8 hours required to prevent sleep debt. The fact that the number of night shifts often reach 10 days suggests that the sleep debt may be enough to create serious safety concerns. Thus, enhanced educational efforts are still critically needed in order to help planners create optimal schedules or environments for adequate sleep; however, it is equally likely that educational efforts directed at individual workers are required to address the importance of proper sleep hygiene among aviation crew members.

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1660.O

Use of Ambulatory Studies to Confirm a High Symptom-Based Prevalence of Sleep Apnea in a Primary Care Population

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Introduction: The Moscow Primary Care Sleep Education and Training Project was initiated in 1996 to increase awareness of sleep disorders within the primary care community and to determine their prevalence within primary care practices. A 1999 report by our group documented that 23.6% of the patients within a Moscow, Idaho primary care population had symptoms of sleep apnea.[1] These "preliminary sleep apnea diagnoses" were based on the patient responses from interviews and questionnaires. To demonstrate that symptomatology gathered from our pilot inquiries could provide information about the prevalence of sleep disorders, we needed to solidify the diagnoses for the identified patients. To confirm diagnoses, we offered a free Edentraceâ sleep apnea screening study to all patients identified with sleep apnea symptoms.

Methods: The site for the pilot study was Moscow, Idaho, a rural community with approximately 22,000 residents. A total of 1,254 patients from the Moscow Clinic agreed to participate. After obtaining written consent, each patient completed four sleep questionnaires. Once the questionnaires were scored, a "preliminary diagnosis" was assigned to each patient whose responses met criteria. Based on their questionnaire responses, 296 patients were found to have symptoms of sleep apnea.[1] These patients received a series of three letters revealing our findings

and offering a free Edentraceâ recording. To date, 30 patients have been screened with an Edentraceâ recording. For those patients testing positive for sleep apnea, it was recommended that they receive polysomnography.

Results: Of the 30 patients who had an Edentraceâ screening study, at least mild sleep apnea was detected in 96.7% of the patients. The mean respiratory disturbance index (RDI) for the Edentraceâ group was 29.7 ± 24.2 and the mean percent desaturation was 79.3% ± 9.4. Additionally, of the 12 patients who had a polysomnogram at the local sleep center, 10 were titrated on CPAP or BiPAP. The mean RDI for the polysomnography group was 50.6 ± 38.7 and the mean percent desaturation was 77.7% ± 15.3.

Table 1

Severity of Disease	Respiratory Disturbance Index (RDI)	Number of Edentrace[â] Patients (Percent)
Normal Sleep	0 – 4.9	1 (3.3)
Mild Sleep Apnea	5 – 19.9	11 (36.7)
Moderate Sleep Apnea	20 – 39.9	11 (36.7)
Severe Sleep Apnea	40 or greater	7 (23.3)

Conclusions: Our results indicate that the questionnaires used to screen the primary care population in Moscow, Idaho were 96.7% effective in diagnosing patients with some degree of sleep apnea. The one patient who had an RDI < 5 was diagnosed with primary snoring. Of the 12 patients who underwent polysomnography, 100% were diagnosed with at least mild sleep apnea. Further, the mean RDI's for the Edentraceâ and the polysomnography patients were considered moderate and severe, respectively. This demonstrates that we are finding patients with moderate to severe disease in primary care. These findings lead us to our current focus, which is to increase the number of patients who receive Edentraceâ screening tests and polysomnography.

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1684.O

Analysis of a Primary Care Population with a High Symptom-Based Prevalence of Restless Legs Syndrome

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Introduction: In 1996, the Primary Care Sleep Education and Training Project was conceived and implemented in Moscow, Idaho to increase awareness of sleep disorders and determine their prevalence within a primary care practice. A report by our group in 1999 documented that 29.3% of the patients within the Moscow Clinic population had symptoms of Restless Legs Syndrome (RLS).[1] These "preliminary RLS diagnoses" were based on responses from on-site interviews and questionnaires. To substantiate the diagnoses for the group of identified patients, we had the patients wear a RLS monitor and complete seven questionnaires. In addition, we asked the physicians to perform a structured diagnostic RLS interview. This abstract consists of data from 16 participants, 7 of which are positive for RLS.

Methods: A study conducted by our group at the Moscow Clinic revealed that 368 out of 1,254 patients had symptoms of RLS.[1] To learn more about this population, letters were mailed out inviting patients for further participation. These letters were delivered to 76 patients with and 68 patients without symptoms of RLS. All subjects were randomly selected. Once a patient agreed to participate, an appointment was scheduled with their physician. During this appointment the physician, who was blinded to the preliminary diagnosis, conducted a RLS diagnostic interview and recorded a positive or negative diagnosis. Following the appointment, all patients were given two RLS questionnaires, four general sleep questionnaires, and a sleep log to complete. All patients were also asked to wear a RLS monitor for two consecutive nights. Following data accumulation, a separate positive or negative diagnosis was made based on the questionnaires. Finally, a RLS expert reviewed the medical charts of all enrolled patients and assessed a positive or negative diagnosis based on the charted information. The expert was blinded to the diagnoses made by the physician and by the project coordinator.

Results: Out of the 16 patients who completed questionnaires, 15 revealed enough information for the expert to evaluate. When compared to the expert's diagnoses, the questionnaires accurately diagnosed 13 of 15 patients (87%) as RLS positive or negative. Further, comparing the diagnoses rendered by the Moscow Clinic physicians and the RLS expert, there was 93% agreement. Fourteen out of fifteen patients were assigned the same diagnosis. Data from the monitors revealed that RLS patients averaged 27.3 ± 16.5 periodic limb movements (PLM) per hour while non-RLS patients averaged 11.4 ± 4.1 PLM/hour.

Conclusions: Our results demonstrate that the questionnaires used to screen the primary care population had a sensitivity of 87%. The two patients who were incorrectly diagnosed by the questionnaires appeared borderline RLS positive, yet were considered negative by the expert. False positives with these questionnaires are not considered detrimental and, in fact, help physicians discover borderline RLS patients who may benefit from treatment. In addition, the Moscow Clinic physicians and the RLS expert assigned only one patient a different diagnosis, making the agreement of diagnoses 93%. This discrepancy may be due to a lack of information in the medical chart. For example, the physician may have asked additional questions which were not documented and therefore not available to the expert. Finally, the preliminary data gathered from the monitors suggest that RLS patients have a higher rate of periodic limb movements per hour than for patients without RLS. These data may be helpful in solidifying further RLS diagnoses. While promising, these results are preliminary and consequently do not allow us to draw any conclusions until data is obtained from a larger sample size. We are currently using an improved method to encourage a greater number of participants in this study.

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(1) Nichols DA, Kushida CA, Simon RD, Young T, Grauke JH, Britzmann JB, Hyde PR, Dement WC. Symptom-Based Prevalence of Sleep Disorders in a Primary Care Population. Sleep 1999; 22(suppl 1):S237-38.

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1045.O

Sleep Medicine Content of Commonly Used Medical Textbooks

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Introduction: Didactic education of physicians and medical students about sleep medicine is limited. Thus, physicians and medical students probably gain much of their knowledge about sleep and sleep disorders from textbooks. We therefore analyzed the sleep medicine content of several widely used textbooks. In addition, for one textbook, we assessed the change in quantity and content of sleep medicine topics from an early edition to a recent one.

Methods: The following textbooks were reviewed: Andreason and Black. Introductory Textbook of Psychiatry, 1995 (700 pp); Nelson Textbook of Pediatrics, 15th Ed, 1996, (2200 pp); Cecil's Essentials of Medicine, 4th Ed, 1997 (949 pp); Cecil's Textbook of Medicine, 20th Ed., 1996 (2222 pp); Harrison's Principles of Internal Medicine, 14th ed. 1998, (2569 pp); 12th Ed., 1991, (2208 pp); and 8th Ed., 1977, (2088 pp); Hazzard WR, et al. Principles of Geriatric Medicine and Gerontology, 3rd ed. 1994, (1373 pp); Merritt's Textbook of Neurology, 9th ed, 1995, (1058 pp); Samuels and Feske. Office Practice of Neurology, 1996 (1236 pp). The sleep medicine content was determined by a review of the chapter headings and an index search for the following: asleep, bruxism, cataplexy, central sleep apnea, circadian, enuresis, hypersomnolence, idiopathic hypersomnia, insomnia, Klein-Levin, melatonin, myoclonus, naps, narcolepsy, nocturia, nocturnal, obstructive sleep apnea, periodic limb movements, polysomnography, REM sleep, restless legs syndrome, snoring, sleep, sleepiness, sleepwalking, sleep apnea, snoring, and somnambulism. For each indexed entry, the number of pages devoted to the topic was determined to the nearest tenth of a page. Material unrelated to sleep, such as non-nocturnal myoclonus, and that related to sleeping sickness was not included.

Results: Of the 10 textbooks, the quantity of sleep medicine content was greatest in the psychiatry textbook (23 pp; 3.2%) and least in a standard textbook of internal medicine (5.8 pp; 0.3%). Apart from the psychiatry text, only one text devoted more than 2 pages to normal sleep. Sleepiness was discussed in 2 texts and mentioned in a third. Insomnia was covered in 0.75 pp or less in 7 texts. Two texts did not mention narcolepsy and four did not describe periodic leg movements or restless legs syndrome. Sleep hygiene was not mentioned in any text and insufficient sleep syndrome in only one. In one text, sleeping sickness received the same amount of coverage as sleep disordered breathing and insomnia combined. In a comparison of two editions of an internal medicine text (1977, 1998), the proportion of content increased from 0.35% to 0.5%, with an increase in pages devoted to sleep disordered breathing (0.7, 3.2) and a decrease in those devoted to insomnia (1.5, 0.6) and parasomnias (1.0, 0.6).

Conclusions: The content related to sleep medicine in commonly used medical texts is scant and uneven. Topics that that receive little coverage include insomnia, sleepiness, and insufficient sleep (sleep deprivation). In one standard text, a modest increase in sleep medicine content over the past 20 years is due mainly to increased coverage of sleep disordered breathing.

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1455.O

General Internal Medicine Sleep Education Needs Assessment

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Introduction: Deficits in health care education regarding sleep medicine are well documented. Recent efforts, including the NHLBI Sleep Academic Award program, have promoted multiple projects directed at medical school curriculum development, as well as educational strategies addressing other training and practicing health care professionals. The current project evolved from the Curriculum Development Workshop of the Johns Hopkins Faculty Development Program employing a six-step approach.[1] A problem identification and general needs assessment process established the following ideal approach: *Health care providers, especially primary care physicians, should be trained to identify and appropriately manage (e.g., educate patients, promote behavioral/lifestyle changes, identify underlying disorders, prescribe medications, refer to sleep specialists) the full spectrum of commonly occurring sleep disorders. Therefore, medical educators should develop and implement effective educational interventions to supply primary health care providers with the necessary resources to manage the sleep problems of their patients, and also to promote greater societal goals of encouraging adequate sleep.*

Methods: General internal medicine (GlM) residents were selected as one target population to assess sleep medicine educational needs. A needs assessment survey instrument was developed incorporating demographics, previous sleep-related training, sense of competency, knowledge, attitudes and beliefs, skills and current practice, and interest in further training in general and specific sleep topics. The survey was distributed to all GIM PGY 1 - 4 housestaff at the Johns Hopkins Bayview Medical Center.

Results: Completed surveys were obtained and analyzed from 28 (61%) of the residents. Only 36% of the sample reported that they believed their medical school and residency training had equipped them to recognize and manage sleep disorders. Less than half responded that they routinely ask about sleep symptoms in a new patient history and review of systems. Questions regarding specific sleep knowledge relevant to clinical symptoms demonstrated a general lack of awareness of fundamental sleep physiology. Only 14% correctly identified the typical circadian peak of sleepiness. Sixty-one percent failed to agree that the human circadian clock typically has a period longer than 24 hours, and only 18% correctly answered a question about periodic limb movement risk factors. All of the respondents concluded that they would benefit from further training in sleep medicine. Greater than 80% of the sample indicated that training in each of the following sleep medicine topics would be helpful in their practice: differential diagnosis of insomnia and excessive sleepiness, obstructive sleep apnea, central sleep apnea, sleep and psychiatric disorders, sleep and aging, insomnia behavioral approaches, current guidelines for hypnotic medication use, and medication side-effects.

Conclusions: The goals of a GIM residency sleep medicine education plan should include: a) the acquisition of basic sleep knowledge relevant to clinical situations, b) the promotion of beliefs and attitudes that encourage the recognition and appropriate management of sleep disorders, and c) the development of skills and practices to effectively diagnose and treat patients with sleep disorders.This GIM resident needs assessment analysis has demonstrated several fundamental knowledge deficiencies; however, there is a positive attitude regarding the importance of identifying and treating patients with sleep disorders, and there is a strong interest in further education in sleep medicine topics.

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1497.O

Reasons for Referral for Sleep Evaluation in a Rural Community

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Kathryn Severyns Dement Sleep Disorders Center, St. Mary Medical Center

Introduction: Our group has demonstrated that sleep disorders permeate the practice of medicine. Community physicians can be trained to diagnosis and treat sleep disorders when appropriately educated and supported by sleep specialists. The current study was undertaken to survey consecutive patients undergoing polysomnography regarding their attitudes about sleep disorders and their experience with sleep disorders.

Methods: From 12/1/98 through 3/15/99, a short 9 question survey was administered to 100 consecutive patients referred to the Kathryn Severyns Dement Sleep Disorder Center (KSDSDC) for polysomnographic evaluation. The surveys were administered to the patients on the evening of their first PSG, after they underwent a full sleep consultation. The questionnaire was administered by one of the polysomnographic technologists (P. Smith), prior to lead placement.

Results: One hundred consecutive patients completed the questionnaire. The majority of the patients were referred for obstructive sleep apnea or periodic limb movements of sleep because in our sleep center polysomnography is rarely performed on patients with insomnia or circadian rhythm disorders. The mean age of the population was 49.8 years. The sex ratio was 61% male and 39% female. Sixty- percent report having a co-sleeper in the same bed, 3% a co-sleeper in the same room, and 37% slept alone. Twenty five percent of patients felt that they had had their sleep problem for 1-5 years, and 47% felt they had had their sleep problem for more than 5 years. When asked if anything would have brought them to the sleep center sooner, 48% responded that physician recommendation would have resulted in a more timely sleep evaluation. Reasons for their visit to the physician who ultimately referred them for polysomnography were evaluated. Twenty percent of patients were referred because the patient suspected a sleep disorder. Seventeen percent requested a sleep consultation because a spouse or friend suspected that they had a sleep disorder. Six percent suspected a sleep disorder for other reasons (problems at work, safety concerns at work). Fifty seven percent of patients presented to their physician with other problems and the physician inquired about their sleep history and habits, suggesting that a sleep disorder may be present.

Conclusions: The majority of patients felt that their sleep problem(s) had existed for many years, and would have come sooner for a sleep evaluation if their physician had recommended it. However, 57% of these patients were referred for sleep evaluation by their physician even though the patient did not present with a primary sleep complaint. This may be a result of extensive continuing medical education provided by the KSDSDC to physicians and medical personnel in the Walla Walla valley. However, even in Walla Walla, significant numbers of patients referred for polysomnographic study (9%) were not aware of the existence of sleep disorders prior to referral. This reinforces our feeling that continued efforts to educate patients and health care providers about sleep disorder will increase diagnosis and treatment of patients in a more timely fashion than is currently the case. We are currently repeating this questionnaire in several other sleep centers throughout the nation in order to obtain comparable results

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1179.O

Patients' Satisfaction with Nurse Practitioner Follow-up in a Pulmonary Sleep Disorders Clinic

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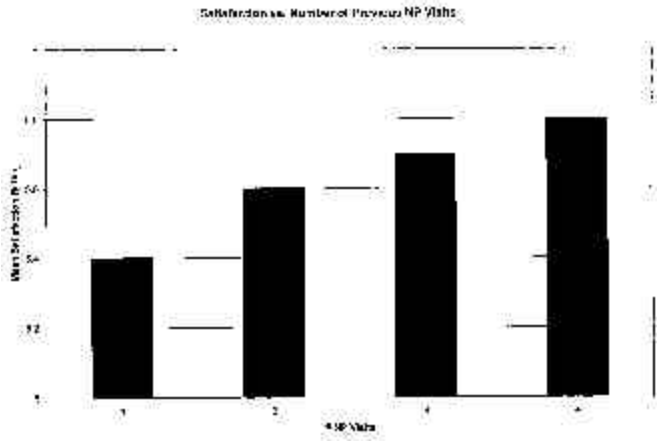
Introduction: Nurse Practitioners (NPs) have been used effectively in cardiology subspecialties (e.g. electrophysiology). To date, the utility of NPs in pulmonary subspecialty medicine has not been evaluated. Patient satisfaction with NP care in the primary care setting has been evaluated with favorable outcomes (Ramsey et al 1993). The purpose of this study was to evaluate patients' overall satisfaction with care provided by a NP in an outpatient pulmonary sleep disorders clinic and to identify any specific variables that may influence patients' satisfaction with care and their choice of future provider.

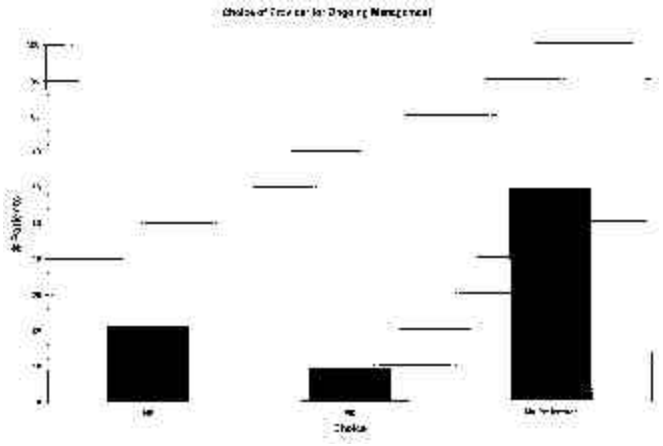
Methods: An investigator-developed questionnaire was administered to a convenience sample of 100 patients who were diagnosed with a sleep disorder and followed in our Pulmonary Sleep Evaluation Center. Patients were asked to complete the questionnaire at time of check-in only if they had seen the NP on at least one previous visit. The 17-item questionnaire consisted of 13 questions addressing the NP, 9 of which used Likert scaling (range: 2=very dissatisfied to 6=very satisfied, 1=not applicable), 4 demographic questions and 1 open-ended question for comments. Patients were asked to rate their satisfaction in terms of length of time spent with them at visit, explanations of treatments, clinical expertise and professional manner of NP and overall care. Patients were asked the number of times previously seen by NP and to indicate choice of provider for future follow-up visits (NP, MD, or doesn't matter). Data were analyzed using SPSS for Windows (Version 9, SPSS Inc, Chicago IL). Descriptive statistics expressed as mean, SD.

Figure 1



Results: One hundred patients were surveyed, 89 of which responded to the demographic questions. Mean age range of sample was 41-50 years with 64% (n=57) male, 80% (n=69) white, and 16% black (n=14). Mean rating for satisfaction with overall care was 5.6 (SD=.50). Mean scores for individual questions regarding the specific aspects of NP care ranged from 4.4-5.6. Patients surveyed had been seen by NP an average of 2.5 times (SD=1.05). Frequency of past experience with NP correlated with higher satisfaction rating (Figure 1). The majority of patients (n=59) did not have a preference of provider for ongoing management. Of those who did choose a subsequent provider, the majority selected the NP (Figure 2). Those who chose to see NP for future visits had a higher rating of overall satisfaction with NP (5.86, SD=.36) than those who chose MD (5.30, SD=.48). There was no association between choice of provider for subsequent visits and gender (X2=.84, p=.66), race (white, nonwhite) (X2=1.13, p=.57), or age (20-40, 41-60, >61yrs) (X2=2.23, p=.73).

Figure 2



Conclusions: 1) Patients surveyed were satisfied with the NP providing ongoing management of their sleep disorder. 2) Patients' satisfaction increased with the number of previous NP visits reported. 3) Most patients (61%) did not have a preference for the type of provider (NP or MD) for subsequent follow-up. 4) No demographic factors predicted preference of the type of provider.

References:

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1854.O

Accuracy in the Diagnosis of the Obstructive Sleep Apnea Syndrome by Physician Level of Training in Sleep Disorders

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Introduction: The Obstructive Sleep Apnea Syndrome (OSA) is a very common disorder that remains largely undiagnosed. We hypothesized that this lack of diagnosis represents a universal unawareness of the disorder amongst the primary care community rather than a paucity of specialists with formal training in sleep disorders. In order to prove our hypothesis, we designed a retrospective, cohort study to determine a difference in the clinical recognition of patients with symptoms suggestive of Obstructive Sleep Apnea amongst physicians with various degrees of training in sleep disorders.

Methods: Records of all patients who underwent nocturnal polysomnography as a diagnostic procedure for the presence of OSA at the Sleep Apnea Center of Staten Island University Hospital from January 1998 to March 1999 were reviewed. Four groups of ordering physicians were identified and stratified according to level of training in sleep disorders: 1) Board Certified (one physician), 2) Formal Training without Board Certification (two physicians), 3) Informal Training (three physicians), and 4) No Training (four physicians). Comparisons were then made amongst all groups according to degree of accuracy in diagnosis. An Apnea-Hypopnea index of 10 or above was considered a positive polysonmographic study. Two-tail Fisher's exact test was used to verify statistical significance.

Results: Data from four hundred and sixty five polysomnographic studies were analyzed. Of these, 348 (74.8%) were positive studies according to our criteria. When data were stratified, Board Certified was correct in 100 of 126 (80%) of cases, Formal Training in 124 out of 175 (70.8%), Informal Training in 69 our 98 (70.4%), and No Training in 55 our 66 (83%) (p = N.S., Figure 1). When examining our data according to severity of disease into mild (AIR 10-20), moderate (AM 20-30) or severe (AM > 30), we found that the Board Certified group was more likely to identify those with mild and moderate disease and the group with Informal Training was more likely to identify severe cases; however, this difference did not reach statistical significance (Figure 2).

Figure 1

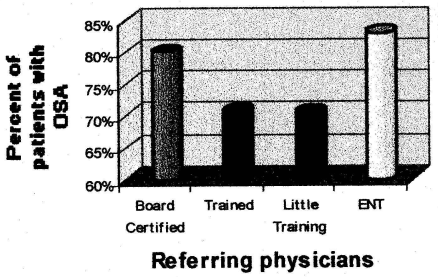
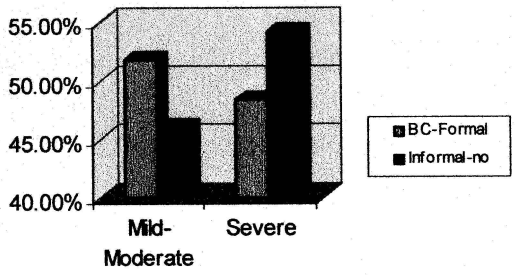


Figure 2



Conclusions: Physicians do not- need formal -training in sleep disorders to be able to identify patients suffering from OSA. They need, however, to be aware of the risk factors as well as clinical signs and symptoms of the disease in order to refer patients for documentation via nocturnal polysomnography. On the other hand, our data seems to suggest that the more formal training a physician has in sleep disorders the better he or she is in identifying mild or subtle disease. Finally, the one limitation of our study is the fact the all data were collected from patients already referred for polysomnography. Thus, it is impossible to determine the rate of false negatives from each group since they would have been discharged from the physicians office without ever being formally studied in the Sleep Apnea Center.

1246.P

A Polymorphism in the Human Timeless Gene is Not Associated with Diurnal Preferences in Normal Adults

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Introduction: In mammals, the hypothesized core components of the cellular clock are Clock, Bmal1, Period 1, Period 2, Period 3 and Timeless[1] genes. Mutations at the level of these genes are likely to produce a circadian phenotype in humans. It was recently published that a Clock polymorphism may influence circadian preference in humans[2] and therefore, it points to the possibility that polymorphisms in other circadian genes can also influence diurnal preferences. In this study the effect of a single nucleotide polymorphism, a glutamine to arginine aminoacid substitution in the human Timeless gene (Q831R, A2634G), on diurnal preferences was analyzed in a sample of normal volunteers.

Methods: A population-based random sample of 528 subjects was used in this analysis. All subjects completed the 19 item Horne-Ostberg questionnaire to evaluate diurnal preferences. DNA extracted from white blood cells was amplified and the resulting 33 bp PCR product was dot-blotted onto Nylon membranes and hybridized with allele-specific digoxin-11-ddUTP labeled oligonucleotides. Horne-Ostberg scores were calculated in all subjects using pre-established values for each question. Linear regression modeling was used to asses differences between groups for Horne-Ostberg scores unadjusted and adjusted for the potential confounded factors of age, sex, and ethnic heritage. The statistical significance of regression coefficients were assessed using t-tests and p values < 0.05 were considered to indicate statistical significance. The SAS statistical package was used for all analysis

Table 1: Horne-Ostberg Scores by hTIM genotypes.

hTIM Genotypes	n	Horne-Ostberg Scores * (unadjusted)	(adjusted)†
2634A/A	124	60.2±0.9	60.4±0.9
2634A/G	271	60.7±0.7	61.4±0.6
2634G/G	133	60.0±0.9	60.2±0.8

* The Horne-Ostberg scores are given as Mean ± Sd. † The scores were adjusted for the possible confounding factors of age, sex and ethnic heritage.

Results: Subjects were categorized in three groups on the basis of their human Timeless (hTim) genotypes (hTim 2634A/A, hTim 2634A/G or hTim 2634G/G). Observed sample sizes for A/A, A/G and G/G were 124/528, 271/528, and 133/528 respectively. Mean Horne-Ostberg scores, unadjusted and adjusted were then compared between genotypes (table 1). The mean Horne-Ostberg scores, unadjusted and adjusted for age, sex and ethnic heritage were not significantly different across the Tim genotype groups.

Conclusions: Our results show that a Single Nucleotide Polymorphism, an A to G substitution at the position 2364 resulting in a glutamine to arginine substitution at amino acid position 831, is not associated with mornigness-eveningness tendencies. The apparent lack of effect of the hTim Q831R substitution on diurnal preferences does not entirely exclude the possibility that others Single Nucleotide Polymorphisms within hTim gene could influence circadian behavior or even that hTim is involved in other component of circadian behavior than diurnal preference.

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1067.P

The Role of Sleep in Hippocampus-Dependent Long-Term Memory

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Introduction: We are interested in examining the molecular processes underlying the role of sleep in the consolidation of hippocampus-dependent long-term memory. Behaviorally, sleep has been shown to be important in rats for the consolidation of hippocampus-dependent spatial memory (Smith and Rose, 1996, Physiol. & Behav. 59: 93-97; Smith and Rose, 1997, Behav. Neurosci. 111: 1197-1204). Sleep deprivation during specific time windows after training in the hidden-platform version of the Morris water maze (hippocampus-dependent), but not the visible-platform version (hippocampus-independent), affects consolidation of this task. Because the Morris water maze requires multiple trials for training, over several days, a distinct time course of molecular changes in the hippocampus may be difficult to ascertain after training for this task. We have begun experiments to examine the effects of sleep deprivation on contextual fear conditioning, a single-trial hippocampus-dependent form of associative learning in which mice learn to associate a particular context with a mild foot-shock. Previous work has used genetic and pharmacological approaches in mice to demonstrate that protein kinase A (PKA) activity is critically important for long-term memory storage (Abel et al., 1997, Cell 88: 615-626; Bourtchouladze et al., 1998, L & M 5: 365-374). Like sleep deprivation, the inhibition of PKA or protein synthesis disrupts memory consolidation only at discrete times following training, and these times vary depending on the strength of the training protocol.

Methods: Contextual fear conditioning was carried out as described (Abel et al., 1997). Sleep deprived mice were kept awake by gentle stroking to arouse them from sleep for five hours, at either 0 hours to 5 hours after training, or 5 hours to 10 hours after training. Mice were tested 24 hours or 12 days after training in both the shocked context and an altered, non-shocked context. Contextual fear was assessed by scoring "freezing" behavior at intervals of 5 seconds.

Results: Total sleep deprivation in mice from 0-5 hours after training impaired retention of contextual fear conditioning when mice were tested at 24 hours or 12 days after training. When contextual fear training was carried out in the presence of a discrete auditory cue, impairments in contetxual fear conditioning were seen at 24 hours, but not 12 days, after training. No impairments were seen in cued fear conditioning, a hippocampus-independent task. We have begun to determine the effects of sleep deprivation at 5-10 hours after training for contextual fear conditioning. Preliminary data suggests that deprivation during this window has no effect on memory consolidation for this task.

Conclusions: We conclude that sleep deprivation after training alters memory consolidation for contextual fear conditioning. This effect is dependent on the training protocol, the time elapsed between testing and training, and the times after training during which the mice are sleep deprived. We have identified a five-hour time window immediately post-training during which total sleep deprivation impairs memory consolidation. With these experiments, we hope to lay the behavioral groundwork for an examination of the molecular processes underlying the effects of sleep deprivation on memory consolidation.

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1086.P

Sleep in Twins: Concordance Rates Between Identical and Fraternal Twins

Mindell JA, Spokas ME, O'Brien EM

Introduction: Little is known about the sleep habits and sleep problems of young twins, especially differences in concordance rates between identical and fraternal twins.

Methods: Seventy-eight sets of twins (18 identical sets, 60 fraternal sets) for a total of 156 children (86 boys, 62 girls, 8 unspecified) between 1 month and 5 years (M = 29.65 months; SD = 17.01 months) served as subjects in this study. All subjects were recruited from Mothers of Twins Club meetings. All subjects' mothers completed a demographic questionnaire and the Sleep Habits Questionnaire (SHQ; Acebo et al., 1994). The SHQ assesses sleep patterns (e.g., usual bedtime, total sleep time) and specific behaviors associated with sleep (e.g., child resists going to bed, child wakes more than once per night). Five subscales are derived from this scale: bedtime problems, sleep problems, night waking, morning problems, and daytime sleepiness.

Results: Overall, there were no significant differences between the sleep habits of identical and fraternal twins for all variables. In looking more specifically at concordance rates, sleep pattern variables revealed significant correlations for 6 of the 6 measures for identical twins (r = .68 to 1.00) and similarly for all of the measures for fraternal twins (r = .42 to .99). Sleep problem subscales also revealed significant correlations for 4 of the 5 subscales for identical twins (r = .67 to .81) and for all of the subscales for fraternal twins (r = .37 to .56). For 9 of the 11 variables, correlations were higher for identical twins than for fraternal twins.

Conclusions: The findings of this study indicate that sleep patterns and sleep problems are highly correlated for both identical twins and fraternal twins. Furthermore, for nine of the eleven variables considered there is a higher concordance rate between identical twins than between fraternal twins. Although these results appear to support a genetic component to sleep, research has shown that identical twins also share a more similar environment, primarily related to more similar parental expectations. Additional research is required to continue to evaluate whether sleep habits and sleep problems are more genetically or environmentally determined.

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