Beta/Gamma EEG Activity in Patients with Primary and Secondary Insomnia and Good Sleeper Controls

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Study Objective: Several studies have shown that patients with insomnia exhibit elevated levels of Beta EEG activity (14-35 Hz) at or around sleep onset and during NREM sleep. In this study, we evaluated 1) the extent to which high frequency EEG activity is limited to the 14-32 Hz domain, 2) whether high frequency EEG activity (HFA) is associated with discrepancies between subjective and PSG measures of sleep continuity, and 3) the extent to which high frequency EEG activity occurs in patients with primary, as opposed to secondary, insomnia.
Design: Three groups (n=9 per group) were compared: Primary Insomnia, Insomnia secondary to Major Depression, and Good Sleeper Controls. Groups were matched for age, sex and body mass. Average spectral profiles were created for each NREM cycle after removing waking and movement epochs and epochs containing micro- or mini-arousals.
Setting: Sleep Research Laboratory
Patients or Participants: Patients with primary and secondary insomnia
Interventions: N/A
Measurements and Results: Subjects with Primary Insomnia exhibited more average NREM activity for Beta-1 (14-20Hz), Beta-2 (20-35Hz) and Gamma activity (35-45Hz) than the other two groups (p.<.01). Group differences were also suggestive for Omega activity (45.0-125Hz) (p.<.10), with MDD subjects tending to exhibit more activity than the other groups. Correlational analyses revealed that average NREM Beta-1 and Beta-2 activity tended to be negatively correlated with subjective-objective discrepancy measures for total sleep time and sleep latency.
Conclusions: Our results confirm that Beta activity is increased in Primary Insomnia. In addition, our data suggest that high frequency activity in patients with Primary Insomnia is limited to the Beta/Gamma range (14-45 Hz), and is negatively associated with the perception of sleep.
Key words: Insomnia; power spectral analyses; sleep; beta; high frequency EEG

INTRODUCTION

HIGH FREQUENCY EEG ACTIVITY IN THE 20—90HZ RANGE WAS FIRST OBSERVED BY BERGER IN 1937. He hypothesized that such activity, observed during mental arithmetic, must be a "material concomitant of mental processes."[1] In the last two decades there has been a substantial amount of work suggesting that high frequency EEG activity in the Beta (14—35Hz), and more probably in the Gamma (35—45Hz),[1] range is associated with attention in animals[2,3] and with attention, perception, and more generally, cognitive function in humans.[4,5-19]

Recently, six investigations have demonstrated that patients with insomnia exhibit an unusual amount of Beta EEG activity during polysomnographically (PSG) monitored sleep.[20-25] The majority of these investigations found that the increase in Beta activity (14—35 Hz) was apparent in patients with insomnia compared to good sleeper controls for time periods at/around sleep onset and/or during NREM sleep.[20-25] The findings were based on 1) EEG measurements from central sites using monopolar or bipolar measures that included C3, Cz, or C4 and 2) relative, as opposed to absolute, measures of power density. The detection of Beta activity at central EEG sites suggests that this form of EEG activity may be maximally distributed over regions which are associated with sensory processing. The detection of Beta activity using relative measures (as opposed to absolute measures of power density) suggests that this form of EEG may be particularly prone to individual difference variability.

There is also limited evidence to suggest that 1) increased Beta activity during sleep occurs specifically in association with primary, as opposed to secondary, insomniam[22,24] 2) patients with insomnia have more Beta activity during REM sleep,[20,23] and 3) Beta activity may vary with clinical state.[25]

The findings from the Beta activity studies are intuitively appealingly; in part because they are consistent with psychological conceptualizations of insomnia and in part because they offer a perspective on the possible links between presenting symptom, cognitive process, and underlying neurophysiology. The Beta findings are consistent with the psychological data suggesting that patients with insomnia may be hypervigilant and/or excessively ruminative at sleep onset and/or during sleep.[26-28] The Beta findings lend themselves to a clearer perspective regarding the pathophysiology of insomnia because they point to processes (sensory and information processing, attention, long term memo-

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Throughout this manuscript we use the term Gamma to indicate frequencies between 35-45Hz. Please note that a common synonym for this band is "40 Hz".

ry) and implicate structures (thalamus, sensory cortex, prefrontal cortex, hippocampus, etc.) that may be related to sleep initiation and maintenance problems.[29]

Despite the intuitive appeal of the findings regarding Beta activity during PSG sleep, little is known about whether high frequency EEG activity in insomnia is:

1) limited to Beta activity (14—35 Hz) or, as the cognitive neuroscience literature would suggest, extends into the Gamma portion (35—45 Hz) of the EEG spectrum.[4-19]

2) actually CNS in origin. It is possible that both Beta and Gamma activity are forms of EMG artifact[30] and as such represent somatic, as opposed to CNS, arousal.

3) derivative of simple micro-architectural phenomena, like an increased number and/or duration of "arousals" (events<15 seconds in duration per epoch).

4) correlated with the subjective perception of sleep quality and quantity.

5) specific to primary insomnia or also characteristic of secondary insomnia, (e.g., insomnia related to Major Depression).

In this study, we evaluate 1) the extent to which high frequency EEG activity is limited to the 14—35 Hz frequency domain, 2) whether Beta and/or Gamma activity are associated with discrepancies between subjective and PSG measures of sleep continuity[31-41] (i.e., can account for the tendency of insomnia patients to overestimate the severity of their sleep problems relative to polysomnography) and 3) whether high frequency activity occurs predominantly in patients with primary insomnia.

METHODS

General protocol

All subjects in these analyses took part in one of three pilot studies undertaken at the University of Rochester Sleep Research Laboratory. Subjects were recruited from two sources and were screened in a two-tier process to insure that they met the inclusion/exclusion criteria. Prior to laboratory study, all subjects completed 14 days worth of sleep diaries. These data were used to verify that subjects retrospective assessments of their sleep were reasonably accurate and to provide an average measure of each subjects preferred bedtime and risetime. After the two week monitoring interval, each subject spent a minimum of two consecutive nights in the laboratory. The first night served as a adaptation night and these data are used in the present analyses. \

Recruitment

Subjects were recruited via newspaper advertisements and from The Behavioral Sleep Medicine Clinic at the Sleep Disorders Center of Rochester. Each patient underwent a two step evaluation process.

First, subjects were interviewed by phone to establish their eligibility for participation. Subjects were ruled out if they reported unstable medical illness, psychiatric conditions other than major depression, sleep disorders or symptoms suggestive of sleep disorders other than primary insomnia, shift work, use of medications with central nervous system effects, substance abuse, and/or a recent history of alcohol abuse (within two years).

After the telephone screen, all potential subjects were interviewed by a research clinician. Subjects were interviewed using the Schedule for Affective Disorders and Schizophrenia-Lifetime version (SADS-L),[42] supplemented by the eating disorders module from the SCID. Symptom severity (Hamilton Rating Scale for Depression [HRSD]),[43] episode, treatment, medical history, and personal and family history of sleep disorders were also ascertained. Family history of psychiatric disorders was obtained according to Family History Research Diagnostic Criteria (FHRDC).[44] Prospective subjects also completed several psychometric instruments including the Beck Depression Inventory,[45] the Beck Anxiety Inventory[46,47] and the Pittsburgh Sleep Quality Index.[48] Eligible subjects completed an informed consent at the end of the clinical interview. Subjects received $150—$200 remuneration.

Subjects

Data from three subject groups were used in the present analysis (n=9 per group). Groups were Primary Insomnia, Insomnia secondary to Major Depression, and Good Sleeper controls. The three groups were matched for age, sex, and body mass. The overall sample was 66% female and the mean age was 37.5 (+/- 10.7).

Criteria for Primary Insomnia (PI) were as follows:

- the complaint of insomnia and impaired daytime function
- an indication of learned sleep-preventing associations
- active help seeking

The complaint of insomnia had one or more of the following characteristics: >30 minutes to fall asleep and/or >2 awakenings per night of >15 minutes duration and/or wake after sleep onset time of >30 minutes, problem frequency >4 nights/ week, and problem duration >6 months.

Criteria for Insomnia secondary to Major Depression (MDD) were as follows:

- patients met DSM IV criteria for MDD

  Five or more symptoms which represented a change from previous functioning for a period of at least two weeks. Depressed mood and/or loss of interest/pleasure were required for the diagnosis of MDD.

- patients presented with the complaint of insomnia

The Criteria for the good-sleeper controls (GS) were that they

- reported no difficulty falling or staying asleep
- characterized their sleep as restorative and relatively unperturbable.

Exclusion criteria for all 3 groups were: 1) significant current medical or psychiatric illness other than unipolar depression, 2) sleep disorders other than Primary Insomnia, 3) memory impairments, 4) history of head injury, 5) prescription medication or recreational drug use within four weeks of laboratory study, 6) use of SSRIs within six months of laboratory study.

Polysomnographic Assessment

The recording montage consisted of a minimum of 15 electrophysiologic signals. The basic montage included two EOGs referenced to a single mastoid [LOC & ROC], six EEGs referenced to linked mastoids [F3, F4, C3, C4, O1, and O2], a bipolar mentalis EMG, bilateral corrugator EMGs, and an EKG. In addition, two channels of tibial EMG and one channel of nasal/oral air flow data were acquired to rule out the presence of occult sleep disorders (e.g., sleep apnea and/or PLMs). All electrophysiologic signals were acquired using a Coulbourn Instruments 16-channel POLYLINC™ system. The EOGs were acquired at a gain of 20K (3.75 Uv/mm equivalent) for an initial frequency bandwidth of 0.3—100Hz (24dB/octave). The EMGs were acquired at a gain of 20K for an initial bandwidth of 30—1000Hz. The EEGs were acquired at a gain of 20K for an initial bandwidth of 0.3—1000Hz. The EEG signals were also passed in series to six Coulbourn Instruments V75-48 bandpass filters (48dB/octave) set at 0.5—125Hz.

Digital acquisition was governed by Stellate Harmonie-Luna™ software and accomplished by a BSMI 519 A-to-D board. The A-to-D board has a notch filter at 60Hz and a 1 pole (6dB/octave) low pass filter at 300Hz. The base sampling rate was 512Hz. On-line decimation was used so that variable sampling rates could be obtained. The variable sampling rates, which were calculated based on the Nyquist frequency (sampling = 2 x highest frequency of interest), were as follows: EOGs at 16Hz, EEGs at 256 Hz and EMGs at 512Hz. The final digital display was additionally modified by digital filtering for optimal on-screen display (no effect on quantitative analysis). The digital band-pass filter settings were as follows: EOGs at 0.3—4Hz, EEGs at 0.3—20Hz, EMGs at 30—250Hz.

Sleep scoring

PSGs were scored in 30-second epochs according to Rechtschaffen and Kales (R&K) criteria.[49] Our scoring procedures slightly deviate from R&K methods and standards in two ways. First, we have both a duration and amplitude criteria for K-complexes. Based on the work of Bastien et al.,[50] K-complexes must be at least 50 mV. Second, based on early work by Dement et al.,[51] an epoch may be scored as stage 2 sleep, in the absence of spindles and K-complexes for three or more minutes, if between 5-19% Delta activity is identified. PSG scorers were extensively trained by the first author and meet or exceed laboratory inter-rater criteria of 90%. That is, 90% of epochs must be identified the same as in a master set of five standard records scored by the PI. In addition to sleep scoring, scorers identified and coded micro (0.1 - 7.0 secs) and mini (7.1-14.9 secs.) arousals. Arousals were identified as transient EEG "speeding", short intervals of "pen blocking" (amplifier saturation), and/or as phasic intrusions of EMG activity.

PSG definitions were as follows: Sleep onset was defined as two consecutive epochs of stage 1 or 1 epoch of stages 2,3,4, or REM. An awakening was defined as an instance of more than 1 minute of wakefulness occurring after sleep onset. These definitions are the default values for the Stellate Harmonie-Luna™ report generation program. Given these definitions, sleep continuity variables were as follows:

1) sleep latency: amount of time elapsed in minutes from "lights off" to "sleep onset,"

2) number of awakenings (NUMA): number of awakenings that occurred after sleep onset and prior to "lights on,"

3) wake after sleep onset (WASO): was the sum of wake time in minutes from sleep onset to "lights on,"

4) total sleep time: sum of NREM and REM sleep in minutes from "lights off" to "lights on."

EEG Frequency Assessment

Power Spectral Analysis (PSA) is a statistical technique for detecting periodicities within time series data. As employed within electroencephalography, the technique is routinely used to decompose complex wave forms into their constituent frequencies. Quantification is accomplished by determining the amount of voltage that occurs per Hz for pre-specified bandwidths.

The Digital EEG from night 1 was subjected to power spectral analyses using Stellate Harmonie-Luna™ software. For the present analysis, the spectral window was set for a two-second interval. Prior to frequency assessment, the data within the two second windows were automatically cosine tapered and detrended (mean detrend) to eliminate non-stationary data. Following the frequency assessment, multiple non-overlapping windows (15/epoch) were averaged to yield mean power spectral distributions for each sleep scored 30-second epoch (0.5 Hz resolution). Power spectra (mV2/Hz) for each of the EEG sites were computed for the following bandwidths: Delta-1 (0.5-2.5Hz), Theta (2.5-7.5Hz), Alpha (7.5-12.0Hz), Sigma (12-14Hz), Beta-1 (14.0-20.0Hz), Beta-2 (20-35Hz), Gamma-1 (35-45.0Hz), and Omega (45.0-125Hz).

Following the PSA routine, an ASCII data set was created for each subject which contained the following items in a columnar format: Time, epoch, NREM/REM cycle, sleep stage, micro-arousal events, mini-arousal events, and eight columns containing absolute power values for each spectral band (Delta – Omega). These files were imported into SAS. Using this platform, each subject's PSA data were manipulated so that 1) waking and movement time epochs and epochs with mini (0.1—7.0 secs) or micro (7.1—14.9 secs.) arousals were deleted, 2) relative power values (power per bandwidth over total power) were computed for each site per epoch. Total power was calculated by summing the power values for each of the 8 bandwidths per epoch, and 3) average values by site (e.g., C3/A2 & C4/A1) and average values across site ([C3/A2+C4/A1] / 2) were calculated for each NREM cycle. NREM and REM cycles were defined as follows:

NREM-1 was defined as extending from Sleep Onset to the first REM period.

NREM-2 was defined as extending from the last epoch of the

first REM period to the first epoch of the 2nd REM period.

NREM-3 is defined as extending from the last epoch of the 2nd REM period to the first epoch of the 3rd REM period.

A REM period was defined as 30 seconds or more of REM sleep. REM periods were identified as distinct—given 15 consecutive minutes of intervening NREM sleep.

The final output data represented average NREM power (relative power) for the first 3 NREM cycles. Relative power measures (e.g., [Beta Power/Total Spectrum Power]*100) were used so as to 1) control for individual difference variability with respect to EEG power and 2) to provide a measurement unit that has intuitive appeal, i.e., the percent of total brain activity that falls within each given frequency range. The analyses were limited to the first three cycles in order insure that there was comparable data across groups. For the present analysis only average NREM central EEG data were used ([C3/A2+C4/A1] / 2).

Sleep Diaries (Morning Reports) and Difference Scores

Sleep diaries were administered to each subject each morning at "lights on." The sleep diary required that subjects estimate in minutes "how long did it take you to fall asleep?" (S_SL), "how long were you awake after sleep onset?" (S_WAS0) and "how much time did you spend asleep during the night?" (S_TST). In addition, subjects were also asked to estimate "how many times did you awaken after sleep onset" (S_NUMA). In order to evaluate the extent to which subjects' perceptions of their sleep differed from PSG measures (subjective-objective discrepancies), difference scores were calculated by subtracting the PSG measures from the sleep diary estimates for Sleep Latency, (S_SL - SL = Δ_SL), Wake After Sleep Onset time (S_WASO - WASO = Δ_WASO) Number of Awakenings (S_NUMA - NUMA = Δ_NUMA), and Total Sleep Time (S_TST - TST = Δ_TST).

Analyses

Groups were compared using one-way ANOVAs with post hoc Duncan Multiple Range Tests. Pearson correlations for the entire sample were used to assess the association of high frequency EEG activity with subjective-objective discrepancy scores for sleep latency, wake after sleep onset time, and total sleep time.

RESULTS

Group Characteristics

As planned (see Table 1), the groups did not differ on age, sex, height, weight, or race. As expected, the groups differed on symptom measures, including the BDI, BAI, HRSD and the PSQI. Depression measures revealed that MDD patients had the most severe symptoms and that PI subjects differed from controls with respect to depression severity, but their scores were within normal limits. On the BAI, both the MDD Ss and the PI Ss exhibited mild levels of anxiety. Finally, as expected, the groups differed on the PSQI global measure of sleep disturbance severity (all contrasts). Patients with insomnia scored highest, and the Good Sleeper controls scored the lowest.

Group Differences on Sleep Continuity Measures

As seen in Table 2, the groups differed on most of the subjective and PSG sleep continuity measures. The exceptions were PSG-measured total sleep time and subjectively measured number of awakenings. Overall, patients with insomnia exhibited the worst sleep continuity profiles.

Difference score measures of the discrepancy between subjective and objective measures revealed that patients with insomnia, compared to the contrast groups, significantly overestimated sleep latency and underestimated total sleep time. Patients with insomnia also significantly underestimated number of awakenings. The groups did not differ with respect to subjective-objective discrepancies for wake after sleep onset time. Patients with Major Depression significantly differed from good sleeper controls only on the number of awakenings difference score. In this instance, patients with MDD did not exhibit the same trend as patients with Primary Insomnia. MDD patients reported awakening about as frequently as was assessed via polysomnography.

Group Differences on Artifact Rejection Procedures

As noted in the Methods, each subject's PSA data were manipulated so that waking and movement time epochs and epochs with mini (0.1—7.0 secs.) or micro (7.1—14.9 secs.) arousals were deleted. Overall, less than 2.5% of epochs containing micros and minis and less than 23% of epochs scored as Wake or

Table 1—Demographic and psychometric data

	PI	MDD	C	ANOVA	PI v MDD	PI v C	C v MDD
Demographic Measures							
Height	65.1 (3.7)	68.0 (5.2)	65.00 (3. 8)	NS	NS	NS	NS
Weight	135. 9 (24.4)	158.1 (28.3)	142.3 (23.1)	NS	NS	NS	NS
Age	36.5 (10.8)	38.3 (10.6)	38.1 (11.2)	NS	NS	NS	NS
Race	33.3% C	29.6% C	33.3% C	NS*	-	-	-
Sex	66.7% F	66.7% F	66.7% F	NS*	-	-	-
Psychometric Measures							
BDI	6.0 (3.0)	21.1 (7.0)	1.1 (0.9)	0.0001	P<.05	P<.05	P<.05
BAI	6.4 (6.8)	10.6 (6.6)	1.7 (1.8)	0.0414	NS	NS	P<.05
HRSD	3.5 (2.1)	16.6 (3.9)	0.0 (0.0)	0.0001	P<.05	P<.05	P<.05
PSQI	11.2 (1.6)	8.7 (1.1)	2.00 (1.18)	0.0001	P<.05	P<.05	P<.05

* Chi Square

Table 2—Sleep continuity measures

	PI	MDD	C	ANOVA	PI v MDD	PI v C	C v MDD
PSG Measures							
SL	21.8 (17.9)	9.5 (9.3)	7.9 (6.8)	0.05	P<.05	P<.05	NS
NUMA	9.3 (3.7)	2.1 (1.7)	4.7 (3.9)	0.0004	P<.05	P<.05	NS
WASO	72.9 (74.5)	24.1 (48.7)	21.0 (16.4)	0.08	NS	P<.05	NS
TST	323.7 (82.6)	366.7 (64.0)	348.3 (32.5)	0.37	NS	NS	NS
Sleep Diary Measures							
S_SL	79.6 (89.0)	22.2 (28.1)	17.6 (18.1)	0.05	P<.05	P<.05	NS
S_NUMA	2.4 (1.3)	3.1 (2.3)	1.8 (1.0)	NS	NS	NS	NS
S_WASO	76.1 (89.1)	23.6 (40.3)	16.2 (23.7)	0.08	NS	P<.05	NS
S_TST	278.9 (119.7)	363.13 (58.9)	370.0 (47.4)	0.05	P<.05	P<.05	NS
Difference Scores							
DSL	57.78 (79.0)	12.50 (19.7)	9.7 (18.3)	0.09	NS	P<.05	NS
DNUMA	-6.9 (3.8)	0.9 (2.5)	-2.8 (3.7)	0.0002	P<.05	P<.05	P<.05
DWASO	3.2 (42.4)	-2.3 (17.7)	-4.8 (22.5)	0.85	NS	NS	NS
DTST	-44.8 (54.7)	8.8 (41.0)	21.7 (48.1)	0.02	P<.05	P<.05	NS

Table 3—PSA Measures—relative power

	PI	MDD	C	ANOVA	PI v MDD	PI v C	C v MDD
Delta (0.5-2.5 Hz)	64.3 (9.0)	53.5 (27.9)	61.8 (22.5)	0.538	NS	NS	NS
Theta (2.5-7.5 Hz)	21.5 (4.9)	11.8 (5.3)	17.4 (6.5)	0.004	p<.05	NS	p<.05
Alpha (7.5-12.0 Hz)	6.3 (3.2)	3.2 (2.6)	4.5 (2.4)	0.073	p<.05	NS	p<.05
Sigma (12.0-14.0 Hz)	1.7 (0.6)	1.0 (1.2)	1.4 (1.1)	0.404	NS	NS	NS
Beta-1 (14-20 Hz)	1.84 (0.63)	0.61 (0.41)	0.96 (0.59)	.0003	p<.05	p<.05	NS
Beta-2 (20-35 Hz)	1.48 (0.58)	0.38 (0.23)	0.66 (0.34)	.0001	p<.05	p<.05	NS
Gamma (35-45 Hz)	0.47 (0.29)	0.13 (0.08)	0.26 (0.18)	.0065	p<.05	p<.05	NS
Omega (45-125 Hz)	2.39 (1.81)	29.4 (34.85)	12.9 (27.00)	0.0973	p<.05	NS	p<.05

* Power = (μV^2/Hz)
Relative Power = ([power per bandwidth] /[total power])
e.g., Delta Relative Power = 0.5-2.5 μV^2/Hz / 0.5-125 μV^2/Hz

MT were identified and removed prior to the calculation of NREM averages. A contingency analysis of the number of epochs deleted by group revealed that more micros and minis were removed from the MDD group while more epochs scored as MT or Wake were removed from the PI records.

Group Differences on PSA Measures

Table 3 presents the results for the PSA data. The groups significantly differed for average NREM activity for Theta, Beta-1, Beta-2 and Gamma activity ($p<.01$). Subjects with Primary Insomnia exhibited significantly more Beta-1, Beta-2 and Gamma activity compared to both patients with MDD (Secondary Insomnia) and Good Sleeper controls. Group trends were also evident for Theta, Alpha and Omega activity ($p<.10$). Within these ranges, MDD subjects tended to exhibit less Theta and Alpha activity and more Omega activity. Post hoc follow up tests (Duncan Multiple Range Tests) revealed that these trends were significant when MDD subjects were compared to Good Sleeper controls.

PSA Correlations with Subjective-Objective Difference Scores

The correlational analyses revealed that Beta-1 and Beta-2 were significantly correlated with Δ_TST measures, tended to be associated Δ_SL measures, and were not associated with Δ_WASO measures. The specific correlations are presented in Table 4. In the case of Δ_TST the direction of the correlation suggests that larger discrepancy scores (less subjective sleep than evident on PSG) are associated with more Beta activity.

DISCUSSION

In the present study, we found that patients with insomnia exhibited more Beta-1, Beta-2, and Gamma activity during NREM sleep than either patients with MDD or good sleeper controls and that Beta activity (12—35 Hz) during unambiguous sleep was correlated with the tendency to underestimate total sleep.

Table 4—Beta/Gamma correlations with subjective-objective descrepancy measures

n = 26

	BETA-1%	BETA-2%	GAMMA%
ΔSL	r = 0.33 p = 0.098	r= 0.28 p = 0.17	r= - 0.03 p = 0.90
ΔWASO	r = 0.03 p = 0.888	r= 0.009 p = 0.967	r= 0.267 p = 0.187
ΔTST	**r = - 0.46 **** **p = 0.019**	**r= - 0.46 **** **p = 0.019**	r= - 0.13 p = 0.532

Why were the between group sleep continuity effects so modest ?

There are at least two potential explanations. First, the data for the present study were culled from the first in-lab study night. As a result, "First Night" (Good Sleepers sleep more poorly)[52] and "Reverse First Night" (Patients with Insomnia sleep better)[53] effects may have attenuated group differences, particularly those between the MDD and Good Sleeper subjects. Second, after the data were collected we found that there had been an unintentional effect of allowing subjects to set their own bedtimes and rise-times; Good Sleepers allotted themselves the shortest sleep periods (total time in bed [TTIB]). As a result the group most likely to increase total sleep time did not accord themselves the opportunity. This problem has since been addressed by fixing TTIB to seven hours.

Do subjective-objective descrepancies occur primarily in patients with insomnia?

There is substantial literature which demonstrates that patients with insomnia tend to overestimate how long it takes them to fall asleep and how much sleep is obtained relative to PSG measures.[31-41] Less clear is 1) whether the bias is uniform across all the sleep continuity parameters including number and duration of awakenings, and 2) the extent to which good sleepers and/or patients with secondary insomnia show similar tendencies. Our data suggest that the bias is not uniform and that subjective-objective discrepancies occur, but much less substantially, in good sleepers and in patients with secondary insomnia. The lack of uniformity is, to us, very suggestive. It indicates that patients with insomnia are not simply reporting, across the board, that their symptoms are more severe; thus ruling out "neuroticism" as the sole explanation for so called sleep state misperception.

Is HFA in Primary Insomnia limited to the Beta portion of the EEG power spectrum ?

Our findings are concordant with the cognitive neuroscience literature suggesting that high frequency EEG activity is not limited to the Beta range, but extends into the Gamma portion of the EEG spectrum. Since both forms of EEG activity are associated with cognitive functioning (sensory processing, attention, perception and long term memory), these data support the view that the pathophysiology of insomnia is, in part, related to the inability to disengage cognitive processes at/around sleep onset and during NREM sleep.[29] Interestingly, the MDD subjects (while exhibiting little in the way of Beta/Gamma activity) exhibited increased activity within the Omega range. If activity within this range is a primary correlate of increased cranio-facial EMG activity, this finding is consistent with the perspective that Major Depression is associated with somatic hyperarousal, as measured by, for example, increased levels of plasma and urinary cortisol and by elevated nocturnal core body temperature.[54-58]

Is high frequency EEG activity in Primary Insomnia CNS in origin?

To address this question directly, one would need to show increased CNS activation using an alternative measurement strategy that is not likely to be influenced by cranio-facial EMG activity. Inter-cranial EEG, M-EEG, SPECT, or PET would be ideal for this kind assessment. Our group is presently acquiring data using SPECT. In the absence of a direct test, the lack of Omega activity offers evidence of specificity. It suggests that the Beta and Gamma activity that occurs in Primary Insomnia is not related to EMG artifact, as has been suggested.[30] Had this been true, insomnia patients would have exhibited increased activity across the entire upper portion of the power spectrum.

Is it possible that high frequency EEG activity, if CNS in origin, is simply related to macro-architectural phenomena (e.g., increased number and/or duration of waking epsiodes, movement times and/or "micro arousals")?

This has been a viable hypothesis in that some of the earlier work has not elaborately dealt with the issue of artifact rejection. Thus, it is possible that an increased number or duration of micro and mini arousals and/or transient episodes of wakefulness could account for the small percentage of power that occurs within the upper spectrum for NREM sleep. While still a possibility, the methods used in our study make this explanation less likely. As previously noted, all epochs with micro- or mini-arousals were removed, as were all epochs scored as Wake or Movement time, prior to calculating the NREM averages. Thus, the NREM spectral profiles were based solely on the sleep EEG.

Is Beta/Gamma activity correlated with the subjective perception of sleep quantity?

We evaluated this question by examining whole sample correlations between average NREM Beta/Gamma activity and subjective-objective discrepancy scores for Sleep Latency (SL), Wake After Sleep Onset Time (WASO) and Total Sleep Time (TST). Our intent was to focus on whether Beta/Gamma activity might explain some of the variance related to the inability to perceive PSG sleep. Our perspective was - If Beta/Gamma (or processes associated with it) during unambiguous sleep interferes with the perception of sleep, then Beta/Gamma during sleep should be, as was the case, negatively associated with the ability to perceive sleep. The lack of correlation with WASO also makes sense. All the subjects in this sample did not have difficulty perceiving PSG defined wakefulness. All three groups were accurate

to within +/- 5 minutes. Given that there was very little variance in the Δ_WASO variable and that there was a considerable amount of variance in Beta/Gamma activity, it follows that significant correlation was not detected. Put differently, there was no subjective objective WASO discrepancy to explain. Finally, the weak positive correlation with Δ_SL measures also seems readily interpretable. If Beta/Gamma activity interferes with the perception of sleep, one might expect such activity would impact on judgments regarding sleep latency. The problem is that average NREM measures of Beta/Gamma activity may not be the same as those derived from some discretely defined sleep onset interval. Thus, average NREM measures are not likely to reflect the intensity of Beta/Gamma activity at sleep onset and thus may only yield only modest correlations based on the loose correlation between sleep onset levels of Beta/Gamma and average NREM levels. Measures such as those used by Merica and colleagues[20-25] (e.g., Delta and Beta slope and or their interaction) might be expected to be more strongly correlated with subjective-objective discrepancies for sleep latency.

Our correlational findings are truly suggestive, but also perplexing. The results were suggestive because Beta was significantly correlated with subjective-objective discrepancy scores for total sleep time and tended to be correlated with subjective-objective discrepancy scores for sleep latency. These findings are consistent with the neurocognitive mode of insomnia which suggests that high frequency EEG activity is related to processes that interfere with the perception of sleep quantity and quality.[29] The results were perplexing because the correlation was limited to the Beta range and was of a moderate magnitude (r=– 0.46). The lack of correlation with Gamma activity suggests to us that, while both forms of activity are thought to be related to cognitive processes, the two spectral domains may not equally represent all the components of information processing. For example, Beta-1 and Beta-2 may be associated with long term memory function while Gamma activity is more specifically related to sensory processing and attention. The magnitude of the correlation suggests that, while Beta activity explains a significant amount of subjective-objective variance, factors other than those associated with NREM Beta activity also account for "sleep state misperception."

Conclusion

Cumulatively, there is good evidence that Beta/Gamma activity at/around sleep onset and during NREM sleep is increased in patients with insomnia, in comparison to both good sleeper controls and MDD patients with secondary insomnia. There are also preliminary data to suggest that Beta EEG activity 1) is negatively correlated with patient's ability to perceive sleep and 2) varies in association with clinical course. The combination of these data suggest that further research in this arena will be fruitful. Possible directions might include EEG brain mapping to determine the topographical distribution of Beta/Gamma activity, brain imaging to determine the source generators of Beta/Gamma activity, and/or chronobiologic studies to determine how Beta/Gamma activity distributes across the 24-hour day and/or varies with non-preferred phase sleep. These types of studies, along with the inclusion of multiple comparison groups and/or the use of longitudinal studies with treatment components, are likely to be maximally informative in our effort to understand the neurobiology and phenomenology of insomnia.

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