http://dx.doi.org/10.5665/sleep.1692

White and Gray Matter Abnormalities in Narcolepsy with Cataplexy

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Study Objectives: The authors applied diffusion-tensor imaging including measurements of mean diffusivity (MD), which is a parameter of brain tissue integrity, fractional anisotropy (FA), which is a parameter of neuronal fiber integrity, and voxel-based morphometry, which is a measure of gray and white matter volume, to detect brain tissue changes in patients with narcolepsy-cataplexy.

Design: N/A.

Patients: Patients with narcolepsy-cataplexy (n = 16) and age-matched healthy control subjects (n = 12) were studied.

Interventions: Whole cerebral MD, FA measures, and the volumes of the gray and white matter compartments were analyzed using statistical parametric mapping.

Measurement and Results: Significant MD increases and concomitant FA decreases were localized in the fronto-orbital cortex (P < 0.001) and the anterior cingulate (FA, P < 0.001; MD, P = 0.03) in narcolepsy-cataplexy. Additional MD increases without FA changes were detected in the ventral tegmental area, the dorsal raphe nuclei (P < 0.001), and the hypothalamus (P < 0.01). FA signal decreases were observed in the white matter tracts of the inferior frontal and inferior temporal cortices of narcolepsy-cataplexy patients (P < 0.001). Brain volume loss was evident in focal areas of the inferior and superior temporal cortices (P < 0.001) and the cingulate (P = 0.038).

Conclusions: Areas of increased diffusivity in the hypothalamus appear consistent with hypocretinergic cell loss reported in narcolepsy-cataplexy. Signal abnormalities in the ventral tegmental area and the dorsal raphe nuclei correspond to major synaptic targets of hypocretin neurons that were associated with the regulation of the sleep-wake cycle. Brain tissue alterations identified in the frontal cortex and cingulate are crucial in the maintenance of attention and reward-dependent decision making, both known to be impaired in narcolepsy-cataplexy.

Keywords: Diffusion tensor imaging, voxel based morphometry, narcolepsy with cataplexy, statistical parametric mapping

Citation: Scherfler C; Frauscher B; Schocke M; Nocker M; Gschliesser V; Ehrmann L; Niederreiter M; Esterhammer R; Seppi K; Brandauer E; Poewe W; Högl B. White and gray matter abnormalities in narcolepsy with cataplexy. *SLEEP* 2012;35(3):345-351.

INTRODUCTION

Narcolepsy-cataplexy is a sleep-wake disorder characterized by excessive daytime sleepiness, sudden loss of muscle tone triggered by emotions (cataplexy), sleep paralysis, and hypnagogic/hypnopompic hallucinations. Symptom onset peaks in the second decade of life and affects 1 in 2,000 people. Biologic markers include sleep-onset rapid eye movement (SOREM) periods on multiple sleep latency test (MSLT) and low or undetectable levels of cerebrospinal fluid hypocretin-1 (orexin A). Narcolepsy-cataplexy has been linked to a loss of hypothalamic neurons containing hypocretin, a neuropeptide implicated in the sleep wake regulation.[1] Conventional structural brain imaging has so far failed to identify consistent abnormalities in patients with narcolepsy-cataplexy. Recently, voxel-based morphometry (VBM), a research tool allowing between-group statistical comparisons of cerebral volume changes, revealed a loss of hypothalamic gray matter in a group of patients with narcolepsy.[2-4] In contrast, three other VBM studies were not able to reproduce this finding but reported volume changes in brain regions other than the hypothalamus, such as the orbitofrontal, frontomesial, and inferior temporal cortex.[5-7] Different from VBM, diffusion-tensor imaging (DTI) is a unique form of magnetic resonance imaging (MRI) contrast able to provide information on the structural integrity of fiber tracts and neuronal tissue. DTI is able to quantify the direction of diffusing water molecules within the entire brain volume. Within fiber tracts, the motion of water molecules perpendicular to the main axonal direction is restricted to a greater extent than is the diffusion along the main axis, resulting in an anisotropic-shaped space termed fractional anisotropy (FA). In addition, the mean diffusivity (MD) reflects the total magnitude of diffusion and hence provides information of alterations in the extracellular volume of both the gray and white matter compartment.[8,9] Both FA and MD were shown to be sensitive to brain tissue alterations in neurodegenerative, inflammatory, and ischemic central nervous system diseases as well as idiopathic rapid eye movement (REM) sleep behavior disorder.[10,11] In combination with DTI, VBM is useful in determining whether DTI signal changes derive from brain atrophy or intrinsic structural reorganization not affecting brain volume changes. In the current study, we therefore applied DTI and VBM to detect structural gray and white matter signal alterations in a group of patients with narcolepsy-cataplexy.

Submitted for publication June, 2011
Submitted in final revised form September, 2011
Accepted for publication September, 2011
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METHODS

Subjects

A total of 16 patients with narcolepsy-cataplexy (12 men, 4 women) were recruited from referrals or follow-up visits at the Sleep Disorders Clinic at the Department of Neurology at

Innsbruck Medical University in Innsbruck, Austria. Only patients age 40 to 70 yr fulfilling the International Classification of Sleep Disorders (ICSD-2) diagnostic criteria for narcolepsy-cataplexy were eligible for the study.[12] All patients were clinically evaluated by neurologists experienced with narcolepsy, and underwent nocturnal overnight polysomnography plus MSLT. Polysomnographic work-up was performed on average 1.9 yr (range, 0-5 yr) prior to MRI. Only patients with clinical clear-cut (no atypical) cataplexy were included in this study. Exclusion criteria were other neurologic or mental disorders. Ten patients were on central nervous system active medication at the time of MRI (modafinil (n = 4); methylphenydate (n = 2); sodiumoxybate (n = 1), histamine H3 antagonist GSK189254; study trial name H3A106104 (n = 1); clomipramine (n = 2); trazodone (n = 1), protriptyline (n = 1); citalopram (n = 1); sertraline (n = 1); reboxetine (n = 1)). Six patients were drug free. Subjects with evidence of structural lesions on T1- and T2-weighted conventional MRI as well as artifacts in DTI were excluded from the study. Twelve age- and sex-matched healthy subjects (7 men, 5 women) without any history suggestive of narcolepsy or any other neurologic or psychiatric illness in the clinical assessment or on MRI served as the control group. The study was approved by the Ethics Committee of the Innsbruck Medical University. Subjects' written informed consent was obtained according to the Declaration of Helsinki.

MRI Data Acquistion

Before each MRI acquisition sequence, patients and control subjects were asked to refrain from sleeping and were supervised by both a clinical research fellow and a technician during the entire MRI acquisition. In addition, the presence of any emotional stimuli during scanning time was controlled. All measurements were performed on a 1.5-Tesla whole magnetic resonance scanner (Magnetom Avanto, Siemens, Erlangen, Germany) by using a circular polarized eight-channel head coil. The MRI protocol comprised diffusion-weighted echoplanar imaging with diffusion-sensitizing gradients in at least six directions with two b-values (0 and 1,000 s/mm^2). The repetition time (TR) was 6,000 ms, the echo time (TE) was 94 ms, the slice thickness was 3 mm, the slice intergap was 0.75 mm, the matrix was 128 × 128 interpolated to 256 × 256 during Fourier transformation, and the field of view was 230 × 230 mm. The brain was covered by 39 slices. Maps of MD and FA were automatically calculated by the magnetic resonance scanner. In addition, all subjects received a coronal three-dimensional magnetization prepared rapid acquisition gradient echo (MPRAGE) with a TR of 1,700 ms, a TE of 2.98 ms, an inversion time of 1,100 ms, a slice thickness of 1.2 mm, a matrix of 256 × 256, and a field of view of 220 × 180 mm.[13]

Image Preprocessing

To avoid previous assumptions through region of interest analysis on brain areas of potential interests, DTI and three-dimensional MPRAGE data were subjected to statistical parametric mapping (SPM), a technique that objectively localizes focal changes of voxel values throughout the entire brain volume.[14] The software package SPM8 (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab 7.8 (Mathsworks Inc., Sherborn, MA, USA) was used to preprocess and analyze DTI and VBM data. To achieve accurate spatial normalization for MD and FA images, T1-weighted images were normalized onto the T1 template in Montreal Neurological Institute (MNI) space and the resulting transformation parameters were applied to the participant's corresponding MD and FA images. A gaussian kernel of 4 × 4 × 4 mm was then convolved with the spatially normalized parametric images to smooth them to accommodate interindividual anatomic variability and to improve signal-to-noise ratios for the statistical analysis.

For VBM analysis, skull was removed from MPRAGE data sets. VBM was then performed using the standard version of the diffeomorphic anatomical registration using exponentiated lie algebra (DARTEL) toolbox implemented in SPM8 to have a high-dimensional normalization protocol.[15] Segmented and modulated images were transformed from group-specific DARTEL templates into MNI space and smoothed by a gaussian kernel of 4 × 4 × 4 mm.

Statistical Analysis

The obtained data sets allowed for categoric comparisons of MD and FA values in analogous voxel regions between healthy volunteers and patients with narcolepsy. A masking threshold of 400 mm^3 was applied to the DTI and VBM analysis of gray and white matter volume. A general linear model was set up comparing gray matter and white matter segments, as well as FA and MD maps of the narcolepsy group and the control group with a two tailed *t* test at P = 0.001 and P = 0.01. The false discovery rate was used to correct for multiple comparisons. For FA and MD analysis, age was included as a covariate. For VBM analysis, age and total intracranial volume were entered as covariates. A linear regression analysis was performed to investigate whether regional brainstem and hypothalamus MD values (dependent variable, weighted for age) can be predicted by patients' MSLT sleep latency and number of SOREM periods (independent variables).

RESULTS

Individual findings on clinical characteristics and the MSLT and HLA status are given in Table 1. There was no significant difference in age and sex distribution between the narcolepsy-cataplexy (age 56.8 ± 10.1 yr; sex female/male: 4/12) and the control cohort (age 59.8 ± 4.4 yr; sex female/male: 5/7). All patients were positive for HLA DQB1*0602 and DRB1*1501. Mean Epworth sleepiness score in the patient group was 20.1 ± 1.9 (range, 17-24). Ten patients (62.5 %) had sleep paralysis and 9 (56.3 %) had hypnagogic/hypnopompic hallucinations. All patients underwent overnight polysomnography and MSLT. In the MSLT, mean sleep latency was 3.0 ± 2.0 min (range, 2.0 – 6.0 min). All but 2 patients on central nervous system active drug medication at time of polysomnography had ≥ 2 sleep-onset REM episodes. Mean number of sleep-onset REMs was 3.29 ± 1.4 (range, 0 - 5).

Significant DTI and VBM changes are outlined in Table 2. SPM localized significant MD increases and concomitant FA decreases in the fronto-orbital cortex bilaterally (BA 11; P < 0.001) and the anterior cingulate (FA ,P < 0.001; MD, P = 0.03) of patients with narcolepsy and cataplexy compared to the control group (Figures 1 and 2). Significant MD increases without FA changes were detected in the ventral tegmental area, the dorsal raphe nuclei (P < 0.001), the right superior temporal gyrus (BA, Brodmann area41 and 42), and the hypothalamus (P < 0.01). No significant decreases of MD values of the nar-

Table 1—Demographic and clinical characteristics of patients with narcolepsy with cataplexy

	Patients, n															
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Sex	f	m	m	f	m	m	m	f	m	f	m	m	m	m	m	m
Age at investigation, yr	57	40	64	59	44	65	49	62	51	51	55	67	68	68	40	70
Age at onset of disease, yr	17	22	14	23	38	40	22	47	28	39	38	14	9	33	16	20
Cataplexy	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sleep paralysis	-	+	+	+	-	+	+	-	+	+	-	+	-	+	-	+
Hypnagogic/hypnopompic hallucinations	-	+	-	-	-	+	+	-	+	+	+	+	+	-	-	+
Epworth Sleepiness Scale	21	21	17	22	18	24	18	20	21	19	18	21	20	18	21	22
MSLT sleep latency, min	33	4.6	2	2.5	6	0.9	2	1.6	1.2*	1.1	5.5*	2	1.2	4.4	3.6	3.4*
MSLT, n SoREMs	4	4	3	4	2	2	5	4	2*	4	0*	2	5	4	3	0*
HLA DQB1*0602	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HLA DRB1*1501	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

m, male; f, female; MSLT, multiple sleep latency test; min, minutes; n, number; SoREMs, sleep onset REM episodes out of 5 nap opportunities. *Patients on CNS active medication at time of polysomnography. Diagnosis of narcolepsy was performed at referring centers. Due to the presence of clear cataplexy anticataplectic medication was not withdrawn.

Table 2—Between-group SPM findings showing the locations of significant changes of MD, FA and gray matter density values in patients with narcolepsy-cataplexy versus healthy control subjects.

Cerebral region	**Cluster size (mm^3)**	**MNI co-ordinates**			**T value**	**P values corrected***	**Height threshold**
		x	**y**	**z**			
Significant MD increases in narcolepsy cataplexy versus controls							
right temp superior gyrus, BA 41	2864	-42	-34	16	8.36	0.001	0.001
BA 42		-58	-40	18	7.49		
left fronto-orbital cortex, BA 11	1064	16	18	-26	7.2	0.001	0.001
ventral tegmental area,	552	4	-24	-6	6.44	0.015	0.001
right fronto-orbital cortex, BA 11	1128	-16	22	-24	6.41	0.001	0.001
anterior cingulate, BA 24	448	4	28	26	5.88	0.03	0.001
left hypothalamus	1704	6	2	-14	6.92	0.015	0.01
right hypothalamus		-6	2	-16	6.73	0.022	0.01
Significant FA decreases in narcolepsy cataplexy versus controls							
right frontal sup orbital gyrus, BA 11	2544	-18	58	-6	5.24	0.0001	0.001
left frontal sup and mid orbital gyrus, BA 11	1320	18	58	-6	5.56	0.0001	
frontal WM adjacent to the anterior cingulate and frontal superior gyrus	1712	-20	20	46	6.33	0.0001	
right frontal mid orbital gyrus, BA 47	568	-36	50	-4	5.33	0.015	
right inf temp gyrus, BA 20	1152	-42	6	-34	5.8	0.001	
left inf temp gyrus, BA 20	848	50	-2	-28	5.26	0.004	
Significant gray matter density decreases in narcolepsy cataplexy versus controls							
left supramarginal gyrus, BA 48	6024	50	-30	30	4.24	0.001	0.001
left inf temp gyrus, BA 20	2272	57	-32	-14	4.3	0.044	
left sup temp gyrus, BA 22, 48	1816	56	-26	8	6.09	0.052	
Significant white matter density decreases in narcolepsy cataplexy versus controls							
Posterior cingulate, BA 23	15192	0	-38	33	4.39	0.038	0.01
Anterior cingulate, BA 11		-5	35	-5	3.37		

MD, mean diffusivity; FA fractional anisotropy; BA, brodmann area; MNI, Montreal neurological imaging space. *P values are false discovery rate-corrected at the voxel-cluster level.

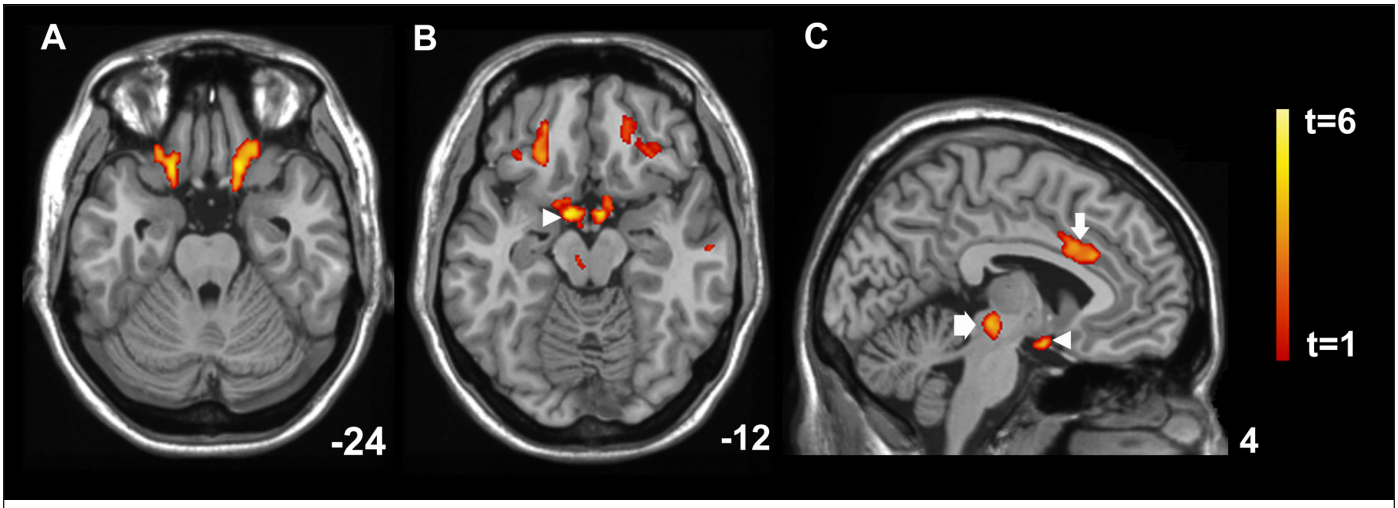

Figure 1—SPM (t) axial intensity projection maps rendered onto a stereotactically normalized MRI scan, showing areas of significant increases of MD values (color code, yellow to orange) in a cohort of patients with narcolepsy-cataplexy versus healthy control subjects. The number at the bottom right corner of each MRI scan corresponds to the z coordinate (**A** and **B**) and x coordinate (**C**) in MNI space. Fronto-orbital cortex (**A**), hypothalamus (**B** and **C**, arrowhead), cingulate (**C**, small arrow), and ventral tegmental area (**C**, large arrow) are identified.

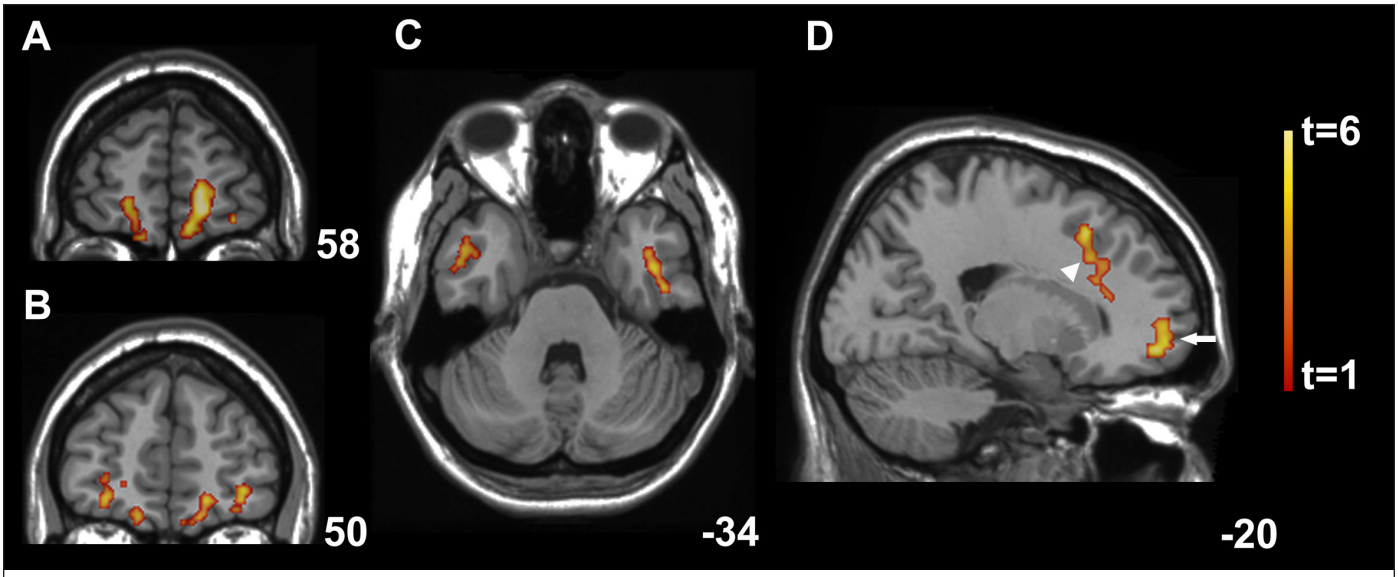

Figure 2—SPM (t) axial maximum intensity projection maps rendered onto a stereotactically normalized MRI scan, showing areas of significant decreases of FA values (color code, yellow to orange) in a cohort of patients with narcolepsy-cataplexy versus healthy control subjects. The number at the bottom right corner of each MRI scan corresponds to the y coordinate (**A** and **B**), the z coordinate (**C**) and the x coordinate (**D**) in MNI space. Right and left frontal superior orbital gyrus (**A**), left and right frontal superior and middle orbital gyrus (**B**), left and right inferior temporal gyrus (**C**), frontal white matter tracts adjacent to the anterior cingulate (**D**, arrowhead), and right frontal superior orbital gyrus (**D**, arrow) are identified.

colepsy cohort were observed throughout the entire brain volume. Significant FA signal decreases were observed in white matter tracts of the inferior temporal cortices ($P < 0.001$) of narcolepsy-cataplexy patients in comparison with the control group. No significant increases of FA values of the narcolepsy group were observed throughout the entire brain volume. Brain volume loss was evident in the gray matter compartment of the inferior temporal gyrus (BA 22; $P < 0.001$), the superior temporal gyrus (BA 22 and 48; $P < 0.001$), and the supramarginal gyrus (BA 48; $P < 0.001$) as well as circumscribed areas within the white matter compartment of the cingulate cortex ($P < 0.038$; Figure 3). There were neither areas of increased gray matter density nor signal increases in the white matter density of the narcolepsy cohort. No differences were found in DTI and VBM measures between nonmedicated and medicated narcolepsy-cataplexy patients. Linear regression analysis revealed no significant correlations between MD values in the hypothalamus or ventral tegmental area and MSLT sleep latency ($r^2 = 0.09$) and number of SOREM periods ($r^2 = 0.12$).

DISCUSSION

In the current study, we combined observer-independent voxel-based analysis of FA, and MD measures, as well as gray and white matter density, in patients with polysomnography-confirmed narcolepsy with cataplexy and normal control subjects. We identified significant DTI signal changes in

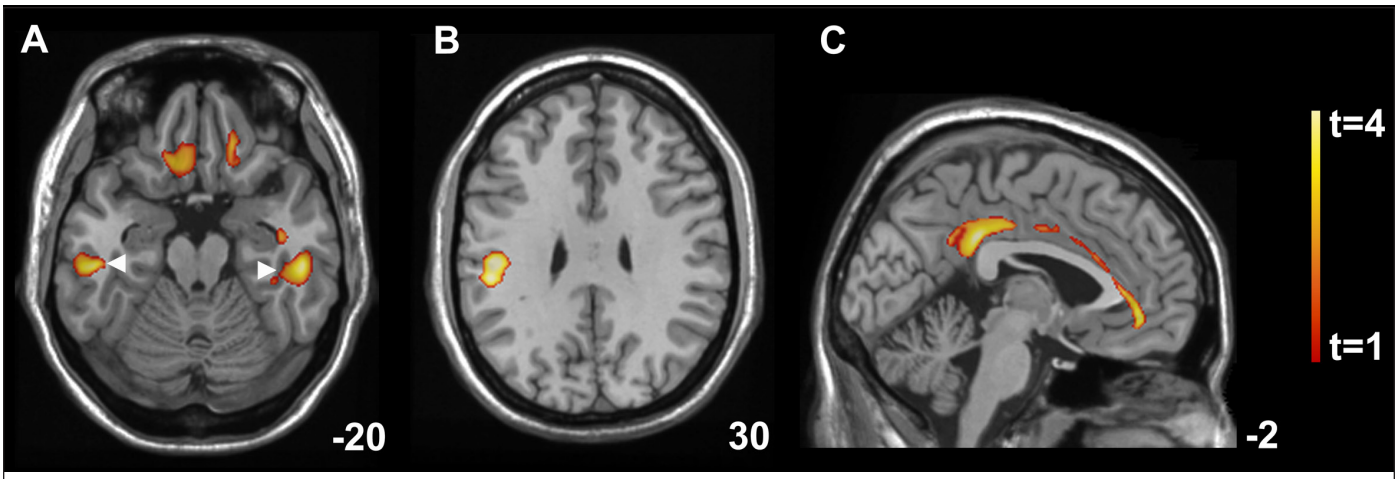

Figure 3—SPM (t) axial intensity projection maps rendered on to a stereotactically normalized MRI scan, showing areas of significant decreases (color code, yellow to orange) of gray matter density values (**A** and **B**) and of white matter density values (**C**) in a cohort of patients with narcolepsy-cataplexy versus healthy control subjects. The number at the bottom right corner of each MRI scan correspond to the z coordinate (**A** and **B**) and x coordinate (**C**) in MNI space. Left and right inferior temporal gyrus (**A**, arrowheads), left supramarginal gyrus (**B**), and anterior and posterior cingulate (**C**) are identified.

the hypothalamus and its hypocretinergic projection sites to the brainstem as well as to cortical areas including the inferior orbital cortex, the cingulate cortex, and the inferior and superior temporal cortices. MD increases without alteration of the FA signal as observed in the hypothalamus and the ventral tegmental area of patients with narcolepsy-cataplexy relate to an increase of the extracellular fluid space without further deformation of its shape and were repeatedly observed in brain regions rich in neurons, such as subcortical or cerebellar nuclei affected by neurodegeneration.[16,17] Increased diffusivity in the region of the caudal and central portion of the hypothalamus comprised a volume of approximately 850 mm^3 on each side and appeared consistent with extensive loss of hypocretin-producing cells as shown in postmortem studies of patients with narcolepsy.[1,18,19] In line with this observation FDG-PET and [^{99m}]Tc-ethyl-cysteinate dimer single-photon emission computed tomography (ECD SPECT) studies reported significant glucose hypometabolism and hypoperfusion respectively in both hypothalami of patients with narcolepsy.[20,21] Decreases of hypothalamus gray matter volume were also observed in three VBM studies, whereas three other studies could not reproduce this finding.[2-7] Divergent VBM results of narcolepsy in the hypothalamus might arise from methodologic differences of image acquisition and image postprocessing as well as the distinct use of inclusion and exclusion criteria for patients with narcolepsy-cataplexy. Our VBM analysis again failed to detect any gray or white matter volume changes in this particular brain area that supports the hypothesis of intrinsic structural brain tissue alterations in the hypothalamus without any volume related brain atrophy.

Significant MD increases were also noted in brainstem nuclei comprising a significant portion of the ascending arousal system including the ventral tegmental area and the dorsal raphe. These nuclei were shown to constitute major projection sites of hypocretin baring neurons originating from the posterior and lateral hypothalamus [22] and have been linked to the maintenance of wakefulness.[23,24] In patients with narcolepsy and cataplexy, the loss of the tonic hypocretin-mediated drive to the ascending arousal system was suggested to interfere with the maintenance of waking periods resulting in sleep attacks.[25,26] The brainstem and hypothalamus MD signals were not correlated with MSLT sleep latency and number of SOREM periods in our cohort, which might be due to intragroup variance of the MD signal resulting from covariates such as age at scanning and disease duration. Hence, prospective longitudinal studies are warranted to investigate the evolution of DTI parameters over time. Significant MD increases and overlapping decreases of FA signal were identified bilaterally in the orbito-frontal cortex (BA 11). Concomitant FA decreases and MD increases are thought to reflect both neuronal and axonal or myelin damage, leading to depletion of restricting barriers to water molecular motion. As a result, anisotropy (which is a measure of the degree of alignment of cellular structures within fiber tracts) decreases and the magnitude of diffusion, a measure of extracellular fluid volume, increases. This antipodal behavior of FA and MD coefficients was observed in brain areas known to be affected by neurodegenerative processes of patients with multiple system atrophy or Alzheimer disease.[27-29] Our finding of DTI signal alterations in the orbito-frontal cortex is consistent with bilateral glucose hypometabolism in BA 11 of patients with narcolepsy-cataplexy, which was suggested to correspond to the decline of hypocretin projection sites from the posterior hypothalamus via thalamic nuclei to various brain areas, including the frontal cortex.[20,30] The orbito-frontal cortex is known to process reward-related information for decision making from inferior prefrontal brain areas and limbic structures.[31,32] Interestingly, recent functional imaging and neuropsychologic investigations of parameters for decision making revealed higher tolerance of uncertainty and less influence of reward contingencies in patients with narcolepsy-cataplexy.[33,34] In this context, further studies are warranted to illuminate the association of structural neuronal damage and the reward dependent influence of decision making in patients with narcolepsy-cataplexy.

Significant MD increases and FA decreases as well as corresponding reduction of white matter volume and, to a lower extent, gray matter volume were also evident in the anterior and posterior cingulate cortex indicating both neuronal and axonal damage in our narcolepsy-cataplexy cohort. This find-

ing is in line with marked hypoperfusion in the cingulate cortex as revealed by ECD SPECT.[21] The cingulate cortex is part of the limbic system and was shown to be activated when subjects were confronted with positive emotional triggers, which was not observed in patients with narcolepsy-cataplexy.[35] Malfunction and structural dysintegrity of hypothalamic-limbic circuits in patients with narcolepsy support the concept of impaired modulation of norepinephrine and 5-hydroxytryptamine positive neurons in the brainstem through inputs from both the limbic system and hypocretin deficient hypothalamic projections which in turn was shown to result in reduced muscle tone and cataplexy.[26]

The cingulate cortex is also a key structure of the "executive attention network" that enables the prolonged and focused processing of information.[36] Gray matter thickness was reported to be correlated with executive control and cortical thinning was detected in patients with attention deficit/hyperactivity disorder.[37,38] In patients with narcolepsy, two neuropsychologic studies showed executive control deficits, which was suggested to be related to a reduction of available cognitive processing resources.[39,40] Recently, event-related potentials for perceptual and cognitive processes were measured in patients with narcolepsy. In 17 drug-free patients, Saletu and colleagues localized prolonged information processing for cognitive processing in the executive attention network including the cingulate cortex.[41] The data from functional imaging, neuropsychology, and electrophysiology together with our structural MRI findings indicate that documented impairment in the executive attention network is not an epiphenomenon resulting from altered sleep regulation mechanisms hypothetically affecting the ability to sustain attention but the correlate of structural dysintegrity of the cingulate cortex in patients with narcolepsy-cataplexy.

Significant MD increases were also observed in the left and to a lower extent in the right superior temporal gyrus corresponding to the primary auditory cortex (BA 41 and 42). These brain areas were shown to filter and process auditory stimuli.[42] Electrophysiologic measures of the activation of auditory stimuli by cortical areas revealed a prolonged latency of auditory evoked potentials in patients with narcolepsy.[42,43] It remains to be shown whether our finding of structural dysintegrity of the primary auditory cortex could serve as the morphologic correlate of alterations of auditory processing in patients with narcolepsy-cataplexy.

Significant FA decreases bilaterally of the inferior temporal cortex (BA 20) in patients with narcolepsy-cataplexy correspond to reduction of volume loss as revealed by our VBM analysis which is in line with two further VBM studies.[4,7] The inferior temporal cortex was associated with the processing of visual information and is part of the recognition memory.[44] The ability of visual discrimination was reported to be impaired in patients with narcolepsy.[45] Further studies are needed to clarify whether visual memory task are associated with signal changes of functional and, according to our study, structural imaging measures in the inferior temporal cortex of patients with narcolepsy-cataplexy.

It might be argued that the cortical findings of the current study are biased by neuro-modulatory effects of the pharmacologic treatment, especially amphetamine derivatives. A significant effect arising from medication is considered unlikely because six patients were drug naïve and showed no significant differences in MD, FA, and gray and white matter volume changes when compared with the medicated patients.

In summary, the observer-independent voxel-based analysis of diffusion and morphometric MRI parameters visualized structural abnormalities in the hypothalamus, the dorsal midbrain, and corticolimbic areas including the orbito-frontal cortex and the cingulate cortex. The severe signal abnormalities identified in the hypothalamus appear consistent with hypocretinergic cell loss identified in postmortem studies of patients with narcolepsy and cataplexy. The signal changes in the dorsal midbrain areas correspond to main synaptic targets of hypocretin neurons which have been associated with the regulation of the sleep wake cycle. DTI also identified brain tissue alterations in the cortical hypocretin projection sites of the inferior frontal and cingulate cortex that were implicated in the maintenance of attention and reward-dependent decision making, both known to be impaired in patients with narcolepsy-cataplexy. DTI and VBM signal alterations argue against the concept of sleep-deficit related impairment of attention and favor the hypothesis of intrinsic structural brain tissue dysintegrity within the executive attention network of patients with narcolepsy-cataplexy.

ABBREVIATIONS

DARTEL, diffeomorphic anatomical registration using exponentiated lie algebra

DTI, diffusion-tensor imaging

ECD SPECT, [^{99m}]Tc-ethyl-cysteinate dimer single photon emission computed tomography

FA, fractional anisotropy

ICSD-2, International Classification of Sleep Disorders

MD, mean diffusivity

MNI, Montreal Neurological Institute

MPRAGE, magnetization prepared-rapid acquisition gradient echo

MSLT, multiple sleep latency test

REM, rapid eye movement

SOREM, sleep-onset rapid eye movement

SPM, statistical parametric mapping

TE, echo time

TR, repetition time

VBM, voxel-based morphometry

ACKNOWLEDGMENTS

The entire research was performed at the Departments of Neurology and Radiology at Innsbruck Medical University.

DISCLOSURE STATEMENT

This was not an industry supported study. Dr. Scherfler reports speaker honoraria from UCB. Dr. Frauscher reports speaker honoraria from UCB and consultancy fees from Pfizer and Mundipharma. Dr. Schocke reports speaker honoraria from GE Healthcare as well as consultant fees from Siemens, Bayer Schering Pharma and AstraZeneca and research support from the Austrian National Bank. Dr. Seppi reports consultancy fees and honoraria from speaking from Novartis, Astra Zeneca, Boehringer Ingelheim, Lundbeck, Schwarz Pharma, UCB, Teva and GSK. Dr. Poewe reports consultancy and lecture fees from Astra Zeneca, Teva, Novartis, GSK, Boehringer-Ingelheim,

UCB, Orion Pharma and Merck Serono in relation to clinical drug development programs for Parkinson's disease. Dr. Högl reports speaker honoraria from UCB, BI, Cephalon, Servier, and honoraria from scientific advisory boards from UCB, BI, Cephalon, Pfizer, Jazz, Lundbeck, Sanofi, and research support from UCB. The other authors have indicated no financial conflicts of interest.

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