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ORIGINAL PAPER

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EEG-mapping differences between narcolepsy patients and controls and subsequent double-blind, placebo-controlled studies with modafinil

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Abstract The aim of the present study was to investigate the role of EEG mapping as an objective and quantitative measure of vigilance in untreated and modafinil-treated narcoleptics, and compare it with the conventional neurophysiological method of the Multiple Sleep Latency Test (MSLT) and the subjective Epworth Sleepiness Scale (ESS). In 16 drug-free narcoleptics and 16 normal controls a baseline 3-min vigilance-controlled EEG (V-EEG) and a 4-min resting EEG (R-EEG) were recorded during midmorning hours. Thereafter, in a double-blind, placebo-controlled crossover design, patients were treated with a 3-week fixed titration of modafinil (200, 300, 400 mg) and placebo. EEG-mapping, MSLT and ESS measures were obtained before and at the end of the third week of therapy. Statistical overall analysis by means of the omnibus significance test demonstrated significant EEG differences between untreated patients and controls in the resting condition only (R-EEG). Subsequent univariate analysis revealed an increase in absolute and relative theta power, a decrease in alpha-2 and beta power as well as a slowing of the dominant frequency and the centroids of the alpha, beta and total power spectrum and thus objectified a vigilance decrement in narcolepsy. Modafinil 400 mg/d significantly improved vigilance as compared with placebo ($p \leq 0.01$), inducing changes opposite to the aforementioned baseline differences (key-lock principle). The MSLT and the ESS also improved under modafinil as compared with placebo, but changes were less consistent. Spearman rank correlations revealed the highest correlations between EEG mapping and the ESS, followed by those between EEG mapping and the MSLT, while the lowest correlation was found between the MSLT and the ESS. In conclusion, EEG mapping is a valuable instrument for measuring vigilance decrements in narcolepsy and their improvement under psychostimulant treatment.

Key words narcolepsy · modafinil · EEG mapping · MSLT · Epworth Sleepiness Scale (ESS)

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Introduction

Narcolepsy is a disabling sleep disorder, which affects 0.03–0.06% of the population in North America and Western Europe (Hublin et al. 1994). Its hallmark characteristics include excessive daytime sleepiness (EDS), cataplexy and REM sleep-related abnormalities. The pathophysiology of narcolepsy involves abnormal hypocretin (orexin) neurotransmission (Overeem et al. 2001). The condition is associated with undetectable hypocretin-1 levels in the cerebrospinal fluid (CSF) and HLA-DQB1*0602 positivity in narcolepsy with typical cataplexy. The subjectively experienced EDS as the most disabling feature at the behavioral level is responsible for the overall disruption of normal daytime functioning and at the neurophysiological level is based on a deterioration of vigilance. Vigilance has been defined as the availability and grade of organization of man's adaptive behavior, which is in turn dependent upon the dynamic state of the neuronal network (Head 1923). The latter can be objectified by quantitative EEG analysis utilizing single-channel (Bente 1977; Saletu and Grünberger 1985) as well as multi-channel recording, which allows topographic mapping (Duffy et al. 1981; Buchsbaum et al. 1985; Itil et al. 1985; John et al. 1988; Maurer

and Dierks 1991; Gevins et al. 1994; Saletu B et al. 1990a, 1991, 2000).

There are a variety of approaches for the quantification of EDS, including subjective behavioral measures, such as the Epworth Sleepiness Scale (ESS) (Johns 1991), and objective electrophysiological ones (Cluydts et al. 2002). The Multiple Sleep Latency Test (MSLT) (Richardson et al. 1978; Carskadon et al. 1986) and the Maintenance of Wakefulness Test (MWT) (Mitler et al. 1982) are the most widely used polysomnographic tests in narcolepsy, measuring different aspects of sleepiness. However, their expense and time requirement of recording and usually visual evaluation have motivated investigators to develop alternative electrophysiological methods using quantitatively analyzed EEG and event-related potential techniques. Regarding event-related potentials, Sangal et al. (1999) reported prolonged P300 latency in narcolepsy, which reflects slowed information processing. The Alpha Attenuation Test is another method of quantitative EEG analysis for measuring variations in physiological sleepiness. In a validation study with normals Stampi et al. (1995) investigated the ratio of eyes-closed to eyes-open EEG alpha power (referred to as Alpha Attenuation Coefficient, AAC). The AAC was found to be sensitive to increased sleepiness after sleep deprivation and to correlate significantly with the MSLT. In another study, narcoleptics had a smaller AAC and lower mean eyes-closed alpha power, whereas their mean eyes-open alpha power did not differ from the values obtained in normals (Alloway et al. 1997). However, EEG mapping may be the most suitable method for measuring vigilance, as it allows objective and quantitative evaluation of 36 EEG variables all over the brain with subsequent visualization by mapping techniques.

In our own studies applying standardized scalp recordings of the human electroencephalogram (EEG) and utilizing computer-assisted quantitative analyses, we indeed described distinct differences between patients and normal controls in standardized EEG descriptors, such as absolute and relative power as well as the centroid of the delta/theta, alpha and beta activity (Saletu B 1997; Saletu B et al. 2002b; Saletu M et al. 2000, 2002). In previous investigations, the quantitative EEG, as a low-cost, non-invasive, objective and quantitative high-time resolution method, has been successfully applied in order to classify psychotropic drugs and determine their bioavailability at the target organ, the human brain (Saletu B et al. 2002a; Saletu-Zyhlarz et al. 2002).

Modafinil, 2- [(diphenylmethyl) sulfinyl] acetamide, is a new central wake-promoting non-amphetamine with a lower risk of CNS, cardiovascular or gastrointestinal adverse events, abuse and dependence (Billiard 1998). As early as in 1986, the first human pharmaco-EEG studies in normal elderly subjects demonstrated a vigilance- promoting effect of modafinil (CRL 40476), characterized by an increase in alpha and slow beta activity and a decrease in delta, theta and very fast beta activity as compared with placebo, which was indeed proven also at the behavioral level by means of psychometry (Saletu B et al. 1986) and confirmed by later clinical trials in patients with an alcoholic organic brain syndrome (Saletu B et al. 1990b, 1993).

The efficacy, safety and tolerance of modafinil in narcolepsy patients have been demonstrated in controlled (Besset et al. 1993; Billiard et al. 1994; Boivin et al. 1993; Broughton et al. 1997; Mitler et al. 2000; Moldofsky et al. 2000; US Modafinil in Narcolepsy Multicenter Study Group 1998, 2000) and uncontrolled trials (Bastuji and Jouvet 1988; Laffont et al. 1994).

The aim of the present study was 1) to investigate daytime brain function of drug-free narcolepsy patients as compared with age- and sex-matched normal controls by means of a multi-channel 3-min vigilance-controlled EEG (V-EEG) and a 4-min resting EEG (R-EEG) recorded during midmorning hours, visualized with subsequent mapping techniques; 2) to objectify vigilance-promoting effects of modafinil in narcolepsy patients by means of EEG mapping as compared with the conventional, standardized MSLT in addition to the subjective evaluation by the ESS; and 3) to explore the relation between EEG mapping, MSLT and ESS by means of correlation analysis.

Experimental procedures

Demographic data, inclusion and exclusion criteria

A total of 16 drug-free patients (10 males, 6 females; aged 21–59 years; mean age 39.1 ± 13.3 years) with the ICD-10 diagnosis of narcolepsy (G 47.4) were included in the study and for baseline EEG examinations matched with 16 normal healthy controls according to age and sex (21–58 years; mean age 37.1 ± 13.5 years). The washout period for psychopharmaceutical agents was 5 times their elimination half-life.

Screened patients complaining of excessive daytime sleepiness first underwent neuropsychiatric, physical and laboratory examinations (including HLA typing for DQB1*0602 or DR 2 positivity) and then spent 2 recording nights in the sleep laboratory (adaptation and baseline night).

Inclusion criteria called for patients of either sex, satisfying the classification criteria of the International Classification of Sleep Disorders ICSD (1997) for narcolepsy. In addition, the symptoms were required to have been stable for 2 weeks before the beginning of the study.

Exclusion criteria. The following groups were excluded from the study: patients with evidence of a medical or psychiatric disorder that might account for the primary complaint; patients with sleep apnea, restless legs syndrome (RLS) or periodic limb movement disorder, pregnant or lactating women; patients with a history of drug abuse or dependency, including alcohol; patients requiring psychoactive medication or unwilling to tem-

porarily discontinue anticataplectic medication or any other drug that might interfere with the study assessments; patients who were unable or unwilling to comply with the protocol; patients who worked at night.

The study was performed in accordance with the relevant guidelines of the Declaration of Helsinki, 1964, as amended in Tokyo, 1975, Venice, 1983, Hong Kong, 1989, and Somerset West, 1996. Informed consent was obtained. The study protocol was approved by the Institutional Review Committee.

Evaluation of daytime brain function in patients and controls (EEG mapping)

Subsequent to two polysomnographic all-night recordings, a 3-min V-EEG and a 4-min R-EEG were obtained at 11 a. m. by means of a 21-channel Nihon Kohden 4321-G polygraph (time constant: 0.3 s, high frequency response: 35 Hertz (Hz); amplification: approximately 20,000 times; maximal noise level; 2 μV peak to peak), with the patient or control lying in a relaxed position with closed eyes in an electrically shielded room. Numerous pharmaco-EEG trials have revealed midmorning hours to be the time of relatively small inter-individual variance of vigilance (Saletu B et al. 2002a). During the V-EEG recording, the technician kept the patients alert. As soon as drowsiness patterns appeared in the record, the subjects were aroused by auditory stimuli (tapping) to stage wake (Rechtschaffen and Kales 1968). Electrodes were attached to the scalp according to the international 10/20 system. The EEG recordings from 19 leads (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1 and O2 to averaged mastoids) as well as the vertical and horizontal electro-oculographic recordings were digitized on-line with a sampling frequency of 102.4 Hz. Artifact-free 5s-epochs were selected after minimizing ocular artifacts by regression analysis in the time domain by an automatic artifact identification method with subsequent visual control (Anderer et al. 1992). Spectral analyses were performed for 5s-epochs (512 sample points), resulting in a frequency resolution of 0.2 Hz (Anderer et al. 1987). The mean spectral curves were averaged over artifact-free 5s-epochs (27.8 ± 9.2 and 30.1 ± 6.9 5s-epochs in narcolepsy patients and normal controls, respectively) and were quantified into 36 EEG variables: total power (TOTAL) (1.3 to 35 Hz); absolute (ABS) (in μV^2) and relative (REL) (%) power in 12 different frequency bands such as delta (D) (1.3–3.5 Hz), theta (T) (3.5–7.5 Hz), alpha-1(A1) (7.5–10.5 Hz), alpha-2 (A2) (10.5–13 Hz), beta-1–5 (B1-B5) (13–15–20–25–30–35 Hz); combined delta and theta (DT) (1.3–7.5 Hz), alpha (A) (7.5–13Hz) and beta (B) (13–35 Hz); dominant alpha frequency (DF) (Hz), absolute (ABS) and relative (REL) power of the DF; further the centroids (C) (center-of-gravity frequencies in Hz) and their standard deviations (CD) of the combined DT, A and B as well as of the total frequency bands (T). Relative power refers to the total power and was calculated for each channel separately. While slow activities generally reflect inhibitory CNS activity, alpha indicates normal brain function and beta excitatory CNS activity.

Pharmacological part

The study was designed as a 3-week, double-blind, randomized, placebo-controlled cross-over trial with the two treatment periods separated by a wash-out phase of one week. The randomization list was generated by an individual who was operationally independent from the study personnel who executed the randomization assignment. Two glasses with medication were prepared for each patient, marked with A (for the first treatment phase) and B (for the second treatment phase). The code was broken only after the end of the study.

Drug administration

For the study, 100 mg modafinil and placebo were prepared in capsules that looked identical. According to the fixed titration schedule, in week 1 patients received one capsule in the morning and one capsule at noon, in week 2 two capsules in the morning and one capsule at noon and in week 3 two capsules in the morning and two capsules at noon. At the beginning and at the end of each 3-week treatment block, EEG mapping and MSLT were performed and the ESS was completed.

Multiple sleep latency test (MSLT)

The MSLT was performed on the day between the first and the second polysomnographic all-night recording to provide accurate documentation of the night preceding the MSLT, as suggested by Carskadon et al. (1986). For this study there were five 20-minute nap opportunities at 2-hour intervals during the assessment day: 9:00, 11:00, 13:00, 15:00, 17:00.

Sleep was recorded using 3 EEG channels (C4-A1, Cz-O2, and C3-A2) according to the international 10/20 system, 2 electro-oculogram (EOG) channels (left/right), and submental electromyogram (EMG). Patients were instructed to lie quietly in the dark and try to fall asleep. The nap opportunity was terminated after 20 min if sleep onset did not occur, or after 15 minutes of sleep. The MSLT was performed at baseline and at the end of each cross-over sequence. Mean sleep latency to sleep stage 1 across the five tests was calculated (maximum score, 20 minutes). For sleep staging, 30 s epochs were visually scored according to the criteria of Rechtschaffen and Kales (Rechtschaffen and Kales 1968). EEG mapping was carried out on another day to avoid interference of the two vigilance test procedures.

Subjective evaluation of sleepiness and sleep and awakening quality

Epworth Sleepiness Scale (ESS). The ESS is an 8-item questionnaire in which the probability of falling asleep is assessed for 8 different everyday life situations (Johns 1991). The majority of questions capture involuntary sleep episodes. Each answer is rated by the subject on a scale from 0 to 3. The original questionnaire refers to "recent times", which, however, in our study was replaced by "the last few weeks" to be more specific and in line with the temporal design of the study. The ESS has been shown to be sensitive to treatment effects.

Statistical analysis

In the exploratory statistical analysis of the EEG data, absolute power variables were log-transformed, while relative power variables were transformed by log (x/(100-x) in order to achieve normal distribution (Gasser et al. 1982), where x is the power in percent.

To display the differences between narcolepsy patients and controls in the distribution of the 36 V-EEG variables, significance probability mapping, based on independent samples t-test, was used (Anderer et al. 1987). For correction of the alpha-inflation due to the multiple tests in the inter-group comparisons (36 EEG variables x 19 electrodes = 684 tests), an omnibus significance test based on the binomial theorem was performed. Even though this test is exact only for independent test situations, at least an upper limit for rejection of the overall null hypothesis is obtained when r significant test results are used to reject a set of n hypotheses when the tests are dependent to an unknown extent (Cross and Chaffin 1982). Thus, to reject the global null hypothesis, more than 13 out of 684 tests had to be significant ($p < 0.01$).

In order to show differences between modafinil- and placebo-induced EEG changes significance probability mapping based on paired samples t-tests was used. Data on sleep latencies in the MSLT and ESS were analyzed by Wilcoxon' s signed rank tests as they were not normally distributed. Normal distribution was tested by means of the 1-sample Kolmogorov Smirnov Test. The null hypothesis was: there are no differences between modafinil and placebo (error probability = 0.05). To explore the relationship between the EEG and sleep latency in the MSLT as well as the ESS score, Spearman rank correlations were calculated and visualized by correlation maps.

Results

The ICSD diagnostic criteria of narcolepsy were fulfilled by 16 patients. Fifteen were HLA-DQB1*0602 positive, one was negative, and 6 patients fulfilled the Honda cataplexy criteria (Honda 1988), while 5 patients had at least 2 SOREMPs.

Of the 16 patients included, 15 completed the pharmacological part of the study. One patient had to be excluded at the end of treatment block one because of incompliance with the protocol requirements (did not appear for scheduled visits).

EEG-mapping results

Baseline EEG-mapping differences between narcolepsy patients and normal controls

Statistical overall analysis by means of the omnibus significance test demonstrated significant differences in the R-EEG between untreated patients and controls, as 31 out of 684 tests [36 EEG variables x 19 electrodes = 684 tests] showed significant findings ($p < 0.01$) (Fig. 1). In the V-EEG no significant inter-group differences were found, as only 7 out of 684 tests were significant (Fig. 2).

Subsequent univariate analysis of the R-EEG data revealed a decrease in absolute total power over the left frontopolar region and an increase in theta power over the left frontotemporal and occipital as well as the midline frontal and central region in narcoleptic patients as compared with normal controls, while absolute alpha-2 power was decreased right frontotemporally, centrally and parietally as well as left temporally (Fig. 1). Absolute beta power was decreased over various regions in all five frequency bands, which was significant in the total beta band over both frontopolar and temporal as well as the right frontotemporal to central regions.

Relative delta power showed an increase over the right central, parietal, occipital and occipitotemporal region as well as the left temporal and high frontal region, while relative theta power was significantly augmented over the whole brain. Relative alpha-2 power was attenuated over both parietal and beta power over both temporal regions.

The dominant frequency was slowed over the vertex and the left temporal and temporofrontal cortex. Moreover, the absolute and relative power of the dominant frequency was significantly attenuated over the right central and occipitotemporal areas.

In regard to center-of-gravity measures, narcoleptics showed a slowed alpha centroid bitemporally, a slowed beta centroid bifrontopolarly, as well as a slowed centroid of the total power spectrum over both frontopolar, temporal, occipital and right frontotemporal, central and temporo-occipital regions as compared with normals.

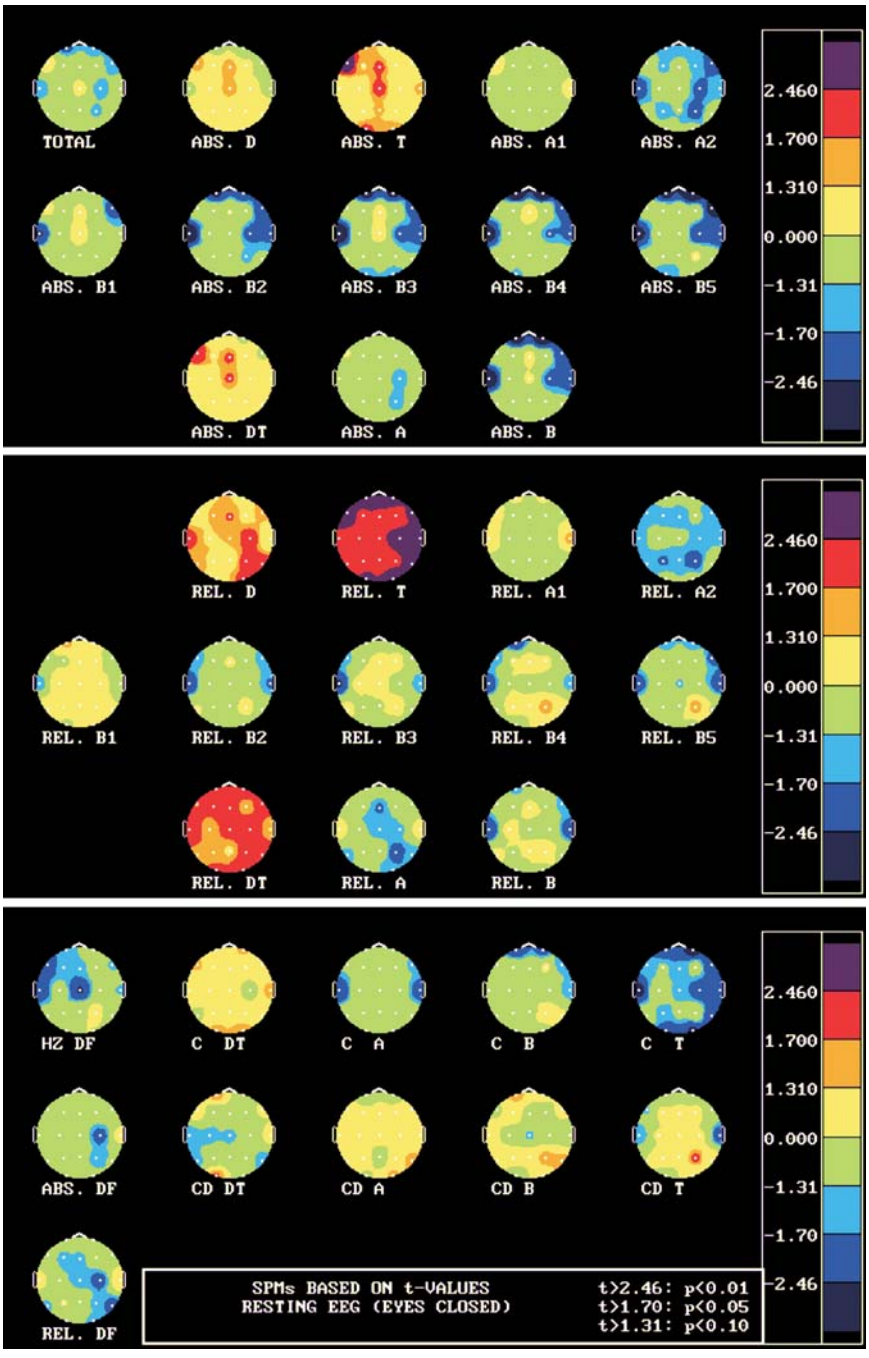

Fig. 1 Maps of EEG differences between narcolepsy patients and normal controls in the resting condition (n = 2 x 16). Omnibus significance based on binomial test (test prop. 0.01; 1-tailed $N_{sig} = 31$ out of 684 ($p < 0.01$). Statistical probability maps on intergroup differences regarding measures of the resting EEG (R-EEG) are demonstrated (bird's eye view, nose at the top, left ear left, right ear right; white dots indicate electrode positions). 13 absolute (ABS.) power variables are shown in the upper part of the figure (*TOTAL* total power; *ABS.D* absolute delta power; *ABS.T* absolute theta power; *ABS.A1–2* absolute alpha-1 and alpha-2 power; *ABS.B1–5* absolute beta-1 to beta-5 power); 12 relative (REL.) power variables are shown in the middle part of the figure and 11 dominant frequency and centroid (center of gravity) variables are shown in the lower part of the figure (*HZ DF* dominant frequency measured in Hertz; *C DT* centroid of delta and theta power; *C A* centroid of alpha power; *C B* centroid of beta power; *C T* centroid of the total power; *ABS.DF* absolute power in the dominant frequency; *CD DT* deviation of the delta and theta centroid; *CD A* deviation of the alpha centroid; *CD B* deviation of the beta centroid; *CD T* deviation of the total centroid; *REL.DF* relative power in the dominant frequency). Orange, red and purple colors indicate increases at the $p < 0.1$, 0.05 and 0.01 level; light blue, dark blue and violet decreases at the $p < 0.1$, 0.05 and 0.01 level as compared to normal controls. Statistical overall analysis by means of the omnibus significance test demonstrated significant EEG differences between untreated patients and controls. Subsequent univariate analysis revealed an increase in absolute and relative theta power, a decrease in alpha-2 and beta power, a slowing of the dominant frequency and the centroids of the alpha, beta and total power spectrum, objectifying vigilance decrements in narcolepsy

EEG mapping differences between modafinil and placebo after three-week therapy

Multivariate analysis

Since out of a total of 684 tests (36 EEG variables x 19 electrodes), 17 tests in the V-EEG and 29 tests in the R-EEG were significant at the $p < 0.01$ level, the global null hypothesis that there is no difference between modafinil and placebo was rejected under both conditions ($n_{sig} > 13$; $p < 0.01$, binomial test). Only the R-EEG findings based on univariate analysis will be described in detail below (Fig. 3).

Univariate analysis

As compared with placebo, modafinil increased total power over the left frontal, temporo-occipital, central and parietal as well as the right central, temporal and occipital cortex (Fig. 3).

While absolute delta and theta power showed only minimal findings, fast alpha power was widely increased bifrontally, bicentrally and left temporo-occipitally, and all beta bands demonstrated a global power increase, with a maximum over the left frontal to temporal and biparietal to right occipital regions.

Concerning relative power, modafinil attenuated

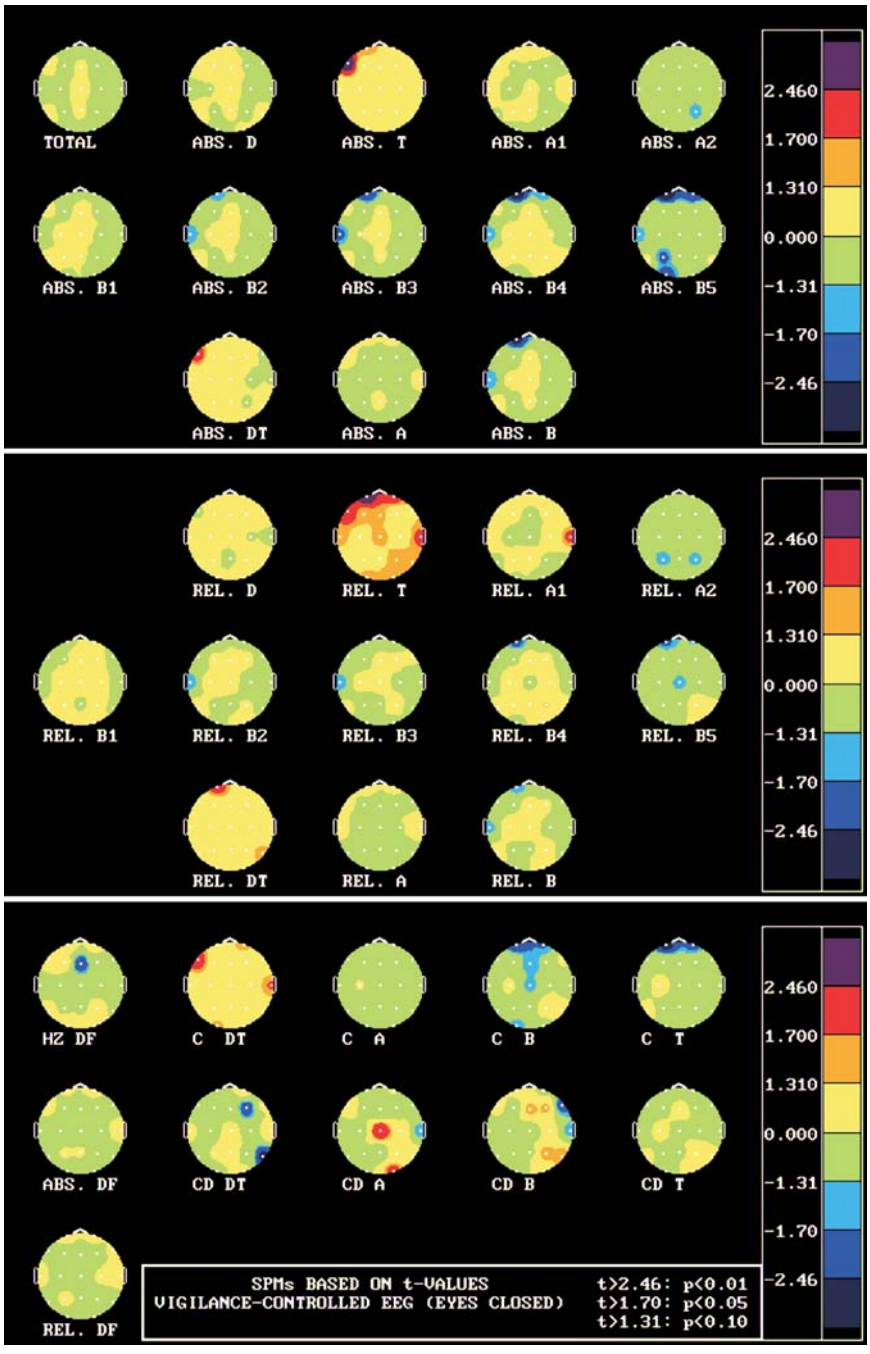

Fig. 2 Maps of EEG differences between narcolepsy patients and normal controls in the vigilance-controlled state (V-EEG): For a technical description of the maps see Fig. 1. Statistical overall analysis by means of the omnibus significance test demonstrated no significant EEG differences between untreated patients and controls. Univariate analysis revealed only few differences between patients and controls

delta high parietally and slow alpha right occipitally, while it augmented beta-2 over the left temporal cortex, beta-3 over the left anterior quadrant and right parietally and beta-4 over left temporal and frontopolar regions as well as bifrontally and right frontotemporally. Beta-5 power was augmented over the left temporal and frontopolar cortex.

The dominant frequency (Hz) was significantly accelerated left occipitally. The delta/theta centroid was accelerated left parietally, the alpha centroid over the left central and the right frontotemporal cortex, the beta centroid left temporally, whereas the centroid of the total power was accelerated left frontopolarly, temporally and right parietally after modafinil as compared with placebo.

The relative power of the dominant frequency was slowed over the left temporal and right occipitotemporal cortex. Moreover, the centroid deviation of the total power was accelerated bitemporally, along with delta/theta power occipitotemporally and beta power midline centrally, whereas the centroid deviation of the alpha band was slowed over the right frontotemporal cortex.

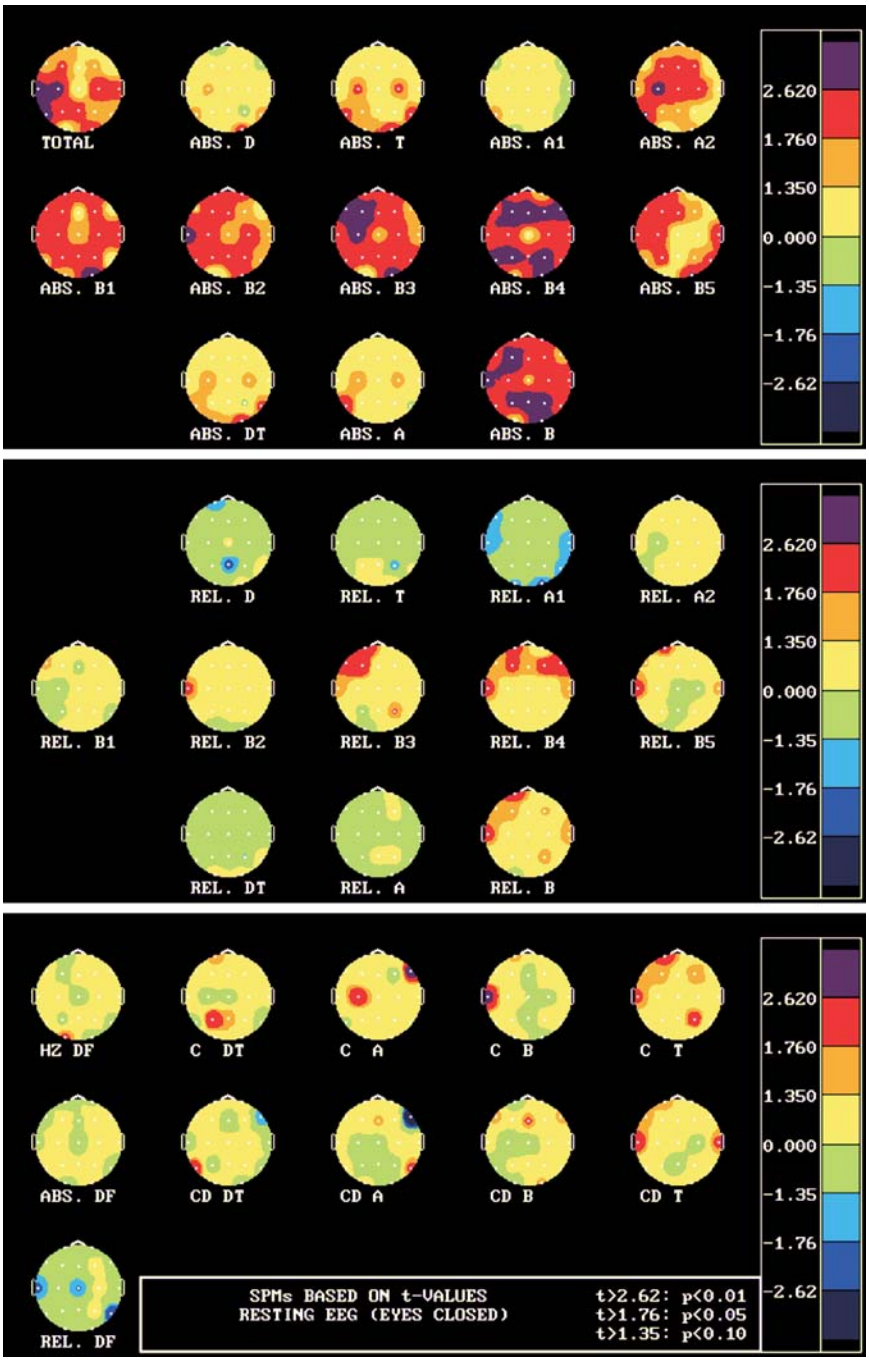

Fig. 3 Pharmaco-EEG maps on differences between modafinil (400 mg) and placebo after three weeks of therapy in narcolepsy patients (n = 15). Omnibus significance based on binomial test (test prop. 0.01; 1-tailed) $N_{sig} = 29$ out of 684 ($p < 0.01$). Statistical probability maps (SPMs) depicting differences between modafinil and placebo, based on independent samples t-values in 13 absolute power measures (upper part of the figure), 12 relative power measures (middle part of the figure) and 11 frequency measures (lower part of the figure) are shown (bird's-eye view, nose at the top; white dots indicate electrode positions). Orange, red and purple colors represent significant ($p < 0.10$, 0.05 and 0.01, respectively) increases; light blue, dark blue and violet indicate significant ($p < 0.10$, 0.05 and 0.01, respectively) decreases as compared with placebo-induced changes. Modafinil increased total power, alpha-2 and beta power and accelerated the centroid as compared with placebo, which reflects a vigilance improvement

Differences between modafinil and placebo in the MSLT and the ESS

In the MSLT, sleep latency to sleep stage S1 significantly increased from a median of 3.2 min after three weeks of placebo to 6.6 min after three weeks of modafinil ($p < 0.05$) (Fig. 4). The ESS score decreased from a median of 14.5 after three weeks of placebo to 12.5 after three weeks of modafinil ($p < 0.05$) (Fig. 4).

Correlations between EEG-mapping, MSLT and ESS findings

Investigating *correlations between EEG-mapping and MSLT* findings at all time periods by means of a Spearman rank correlation analysis (Fig. 5), a significant relationship between the two data sets was found, as the omnibus significance test showed that the number of significant correlations ($p < 0.01$) was 35 out of 684 tests ($n_{sig} > 13$; $p < 0.01$, binomial test).

In detail, the greater the total power, absolute alpha and beta power, the longer the MSLT sleep latency to

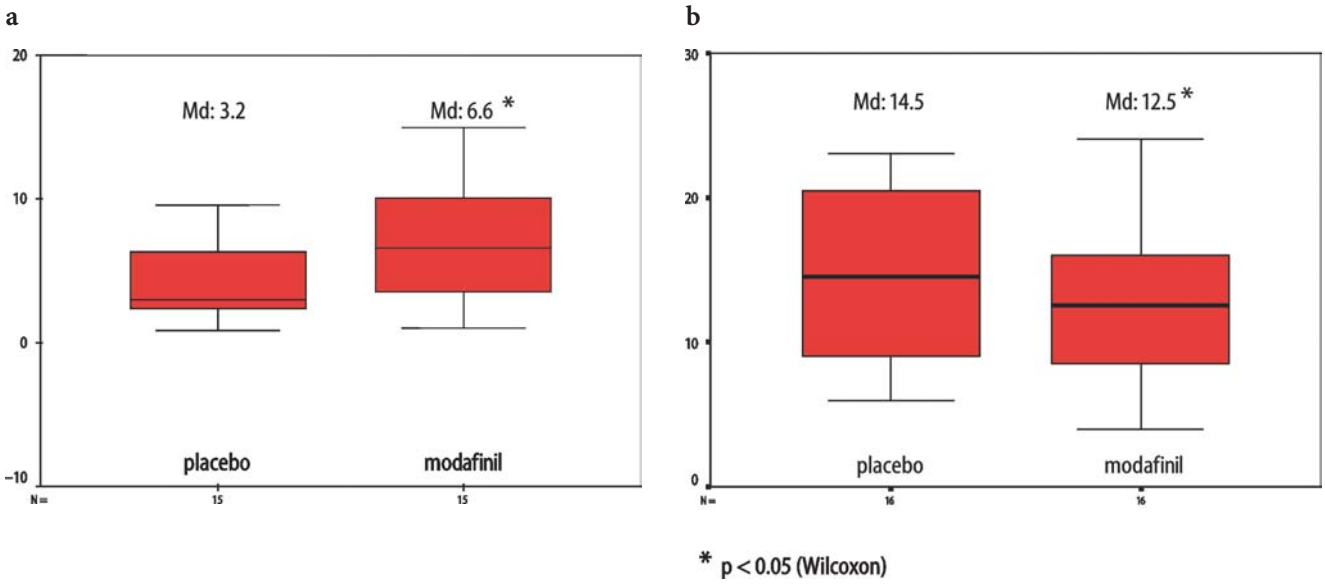

Fig. 4 **a** Multiple Sleep Latency Test (MSLT) and **b** Epworth Sleepiness Scale (ESS) results in narcoleptic patients after 3 weeks of therapy with placebo and modafinil (400 mg/d). Results are presented as box plots. The upper and lower limit of each box represents the 75th and 25th percentile, and the line through each box is the median (50th percentile). Extension bars represent the 90th and 10th percentile. Modafinil is significantly superior to placebo concerning both subjective and objective measures of sleepiness

sleep stage S1 (Fig. 5). Furthermore, the less relative delta/theta power, and the more relative alpha power, the longer sleep latency in the MSLT. Finally, the faster the delta/theta centroid, the slower the alpha and beta centroid and the faster the centroid of the total power spectrum, the longer MSLT latency. Topographically, the highest correlations were generally found over posterior brain regions, with correlation coefficients reaching up to ±0.47.

Investigating *correlations between objective EEG-mapping and subjective ESS* findings at all time periods by means of a Spearman rank correlation analysis (Fig. 6), a significant relationship between the two data sets was found, as the omnibus significance test showed that the number of significant correlations ($p < 0.01$) was 51 out of 684 tests ($n_{sig} > 13$; $p < 0.01$, binomial test).

In detail, the less total power, the more delta and the less alpha and beta power, the higher the ESS score, reflecting subjective daytime sleepiness (Fig. 6). Moreover, the slower the centroids of the delta/theta power and of the total power spectrum, the slower the dominant frequency (Hz) and the less absolute and relative power of the dominant frequency, the higher the ESS. Topographically, these correlations were generally found all over the brain, with correlation coefficients reaching up to ±0.48.

Investigating *correlations between objective MSLT and subjective ESS* findings at all time periods by means of Spearman rank correlations, a correlation coefficient of –0.37 ($p < 0.05$) was found.

Side-effects

Side-effects were only mild and did not differ significantly between the two treatment regimens. Under modafinil and placebo therapy, headache was reported by 8 and 7 patients, respectively; dry mouth by 4 and 9; dizziness by 4 and 6; coordination difficulties by 1 and 4; nausea by 2 and 2; back pain by 1 and 2; feeling dazed by 1 and 1; menstrual complaints by 1 and 1, respectively. Furthermore, under modafinil, influenza, tenseness, cardiac pain and tachycardia were reported by one patient only; under placebo, otitis externa, paresthesia and toothache occurred. In no case did side-effects lead to withdrawal from the study.

Discussion

To our knowledge the present study is the first to show differences in brain function between drug-free narcoleptic patients and controls by means of EEG mapping, which – as compared with neuroimaging techniques – is a readily and widely available, low-cost, non-invasive, high time resolution multi-lead analysis method for objectively and quantitatively studying the neurophysiology of neuropsychiatric disorders and their treatments. The differences observed were characterized by a significant increase in absolute and relative theta power, a decrease in alpha-2 and beta power, a slowing of the dominant frequency and the centroids of the alpha, beta and total power spectrum, which demonstrates a deterioration of vigilance in narcolepsy. Interestingly, in the multivariate analysis the differences reached the level of statistical significance in the resting

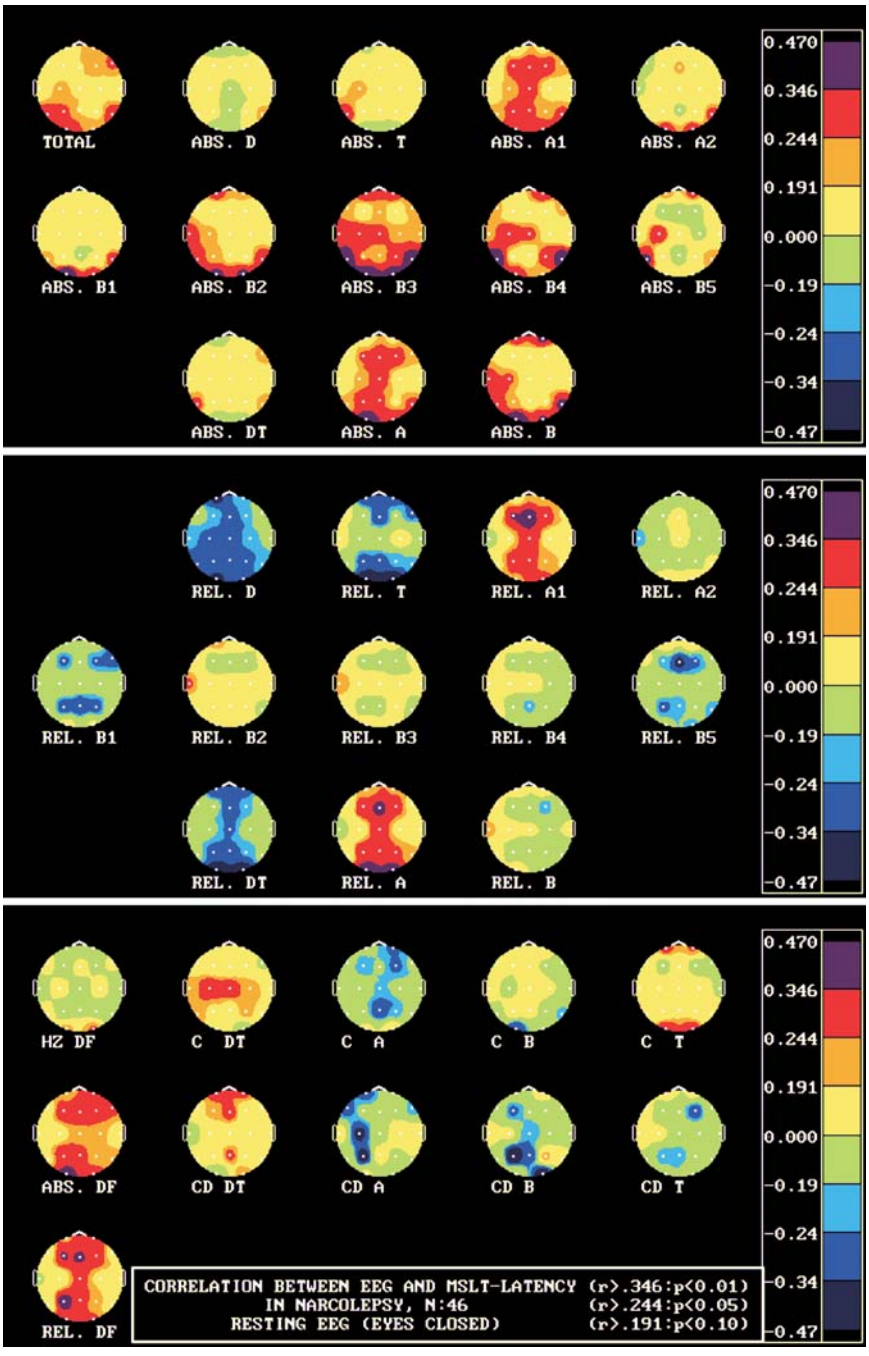

Fig. 5 Brain maps showing correlations between 36 R-EEG variables and MSLT sleep latency in narcolepsy. For abbreviations see Fig. 1. The color key indicates correlation coefficients (warm colors = positive correlations, cold colors = negative correlations). A significant relationship between the two data sets was found by means of a Spearman rank correlation analysis, as the omnibus significance test showed that the number of significant correlations ($p < 0.01$) was 35 out of 684 tests ($n_{sig} > 13$; $p < 0.01$, binomial test). The greater the total power, absolute alpha and beta power, the longer MSLT sleep latency to sleep stage S1. Furthermore, the less relative delta/theta power, and the more relative alpha power, the longer MSLT latency. Finally, the faster the delta/theta centroid, the slower the alpha and beta centroid and the faster the centroid of the total power spectrum, the longer MSLT latency. The better vigilance in the EEG, the longer the time to fall asleep

condition, but not in the vigilance-controlled recordings. This neurophysiological finding reflects clinical experience, since narcoleptic patients suffer from their vigilance decrements predominantly in monotonous situations.

An attempt to utilize quantitative EEG methods for assessing EDS in narcolepsy had been made previously by Alloway et al. (1997), who applied the Alpha Attenuation Test (AAT). Participants were recorded for 8 minutes while seated in an illuminated room with their eyes alternately open and closed. Power spectral analyses of a single EEG lead (02-A1–10 second epochs) were calculated using fast Fourier transformations (FFT) within the alpha frequency range (8–12 Hz) to obtain ratios of mean eyes-closed to mean eyes-open alpha power (i. e. the alpha attenuation coefficient, AAC). It was found that, as predicted, mean eyes-closed alpha power was significantly reduced in narcoleptics as compared to normals. However, mean eyes-open alpha power did not differ between narcoleptics and controls. It appears that in the more vigilance-controlled state the task of focusing on a target on the wall acted as an alerting stimulus for the narcoleptic patients. In our V-EEG recording the technician kept the patients alert and as soon as drowsi-

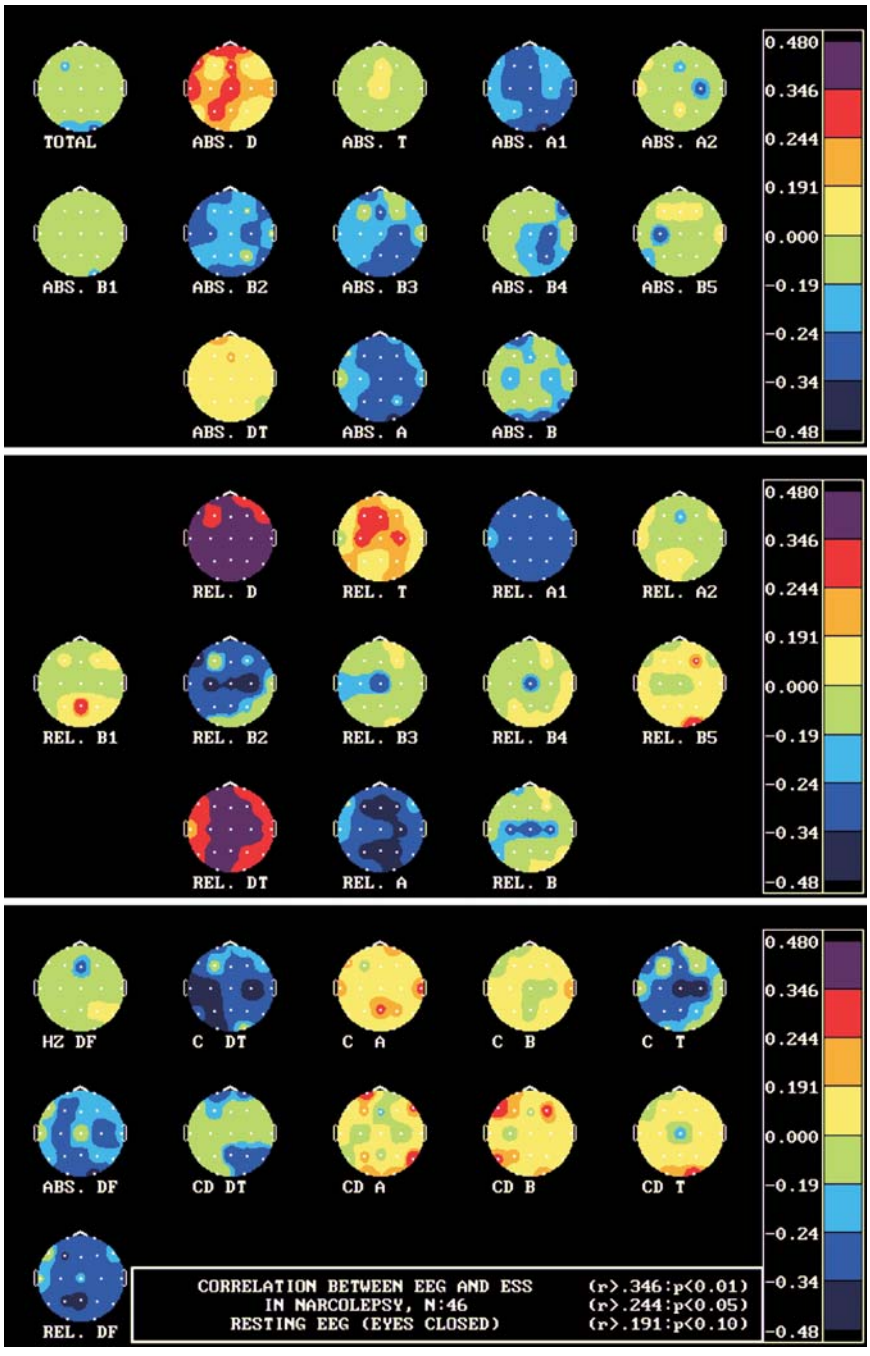

Fig. 6 Brain maps showing correlations between objective EEG mapping and the subjective ESS in narcolepsy (For the color key see Fig. 5. For abbreviations see Fig. 1). A significant relationship between the two data sets was found by means of a Spearman rank correlation analysis, as the omnibus significance test showed that the number of significant correlations ($p < 0.01$) was 51 out of 684 tests ($n_{sig} > 13$; $p < 0.01$, binomial test). The less total power, the more delta and the less alpha and beta power in the EEG, the higher the ESS score, reflecting subjective daytime sleepiness. Moreover, the slower the centroids of the delta/theta power and of the total power spectrum, the slower the dominant frequency (Hz) and the less absolute and relative power of the dominant frequency, the higher the ESS. Thus, the lower vigilance, the greater sleepiness

ness patterns appeared in the record, the subjects were aroused by auditory stimuli (tapping), thereby enabling the suppression of the latent physiological sleepiness.

In the psychopharmacological part of our study, modafinil significantly improved daytime sleepiness, measured at the behavioral level by the ESS and at the neurophysiological level by the MSLT and EEG mapping.

EEG mapping made it possible to visualize significant vigilance improvements under modafinil 400 mg/d ($p \leq 0.01$), as total power, alpha-2 and beta power increased and the centroid became accelerated. These vigilance improvements are in line with the first human pharmaco-EEG data obtained in normal elderly subjects (Saletu B et al. 1986), as well as with findings in patients with vigilance decrements. As compared with placebo, modafinil augmented the spontaneous restitution of the alcoholic organic brain syndrome in doses of 200 mg per day given over six weeks (Saletu B et al. 1990 b), which, however, became even more evident after a higher dose of 400 mg (Saletu B et al. 1993). In the latter study, the drug caused an increase in total power, an acceleration of the centroid of the total power spectrum and a decrease in relative delta/theta power as compared with

placebo, while alpha and beta power increased. This vigilance-promoting effect was accompanied at the behavioral level by a significant improvement of the noopsyche, i. e. mental performance, while the thymopsyche and psychophysiological measures were not affected. Thus, the drug differed considerably from the classical psychostimulants, such as amphetamines, which had been demonstrated earlier by all-night sleep studies in young and elderly volunteers (Saletu B et al. 1989 a, b).

The efficacy, safety and tolerance of modafinil in narcolepsy patients has been demonstrated in controlled (Besset et al. 1993; Billiard et al. 1994; Boivin et al. 1993; Broughton et al. 1997; Mitler et al. 2000; Moldofsky et al. 2000; US Modafinil in Narcolepsy Multicenter Study Group 1998, 2000) and uncontrolled trials (Bastuji and Jouvet 1988; Laffont et al. 1994). In two large 9-week, multi-center, placebo-controlled, fixed-dose trials, daily treatment with 200 or 400 mg of modafinil resulted in significant improvements of the MSLT, the MWT, the ESS and the Clinical Global Impression of Change (CGI-C) scores (US Modafinil in Narcolepsy Multicenter Study Group 1998, 2000).

In our present study the MSLT and the ESS improved as well under modafinil as compared with placebo ($p \leq 0.05$), but not to the same statistical extent shown for EEG mapping ($p \leq 0.01$). Therefore, EEG mapping, as a computer-assisted objective and quantitative method to document EDS, may be considered an easily and quickly applicable technique that can be used in addition to the very time- and staff-consuming methods of the MSLT/MWT. As is known, in the MSLT paradigm patients are initially asked to fall asleep (Carskadon et al. 1986), in the MWT to stay awake in a resting position during a recording period of up to 20 minutes (Mitler et al. 1982), which is repeated 5 times during the day with intervals of 2 hours in between. The MWT measuring the strength of the arousal system is able to discriminate between highly increased levels of sleepiness, while it has problems in discriminating lower levels of sleepiness, as a result of a ceiling effect clumping the alert subjects together (Cluydts et al. 2002). The MSLT, on the other hand, focuses on the role of sleep drive and is better at showing differences between people who are more alert, while sleepy patients are clumped together as a result of a floor effect (Cluydts et al. 2002). Both tests are based on visual Rechtschaffen and Kales criteria (Rechtschaffen and Kales 1968) with all their shortcomings (the scientific basis is poor, because the standard is based on a committee decision; the rules are meant for young healthy adults and are not validated in patients suffering from various diseases; inter-scorer reliability is poor; it is meant to be a reference method, not a gold standard; temporal resolution is poor; no attention is paid to spatial information; sleep is not a discrete phenomenon, but continuous (e. g. delta sleep); some epochs cannot be attributed to any sleep stage, and others may belong to several sleep stages; no attention is given to the microstructure of sleep) (Himanen and Hasan 2000).

The above-mentioned three most widely used tests of daytime sleepiness, the MSLT, the MWT, and the ESS, give results that are significantly correlated in a statistical sense, but are not closely related (U. S. Modafinil in Narcolepsy Multicenter Study Group 1998). Spearman rank correlations revealed the highest correlations between EEG mapping and the total score of the ESS ($r = \pm 0.48$), followed closely by those between EEG mapping and mean sleep latency in the MSLT ($r = \pm 0.47$). Correlations were found in the total, alpha, beta, and delta/theta power as well as in all important centroid variables. Interestingly, the lowest correlation was found between the MSLT and the ESS ($r = -0.37$).

Though a great number of reports on the correlation between ESS scores and mean sleep latencies in the MSLT have been published, none of them revealed a high correlation (e. g. $r = -0.27$, $n = 522$, $p < 0.001$) (Mitler et al. 1998). The mean of nine correlation coefficients published so far is –0.3. Most – but not all – were statistically significant. In a more detailed analysis of this relationship, Chua et al. (1998) showed a higher correlation ($r = 0.57$, $p < 0.001$) between ESS scores and mean MSLT sleep latencies for tests in which the subject fell asleep at each opportunity than for those in which the subject did not always fall asleep ($r = 0.009$, $p > 0.1$). Patients with EDS often describe dozing off inadvertently in monotonous situations. In a large survey, adults in New Mexico were asked about their frequency of falling asleep in five situations (Schmidt-Nowara 1989). The author derived a score from the three questions referring to the most soporific situations, i. e. falling asleep while "inactive in a public place", "at work", and "in a moving vehicle as passenger or driver". MSLTs in 116 of these subjects showed a significant correlation between their sleep latency and their answers to these three questions. The ESS is based on questions referring to eight situations, some known to be very soporific, others less so (Johns 1991). The ESS is dependent on subjects' awareness of falling asleep. A linear regression model of Van Ert showed that the ESS score only correlated with the MSLT results when it was completed by significant others, not when subjects themselves answered it (Van Ert et al. 1999). This offers an explanation for the poor correlations between the ESS and the MSLT. One study that tested subjective responses to the ESS item that asks about 'lying down to rest in the afternoon when circumstances permit' failed to show any robust association with objective measures in this specific situation, namely the afternoon naps in the MSLT (Chervin et al. 1997).

The search for a gold standard for the assessment of sleepiness seems meaningless at this time, as sleepiness cannot be considered a universal phenomenon. Different assessment tools for sleepiness are always operationalizations reflecting the theoretical framework the investigator has on sleepiness. While the MSLT is a standardized and internationally widely used method for the diagnosis of narcolepsy, EEG mapping turned out to be a valuable instrument for objectively and quantita-

tively measuring the vigilance decrement in narcolepsy and its improvement under treatment.

In the context of the differences shown between quantitative EEG analysis, polygraphic tests and the ESS, it is important not to rely exclusively on either subjective or objective indices of sleepiness. A combination of these methods has to be used when making clinical decisions.

Further studies in narcolepsy patients will be necessary in order to confirm correlations between objective quantitative EEG measures and subjective clinical ratings. Specifically, it may be of interest to utilize advanced methods of brain electric source localization such as low-resolution brain electromagnetic tomography (LORETA) (Pascual-Marqui et al. 2002), since this modern electrophysiological neuroimaging method may help to elucidate not only the complex pathophysiology of narcolepsy, but also the mode of action of its treatment of choice with modafinil. Last but not least, electrophysiological neuroimaging techniques may be utilized in the diagnosis of neuropsychiatric disorders and their treatment with neuropsychopharmacological agents according to a key-lock principle (Saletu B et al. 2002 b). The present study indeed shows that vigilance decrements in narcolepsy can be counteracted by the vigilance-promoting effect of modafinil. Thus, by considering differences between neuropsychiatric disorder patients and normal controls and between psychotropic drugs and placebo in normal subjects it may be possible to choose the optimum drug for a specific patient according to a key-lock principle, since the drug should normalize the deviant brain function.

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