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EEG mapping, psychometric, and polysomnographic studies in restless legs syndrome (RLS) and periodic limb movement disorder (PLMD) patients as compared with normal controls

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Abstract

Objectives: Investigation of daytime brain function, psychopathology, and objective and subjective sleep and awakening quality in restless legs syndrome (RLS) and periodic limb movement disorder (PLMD).

Methods: Thirty-three RLS and 26 PLMD patients free of psychotropic drugs were studied as compared with age- and sex-matched normal controls, utilizing electroencephalographic (EEG) mapping and clinical evaluations by the Zung Self-Rating Depression (SDS) and Anxiety Scale (SAS), the Quality of Life Index, the Pittsburgh Sleep Quality Index (PSQI), and the Epworth Sleepiness Scale. In a subsample of 12 RLS patients, 12 PLMD patients, and 12 controls, objective and subjective sleep and awakening quality were evaluated in two sleep laboratory nights (adaptation and baseline night).

Results: Scores of the PSQI, SDS, and SAS were found increased in both patient groups; RLS patients showed reduced quality of life, while in the PLMD group daytime sleepiness was increased. EEG mapping demonstrated findings characteristic of major depression in RLS patients and of generalized anxiety disorder in PLMD patients. Polysomnography showed a significant deterioration of sleep efficiency only for RLS patients, while nocturnal awakenings were increased in both patient groups. Concerning sleep architecture, both groups exhibited increased S1 and stage shifts and decreased S2, while only PLMD patients showed an increase in S4. The PLM/$_{h\ TST}$, the PLM/$_{h\ wake}$ and the PLMS-arousal index were significantly increased in both patient groups as compared with controls. Subjective sleep and awakening quality and thymopsychic measures were deteriorated in RLS. Morning mental performance and fine motor activity were deteriorated in both groups, reaction time only in RLS, numerical memory and attention variability only in PLMD.

Conclusion: EEG mapping revealed neurophysiological correlates of depression and anxiety in RLS and PLMD, respectively, which were confirmed by self-ratings of symptoms.

Keywords: Restless legs syndrome (RLS); Periodic limb movement disorder (PLMD); EEG mapping; Depression; Anxiety; Polysomnography; Psychometry; Sleep quality

1. Introduction

Restless legs syndrome (RLS) and periodic limb movement disorder (PLMD) are of increasing interest to both the medical profession and health authorities because their prevalence rates are relatively high. While in an earlier epidemiological study involving 1000 Austrians a prevalence of 8% was found [1], a more recent survey based on the four minimal standard criteria developed by the International RLS Study Group [2] revealed a higher prevalence rate of 18%. There was a significant gender difference (22% in women versus 12% in men) and a considerably higher prevalence in the elderly [3].

RLS and periodic leg movements in sleep (PLMS) are distinct by definition but can coexist [4]. In PLMD, an independent intrinsic sleep disorder, the patient has no evidence of a medical or mental disorder (e.g. sleep apnea or depression) that can account for the primary complaint of insomnia or excessive daytime tiredness, so it is assumed that the PLMS cause sleep disruption, non-restorative sleep, and the patient's sleep-related symptoms [5].

In contrast to the wealth of clinical studies on RLS and PLMD, there is a paucity of sleep laboratory data on objective and subjective sleep and awakening quality. While some findings are available concerning deteriorated sleep in RLS/PLMD patients, very little is known about objective awakening quality, such as intellectual, mnestic, and motor performance and electrophysiological function during daytime. EEG mapping is an objective and quantitative

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neurophysiological method that makes it possible to measure and visualize fluctuations in vigilance during a short time period (3 min) [6–9] and describe 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 [9,10].

The aim of our present clinical and neurophysiological studies was twofold: (1) to investigate daytime brain function of 33 RLS and 26 PLMD patients free of psychotropic drugs, as compared with age- and sex-matched normal controls, by means of EEG mapping and psychopathology; and (2) to investigate objective and subjective sleep and awakening quality in a subsample of 12 RLS and 12 PLMD patients free of psychotropic drugs as compared with 12 normal controls.

2. Methods

2.1. Daytime brain function and psychopathology

2.1.1. Patients

Thirty-three RLS patients (15 men, 18 women) free of psychotropic drugs, aged between 31 and 82 years (59.0 ± 11.5 years), were compared with 33 age- and sex-matched normal healthy controls aged between 31 and 82 years (57.0 ± 11.6 years). Twenty-six PLMD patients (20 men, six women) free of psychotropic drugs, aged between 21 and 78 years (48.4 ± 15.0 years), were compared with 26 age- and sex-matched normal healthy controls aged between 22 and 78 years (48.8 ± 14.9 years). Before entering the study, all patients underwent a complete neuropsychiatric and general medical examination, including serum chemistry and laboratory tests.

Inclusion criteria in the RLS group called for patients of either sex, satisfying the classification criteria for RLS (780.52-5), as determined by the International Classification of Sleep Disorders (ICSD) [5], and the International RLS Study Group [2]. Inclusion criteria in the PLMD group called for patients of either sex, satisfying the classification criteria for PLMD (780.52-4), as determined by the ICSD [5]. Baseline polysomnography had to reveal an abnormal PLM index (more than five PLM per hour of sleep).

Exclusion criteria were: patients with evidence of a medical or psychiatric disorder that might account for the primary complaint, patients with signs of secondary RLS, sleep apnea patients, pregnant or lactating women, women of child-bearing age who were not applying adequate contraceptive methods, patients with a history of drug abuse or dependency including alcohol, patients requiring psychoactive medication or any other drug that might interfere with the study assessments, patients who were unable or unwilling to comply with the protocol, and 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.

2.1.2. Clinical evaluation

All subjects had to complete the following subjective clinical rating scales:

The Pittsburgh Sleep Quality Index (PSQI) [11]
– a self-rated questionnaire that assesses sleep quality and disturbance over 1 month
The Zung Self-Rating Depression Scale (SDS) [12]
– a self-rating instrument for depressive syndromes
The Zung Self-Rating Anxiety Scale (SAS) [13]
– a self-rating instrument for anxiety syndromes
The Quality of Life Index (QLI) [14]
– a self-administered questionnaire for assessment of elementary components of general health-related quality of life
The Epworth Sleepiness Scale (ESS) [15]
– a self-administered questionnaire for assessment of daytime sleepiness.

2.1.3. Evaluation of daytime brain function (EEG mapping)

The methodology of EEG recordings, spectral analysis, and brain mapping has been described in detail elsewhere [16,17]. A 3-min vigilance-controlled EEG (V-EEG) was obtained during midmorning hours (10–11 h). The patients were lying in a relaxed position with closed eyes in an electrically shielded room. They were kept alert by a technician. As soon as drowsiness patterns appeared in the record, they were aroused by auditory stimuli (tapping). The EEG recordings from 19 leads were digitized on-line and spectral analyzes were performed for 5 s-epochs. The mean spectral curves, which contained data from 1.3 to 35 Hz, were quantified into 36 EEG variables: Total power (TOTAL) (1.3–35 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) (7.5–13 Hz), 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 central nervous system (CNS) activity, alpha indicates normal brain function and beta, excitatory CNS activity.

2.1.4. Statistical analysis

In the exploratory statistics, the Mann–Whitney *U*-test was used to compare subjective clinical ratings of RLS

and PLMD patients and normal controls. To display the differences between RLS patients and controls in the distribution of the 36 V-EEG variables, significance probability mapping, based on independent samples *t*-test, was used [8,16]. In order to correct for the alpha-inflation due to the multiple tests (36 EEG variables × 19 electrodes = 684), an omnibus significance test based on the binomial theorem was performed. Thus, to reject the global null hypothesis, more than 44 out of 684 tests had to be significant at the $P < 0.05$ level.

2.2. Sleep laboratory studies

2.2.1. Patients

A subsample of 12 RLS patients (four men, eight women), aged between 35 and 74 years (mean 57.2 ± 11.7 years), and 12 age- and sex-matched normal healthy controls, aged between 33 and 75 (mean 59.0 ± 15.9) years, as well as a subsample of 12 PLMD patients (nine men, three women), aged between 21 and 68 years (mean 49.1 ± 14.6 years), and 12 age- and sex-matched normal healthy controls, aged between 21 and 68 (mean 59.0 ± 15.9) years were included. RLS and PLMD patients continued with treatment in single-blind, placebo-controlled, cross-over design studies described elsewhere [18–20].

2.2.2. Study design

Each patient spent one adaptation and one baseline night in the sleep laboratory with the baseline night utilized for statistical purposes (subsequent drug nights were dependent on the protocols of the respective neuropsychopharmacologic studies).

At the time of the investigations, the patients had to be free of psychotropic drugs for a period of five times the half-life of the last given psychoactive substance.

Normal controls also spent two nights in the sleep laboratory, with the second night used for comparative purposes.

2.2.3. Measures

The evaluation of objective and subjective sleep and awakening quality of the two patient groups has been described in detail elsewhere [18–20].

2.2.4. Biometric planning and evaluation

The sample size was based on previous studies on differences between sleep disorder patients and normal controls [21,22]. The Mann–Whitney *U*-test was used to compare objective and subjective sleep and awakening quality of 12 RLS and 12 PLMD patients as compared with 12 normal controls.

3. Results

3.1. Differences in clinical symptoms between RLS patients and controls

Subjective sleep quality and sleep efficacy, evaluated by the Pittsburgh Sleep Quality Index, were significantly deteriorated in RLS patients as compared with controls (Table 1). Moreover, RLS patients complained about significantly more symptoms of depression (SDS) and anxiety (SAS) than controls, which also contributed to a significantly lower quality of life. There were no intergroup differences in regard to daytime sleepiness.

3.2. Differences in daytime EEG mapping between RLS patients and controls

RLS patients demonstrated significant differences in electrophysiological brain function in comparison to controls, as confirmed by the omnibus significance test (Fig. 1). Univariate analysis showed that the differences were characterized by a significant increase in delta and fast alpha power and a significant decrease in slow alpha power. The centroid of the delta/theta band was slowed, and that of the alpha centroid accelerated, as was the dominant frequency. The absolute power of the dominant frequency was attenuated, and the centroid deviation of the combined delta/theta and beta power was slowed. Total power was not significantly attenuated.

3.3. Differences in sleep and awakening quality between RLS patients and controls

Polysomnography demonstrated a decreased total sleep time (TST) and sleep efficacy, increased wakefulness during

Table 1
Differences in clinical variables between RLS/PLMD patients and normal controls[a]

Variable	Controls ($n = 33$)	RLS patients ($n = 31$)	Controls ($n = 33$)	PLMD patients ($n = 30$)
Pittsburgh Sleep Quality Index	3.7/1.1	12.2/4.5[b]	3.3/1.5	9.1/5.2[b]
Self-Rating Depression Scale	29.6/4.6	39.9/8.5[b]	26.1/3.6	35.1/7.3[b]
Self-Rating Anxiety Scale	26.9/3.8	36.8/8.4[b]	24.9/3.2	32.6/7.4[b]
Quality of Life	8.3/0.8	7.1/1.4[c]	8.1/0.9	7.6/1.5
Epworth Sleepiness Scale	5.1/2.1	5.9/4.5	4.3/1.7	9.2/5.2[d]

[a] Data are given as mean/SD.
[b] $P < 0.001$.
[c] $P < 0.01$, differences between RLS/PLMD patients and controls (Mann–Whitney *U*-test).
[d] $P < 0.05$.

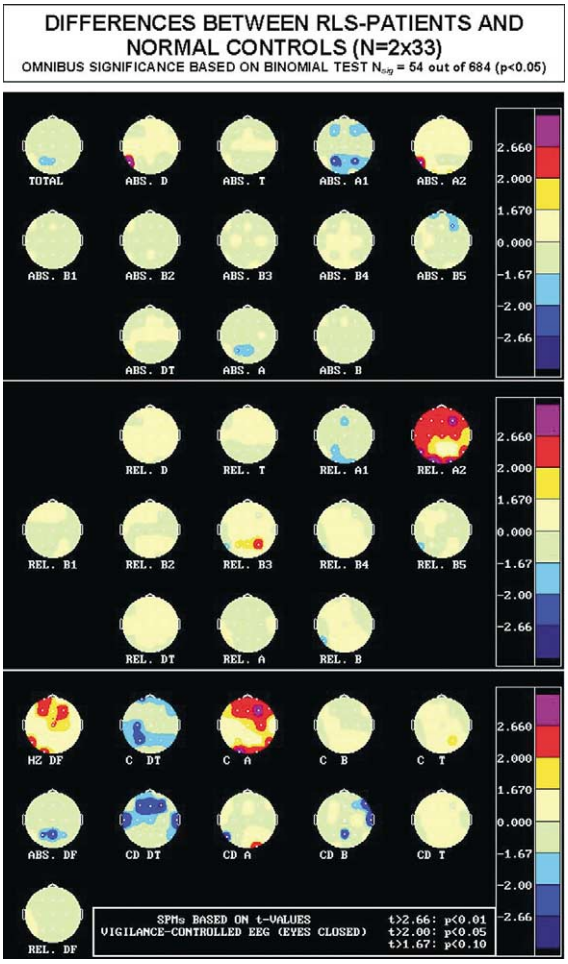

Fig. 1. Maps on V-EEG differences between RLS patients and normal controls (n: 2×33). Statistical probability maps regarding measures of vigilance-controlled EEG (V-EEG) are demonstrated (bird's eye view, nose at the top, left ear left, right ear right; white dots indicate electrode positions). Thirteen 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 $P < 0.1$, 0.05 and 0.01 level; blue, dark blue and violet decreases at $P < 0.1$, 0.05 and 0.01 level as compared to normal controls. RLS patients demonstrate a decrease in total power, an increase in absolute delta and absolute and relative alpha-2 power, a decrease in absolute and relative alpha-1 power, an acceleration of the dominant frequency and the alpha centroid and a slowing of the delta/theta centroid in various locations at different level of probabilities.

the total sleep period, frequency of nocturnal awakenings (Table 2), sleep stages S1 and stage shifts as well as decreased sleep stages S2 (Table 3) in RLS patients as compared with normal controls. The index PLM/hour of sleep [PLM/$_{h\ TST}$] along with all other PLM indices including the PLM-arousal index was significantly increased in comparison to controls (Table 4).

Subjective sleep quality tended to decrease and morning well-being, mood, affectivity and wakefulness showed a deterioration (Table 5). Concerning morning mental performance, fine motor activity, and reaction time performance were deteriorated (Table 6).

3.4. Differences in clinical symptoms between PLMD patients and controls

PLMD patients had higher PSQI, ESS, SDS, and SAS scores than controls, while differences in quality of life did not reach the level of statistical significance (Table 1).

3.5. Differences in daytime EEG mapping between PLMD patients and controls

PLMD patients demonstrated significant differences in electrophysiologic brain function in comparison to controls, as confirmed by the omnibus significance test (Fig. 2). Further, univariate analysis revealed an increase in total power and absolute and relative alpha-1 power along with a decrease in absolute and relative delta and beta power (Fig. 2). The centroid of the total and beta power was significantly slowed as compared with controls. The absolute and relative power of the dominant frequency was increased.

3.6. Differences in sleep and awakening quality between PLMD patients and controls

PLMD patients demonstrated, as compared with normal controls, an increase in nocturnal awakenings (Table 2), sleep stages S1 and S4, and stage shifts as well as a decrease in S2 (Table 3). The index PLM/hour of sleep [PLM/$_{h\ TST}$] along with all other PLM indices including the PLM-arousal index were significantly increased in comparison to controls (Table 4).

There were no significant differences concerning subjective sleep quality and morning measures of mood, drive, and drowsiness, while affectivity was increased (Table 5). Attention variability, numerical memory, fine motor activity, and reaction time performance were impaired (Table 6).

4. Discussion

Concerning psychopathology, RLS patients demonstrated significantly higher depression and anxiety scores as well as lower quality of life than the sex- and age-matched normal control group, which is in line with findings from other reports. In a population-based study, RLS-positive subjects showed significantly higher depression scores than RLS-negative ones, even if the question about sleep disorders was excluded [23].

These psychopathological findings of depression in RLS were also in agreement with our results at the neurophysio-

Table 2
Differences in sleep initiation and maintenance between RLS/PLMD patients and normal controls[a]

Variable[b]	Controls ($n = 12$)	RLS patients ($n = 12$)	Controls ($n = 12$)	PLMD patients ($n = 12$)
Latency to S1 (min) ↓	13.9/12.3	21.3/12.8	20.9/33.9	19.0/20.1
Latency to S2 (min) ↓	22.4/17.2	34.3/18.9	25.6/33.8	35.3/38.4
Latency to S3 (min) ↓	77.6/119.2	73.7/59.9	101.3/129.2	70.7/52.4
Latency to S4 (min) ↓	226.6/193.0	150.2/139.3	178.4/164.1	110.9/117.5
Latency to SREM (min) ↓	124.2/57.0	160.4/99.4	111.3/73.1	113.0/43.6
Wake within TSP (min) ↓	36.2/27.2	92.4/73.7[c]	24.0/20.8	39.1/32.8
Wake before buzzer (min) ↓	6.8/11.6	5.5/13.7	6.1/20.0	1.0/2.5
Awakenings (N) ↓	7.4/4.0	12.2/6.2[c]	5.5/3.9	11.7/5.6[c]
Total sleep period (min) ↑	421.5/20.3	419.8/27.0	417.4/36.7	427.3/22.4
Total sleep time (min) ↑	383.3/35.8	326.3/73.0[c]	390.0/42.6	387.2/39.8
Sleep efficiency (%) ↑	86.6/8.2	73.2/16.7[c]	87.7/9.2	86.5/8.5

[a] Data are given as mean/SD.
[b] ↑ ↓, direction of improvement.
[c] $P < 0.05$, differences between RLS/PLMD patients and controls (Mann–Whitney U-test).

logical level. Daytime EEG mapping showed findings similar to those in major depression, suggesting a deterioration of vigilance in the sense of a dissociated state. Interestingly, the greatest differences between RLS patients and normal controls occurred in those EEG measures that in depression showed the highest correlations to the Hamilton Depression score, e.g. the centroid of the delta/theta and alpha power and the dominant frequency and relative alpha 1 and alpha 2 power [10]. The dissociated vigilance state would explain the remarkable fact that in RLS there is no increased daytime sleepiness (albeit patients often complain about daytime tiredness) despite marked sleep disturbances (such as a decrease in sleep efficiency, TST, and an increase of nocturnal awakenings and wake time). Indeed, one would expect increased daytime sleepiness as is usually seen after severe sleep disorder, such as sleep apnea. In sleep architecture RLS patients demonstrated increased S1 and decreased S2, but no significant attenuation of REM and slow wave sleep, as, for instance, in sleep apnea [24].

In addition, EEG maps of RLS patients differed from those observed in sleep apnea patients, who clinically show reduced subjective sleep quality and increased morning drowsiness. Their daytime EEG maps were characterized by an increase in delta/theta power and a decrease in alpha-1, alpha-2, and beta power as well as well as a slowing of the dominant frequency and the total centroid, reflecting a pronounced vigilance decrement. Moreover, correlation maps demonstrated that the higher the respiratory indices of sleep-related breathing disorders, the more pronounced the deterioration of vigilance. In the present study, a delta/theta increase was not observed. This was in agreement with the clinical rating of the ESS, which was also not found to be elevated.

In contrast to the RLS group, PLMD patients had signifi-

Table 3
Differences in sleep architecture between RLS/PLMD patients and normal controls[a]

Variable		Controls ($n = 12$)	RLS patients ($n = 12$)	Controls ($n = 12$)	PLMD patients ($n = 12$)
Sleep stage	1 (%)	6.4/3.7	15.7/8.6[b]	6.2/3.1	14.8/7.4[b]
	1 (min)	23.8/12.5	48.9/23.9[c]	24.2/11.7	57.2/27.3[b]
Sleep stage	2 (%)	58.6/10.0	47.1/10.3[b]	56.5/6.8	45.3/10.9[b]
	2 (min)	223.1/35.3	155.3/53.9[b]	219.9/32.1	174.3/42.5[b]
Sleep stage	3 (%)	11.2/7.4	9.9/4.8	10.0/4.1	9.1/4.9
	3 (min)	43.0/27.4	31.8/16.8	39.2/16.1	35.6/22.0
Sleep stage	4 (%)	6.0/17.1	9.5/6.2	4.1/4.2	9.6/8.4[c]
	4 (min)	24.3/28.5	28.3/17.7	15.5/14.8	37.6/33.5[c]
Sleep stage	3 + 4 (%)	17.2/9.9	19.4/7.3	14.1/6.9	18.6/8.4
	3 + 4 (min)	67.3/39.6	60.1/21.2	54.7/24.7	73.2/36.7
Sleep stage	REM (%)	17.8/5.3	17.9/7.6	23.2/6.0	21.2/5.4
	REM (min)	69.1/24.6	62.0/36.6	91.3/28.1	82.5/23.7
Movement time (min)		2.1/2.5	1.1/1.2	3.4/2.9	1.1/1.1[b]
REM latency (min)		101.8/58.1	126.1/87.7	85.6/52.6	77.7/33.8
Stage shifts (N)		53.8/13.8	80.5/20.0[b]	53.8/12.3	74.3/16.5[b]

[a] Data are given as mean/SD.
[b] $P < 0.01$.
[c] $P < 0.05$, differences between RLS/PLMD patients and controls (Mann–Whitney U-test).

Table 4
Differences in periodic leg movements (PLM) and arousals in RLS/PLMD patients and normal controls[a]

Variable	Controls ($n = 12$)	RLS patients ($n = 12$)	Controls ($n = 12$)	PLMD patients ($n = 12$)
PLM (total #)	70.3/95.9	368.1/150.8[b]	57.9/62.1	344.6/256.1[b]
Index PLM/h TIB	9.2/12.1	49.4/20.1[b]	7.6/8.1	46.3/34.5[b]
PLM during sleep (total #)	40.4/83.8	222.9/144.2[b]	26.7/46.7	254.8/193.6[b]
Index PLM/h TST (normal: 0–5/h)	5.9/11.6	39.7/20.5[b]	4.0/6.8	41.9/34.8[b]
Index PLM/h REM	3.2/8.4	11.3/11.8[b]	1.3/2.4	40.8/37.0[b]
Index PLM/h NREM	6.5/12.4	45.6/24.8[b]	4.7/8.4	41.6/36.3[b]
PLM during wake (total #)	29.9/37.9	145.2/137.0[b]	31.3/38.0	89.8/78.0[c]
Index PLM/h W	15.7/18.7	60.6/37.2[b]	13.7/16.5	83.2/45.7[b]
PLM average interval (s)	34.8/10.8	33.6/6.5	46.4/8.6	35.4/9.1[c]
PLM interval SD (s)	25.9/8.2	22.6/6.7	27.6/7.8	27.0/7.5
PLM-arousal index	2.6/3.1	12.8/7.7[b]	2.6/3.2	10.3/3.4[b]
Arousal index	17.4/8.5	31.8/19.8	17.2/19.8	24.0/11.5
Spontaneous arousals	89.3/82.7	57.3/32.7	73.6/93.9	43.3/27.5

[a] Data are given as mean/SD.
[b] $P < 0.01$.
[c] $P < 0.05$, differences between RLS/PLMD patients and controls (Mann–Whitney U-test).

cantly higher ESS scores than normal controls. EEG maps of PLMD patients were reminiscent of those of patients suffering from generalized anxiety disorder (GAD) [25]. Indeed, in the present study anxiety and depression scores were increased, but not to the same extent as in patients with the primary diagnosis of GAD.

RLS patients had a substantially elevated PSQI global score (12.23 ± 4.47), which according to Buysse et al. [11] reflects a disorder of initiating and maintaining sleep due to depression rather than a disorder of excessive somnolence. In contrast to PLMD patients, their quality of life was slightly but significantly reduced (mean QLI score 7.1) as compared with normal controls (mean QLI score 8.2), but did not reach by far the low values observed in non-organic insomnia due to psychiatric disorders.

Obviously, in RLS patients sleep efficiency and total sleep time were more severely disturbed, whereas nocturnal awakenings were increased in both patient groups. Concerning sleep architecture, both groups showed an increase in S1 and stage shifts and a decrease in S2, but S4 was increased only in PLMD patients. An increase in S4 had also been described by us in insomniac GAD patients [26]. Subjective sleep and awakening quality and thymopsychic measures were more severely affected in RLS patients. When it comes to mental performance, fine motor activity was deteriorated in both groups, whereas in RLS reaction time and, in PLMD, numerical memory and attention variability were impaired as compared with controls. The additional decrement in reaction time performance in RLS may reflect the more pronounced movement disorder in RLS than in PLMD patients.

Most of our knowledge concerning pathophysiology and pharmacologic treatment of PLMD has been gained from RLS studies. In this context it seems important to stress that not all patients with PLMS have RLS symptoms and not all treatments tested against RLS are valid for the clinical condition of PLMD. The fact that no significant deterioration in sleep efficiency or TST was found in PLMD patients

Table 5
Differences in subjective sleep/awakening quality and morning thymopsyche between RLS/PLMD patients and normal controls[a]

Variable[b]	Controls ($n = 12$)	RLS patients ($n = 12$)	Controls ($n = 12$)	PLMD patients ($n = 12$)
Sleep quality (score) ↓	12.1/3.8	14.8/4.8	14.2/5.1	12.3/4.1
Awakening quality (score) ↓	14.5/5.1	16.1/4.3	16.3/4.7	15.4/6.2
Somatic complaints (score) ↓	5.8/1.2	6.0/1.2	6.0/1.1	6.3/2.7
SSA total (score) ↓	32.6/7.8	36.9/7.7	36.5/9.0	33.9/10.7
Well-being evening (score) ↓	9.2/6.5	15.9/11.1	12.3/11.9	17.7/13.7
Well-being morning (score) ↓	11.1/7.7	18.3/9.1[c]	15.1/11.3	14.8/14.4
Drive (mm) ↓	40.0/33.1	52.0/31.6	54.5/20.2	43.5/23.2
Mood (mm) ↑	80.3/17.2	61.2/19.3[c]	63.3/16.0	69.8/15.8
Affectivity (mm) ↑	84.8/13.3	62.3/25.9[c]	58.7/15.5	74.3/21.9[d]
Drowsiness (mm) ↓	30.9/30.4	57.0/30.8[c]	51.1/21.7	43.7/27.0

[a] Data are given as mean/SD.
[b] ↑ ↓, direction of improvement.
[c] $P < 0.05$, differences between RLS/PLMD patients and controls (Mann–Whitney U-test).
[d] $P < 0.01$.

Table 6
Differences in morning mental performance between RLS/PLMD patients and normal controls[a]

Variable[b]	Controls ($n = 12$)	RLS patients ($n = 12$)	Controls ($n = 12$)	PLMD patients ($n = 12$)
Attention (score) ↑	482.0/121.4	500.0/163.4	513.5/167.2	492.6/102.5
Concentration (% errors) ↓	4.9/5.4	4.2/3.2	4.6/3.8	3.5/2.9
Attention var. (score) ↓	13.4/3.3	15.1/3.2	14.1/3.7	16.5/3.9[c]
Numerical memory (*N*) ↑	5.2/1.7	4.6/2.3	6.0/1.5	4.0/1.8[d]
Fine motor activity RI ↑	42.0/10.6	32.9/7.8[c]	46.5/10.2	39.0/10.1[c]
Fine motor activity LE ↑	31.8/10.9	25.6/7.1	36.3/9.4	33.7/8.5
Fine motor activity RI + LE ↑	73.8/19.1	58.5/14.4[c]	82.4/17.9	71.8/16.6
Reaction time (RT) (ms) ↓	508.7/102.9	610.7/118.1[c]	499.9/138.8	573.0/85.7
RT variability (ms) ↓	95.8/39.9	133.4/50.7[c]	83.9/42.4	107.4/40.4
RT errors/commission (*N*) ↓	3.4/4.3	5.2/4.9	1.0/0.9	3.3/3.5[c]
RT errors/omission (*N*) ↓	0.1/0.3	1.1/1.2[c]	0.6/1.2	0.6/1.2

[a] Data are given as mean/SD.
[b] ↑ ↓, direction of improvement.
[c] $P < 0.05$, differences between RLS/PLMD patients and controls (Mann–Whitney *U*-test).
[d] $P < 0.01$.

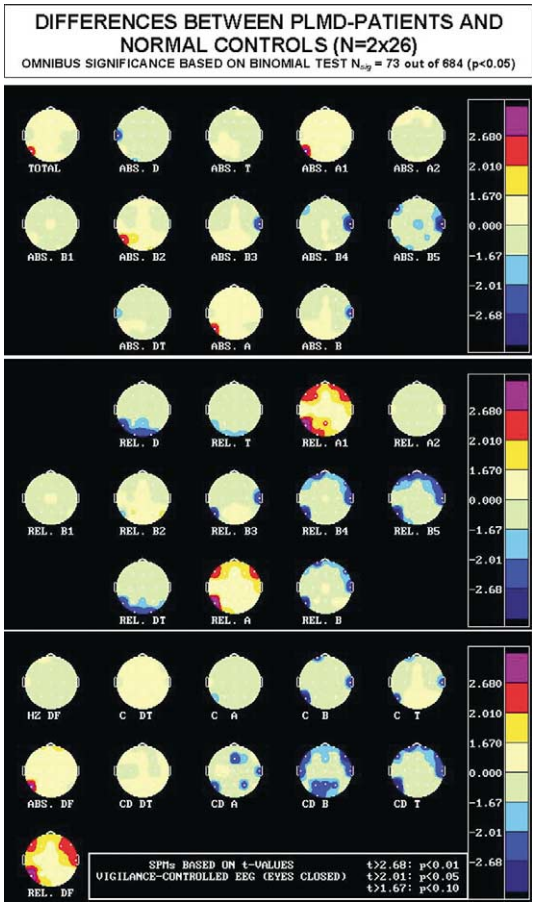

Fig. 2. Maps on V-EEG differences between PLMD patients and normal controls (*n*: 2×26). For a technical description of the maps, see Fig. 1. The omnibus significance based on the binomial test exhibits significant differences between RLS patients and controls, as the number of significant tests is 73 out of 684 ($P < 0.05$). PLMD patients demonstrate an increase in total power and absolute and relative alpha-1 power along with a decrease in absolute and relative delta and beta power. The centroid of the total and beta power is significantly slowed as compared with controls. The absolute and relative power of the dominant frequency is increased.

as compared with normal controls is probably due to the very mixed sample of PLMD patients in our study. It comprised patients with insomnia, hypersomnia, and excessive daytime somnolence, but also with primary snoring and a mild form of obstructive snoring. This may also explain why there were no significant differences between PLMD patients and controls for subjective sleep and awakening quality We may have missed some upper-airway resistance or airflow restricted breathing events, since we did not use esophageal balloons or nasal cannula, but then we did not use these techniques in PLMD patients and normal controls either.

In conclusion, EEG mapping revealed neurophysiological correlates of depression and anxiety in RLS and PLMD, respectively, that were consistent with the patients' subjective ratings of depression and anxiety symptoms.

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References

[1] Stepansky R, Schmeiser-Rieder A, Holzinger B, Saletu B, et al. Selbsteinschätzung von Parasomnien und Beinunruhe beim Einschlafen – Ergebnisse einer epidemiologischen Untersuchung. Somnologie 1999;3:78–82.
[2] Walters AS, and The International Restless Legs Syndrome Study Group. Toward a better definition of restless legs syndrome. Mov Disord 1995;10:634–642.
[3] Saletu B, Anderer P, Saletu M, Semler B, et al. Restless-legs-syndrome (RLS) – neue schlafmedizinische Erkenntnisse in Diagnose

und Therapie. In: Dézsy J, editor. Medizin 2001 – aus Forschung und Praxis. Wien: Dr Peter Müller Verlag, 2000. pp. 263–280.
[4] Saletu M. Periodic limb movement disorder (PLMD) – aetiology and treatment. Brain Pharmacol 2002;1:103–119.
[5] American Sleep Disorder Association. The International Classification of Sleep Disorders, revised: Diagnostic and Coding Manual. Rochester, MN: American Academy of Sleep Medicine, 1997.
[6] Duffy FH, Albert MS, McAnulty G. Brain electrical activity in patients with presenile and senile dementia of the Alzheimer type. Ann Neurol 1984;16:439–448.
[7] John ER, Prichep LS, Fridman J, Easton P. Neurometrics: computer-assisted differential diagnosis of brain dysfunctions. Science 1988;239:162–169.
[8] Saletu B, Anderer P, Kinsperger K, Grünberger J. Topographic brain mapping of EEG in neuropsychopharmacology – part II. Clinical applications (Pharmaco EEG imaging). Methods Find Exp Clin Pharmacol 1987;9:385–408.
[9] Saletu B, Anderer P, Paulus E, Grünberger J, et al. EEG brain mapping in diagnostic and therapeutic assessment of dementia. Alzheimer Dis Assoc Disord 1991;5(Suppl. 1):57–75.
[10] Saletu B, Brandstätter N, Metka M, Stamenkovic M, et al. Hormonal, syndromal and EEG mapping studies in menopausal syndrome patients with and without depression as compared with controls. Maturitas 1996;23:91–105.
[11] Buysse DJ, Reynolds III CF, Monk TH, Berman SR, et al. The Pittsburgh sleep quality index. A new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193–213.
[12] Zung WWK. A self-rating depression scale. Arch Gen Psychiatry 1965;12:63–70.
[13] Zung WWK. Self-Rating Anxiety Scale [SAS]. In: Guy W, editor. ECDEU assessment manual for psychopharmacology. Rev ed, Rockville, MD: U.S. National Institute of Health, Psychopharmacology Research Branch, 1976. pp. 337–340.
[14] Mezzich JE, Ruiperez MA, Perez C, Yoon G, et al. The Spanish version of the quality of life index: presentation and validation. Nerv Ment Dis 2000;188:301–305.
[15] Johns MW. A new method for measuring daytime sleepiness: The Epworth Sleepiness Scale. Sleep 1991;14:540–545.
[16] Anderer P, Saletu B, Kinsperger K, Semlitsch H. Topographic brain mapping of EEG in neuropsychopharmacology – part I. Methodological aspects. Methods Find Exp Clin Pharmacol 1987;9:371–384.
[17] Anderer P, Semlitsch H, Saletu B, Barbanoj M. Artifact processing in topographic mapping of electroencephalic activity in neuropsychopharmacology. Psychiatry Res 1992;45:79–93.
[18] Saletu B, Gruber G, Saletu M, Brandstätter N, et al. Sleep laboratory studies in restless legs syndrome patients as compared with normals and acute effects of ropinirole: (I) Findings on objective and subjective sleep and awakening quality. Neuropsychobiology 2000;41:181–189.
[19] Saletu M, Anderer P, Saletu B, Hauer C, et al. Sleep laboratory studies in restless legs syndrome patients as compared with normals and acute effects of ropinirole. 2. Findings on periodic leg movements, arousals and respiratory variables. Neuropsychobiology 2000;41:190–199.
[20] Saletu M, Anderer P, Saletu B, Hauer C, et al. Sleep laboratory studies in periodic limb movement disorder (PLMD) as compared with normals and acute effects of ropinirole. Hum Psychopharmacol Clin Exp 2001;16:177–187.
[21] Saletu B. Psychopharmaka, Gehirntätigkeit und Schlaf. Basel: Karger, 1976.
[22] Benca RM, Obermeyer WH, Thisted RA, Gillin JC. Sleep and psychiatric disorders. Arch Gen Psychiatry 1992;49:651–668.
[23] Rothdach AJ, Trenkwalder C, Haberstock J, Keil U, et al. Prevalence and risk factors of RLS in an elderly population: the MEMO study. Memory and Morbidity in Augsburg Elderly. Neurology 2000;14:1064–1068.
[24] Saletu M, Hauer C, Anderer P, Saletu-Zyhlarz G, et al. Tagesmüdigkeit korreliert mit nächtlichen Atmungs- und Arousal-Variablen bei Schlafapnoepatienten: Polysomnographische und EEG-Mapping-Untersuchungen. Wien Klin Wochenschr 2000;112:281–289.
[25] Saletu-Zyhlarz G, Saletu B, Anderer P, Brandstätter N, et al. Nonorganic insomnia in generalized anxiety disorder. 1. Controlled studies on sleep, awakening and daytime vigilance utilizing polysomnography and EEG mapping. Neuropsychobiology 1997;36:117–129.
[26] Saletu B, Anderer P, Brandstätter N, Frey R, et al. Insomnia in generalized anxiety disorder: polysomnographic, psychometric and clinical investigations before, during and after therapy with a long- versus a short-half-life benzodiazepine (quazepam versus triazolam). Neuropsychobiology 1994;29:69–90.