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Original Article

Electrophysiologic disturbances during daytime in patients with restless legs syndrome: Further evidence of cognitive dysfunction?

Ki-Young Jung [a,*], Yong-Seo Koo [a], Byung-Jo Kim [a], Deokwon Ko [a,b], Gwan-Taek Lee [a], Kyung Hwan Kim [c], Chang Hwan Im [d]

[a] Department of Neurology, Korea University College of Medicine, Seoul, South Korea
[b] BK21 Program for Biomedical Science, Korea University College of Medicine, Seoul, South Korea
[c] Department of Biomedical Engineering, College of Health Science, Yonsei University, Wonju, South Korea
[d] Department of Biomedical Engineering, Hanyang University, Seoul, South Korea

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ABSTRACT

Backgrounds: It has been reported that patients with restless legs syndrome (RLS) may have cognitive deficit. The authors performed EEG and ERP analysis during daytime to identify electrophysiologic relations with cognitive dysfunction in unmedicated RLS patients.
Methods: Seventeen drug naive RLS patients (53.7 ± 9.6 years) and 13 age-matched healthy controls participated in the present study. EEG was recorded during the waking–resting state and during a visual oddball task. RLS severities were determined using the International RLS Severity Scale. Stanford sleepiness scale (SSS) and bothersomeness visual analog scale (VAS) scores were determined immediately after ERP sessions. EEG power spectra and P300 amplitude and latency were compared for patients and controls. Clinical variables were correlated with P300 findings.
Results: Waking–resting EEG showed that RLS patients had significantly higher beta activity in frontocentral regions than controls. SSS scores were not different in the two groups. But the bothersomeness VAS scores of RLS patients were significantly higher than those of controls. Furthermore, P300 latency was significantly longer in patients, and patients had significantly lower P300 amplitudes in frontal and central locations. In addition, P300 latency was found to be significantly correlated with bothersomeness during the ERP test, whereas P300 amplitude showed no such tendency.
Conclusions: Our study supports the notion that RLS patients have an underlying cognitive dysfunction. Significant correlations found between P300 latency and bothersomeness, a lack of sleepiness during the ERP test, and increased beta activity in resting state EEGs suggest that a combination of inattention and cortical dysfunction underlie cognitive dysfunction in RLS.

1. Introduction

Restless legs syndrome (RLS) is a sensorimotor neurologic disorder, in which the primary symptom is a compelling urge to move the legs accompanied by unpleasant and disturbing sensations in the legs [1]. Recent studies have reported that patients with RLS may have underlying cognitive deficit [2]. RLS patients suffer from sleep disturbance [3], which causes chronic partial sleep loss, and because cognitive function appears to be particularly sensitive to sleep loss, sleep deprivation due to the symptoms of RLS might be the cause of cognitive dysfunction. Pearson et al. reported that RLS patients show cognitive deficits, particularly in prefrontal function, which are comparable to the loss of a night's sleep [2]. In a subsequent comparative study of RLS patients and sleep-restricted controls, however, the same group found that RLS patients performed significantly better on prefrontal function tests than controls [4]. Although the authors proposed that RLS subjects might adapt to sleep loss to some extent, sleep loss alone does not appear to explain cognitive dysfunction in RLS.

Decreased attention due to the symptoms of RLS is another possible mechanism of cognitive dysfunction. Sleep disruption associated with RLS might lead to inattentiveness, moodiness, and paradoxical overactivity. Furthermore, attention deficit hyperkinetic disorder (ADHD) symptoms are more common in RLS patients than in insomnia patients or normal controls [5,6]. Leg discomfort and/or attention deficit in RLS may theoretically lead to hyperactivity and lack of concentration, and these may cause cognitive dysfunction. Recently, Gamaldo et al. reported that RLS patients have a higher degree of alertness than partial sleep-restricted controls regardless of increased leg activity [7]. Furthermore,

* Corresponding author. Address: Department of Neurology, Korea University Medical Center, Korea University College of Medicine, #126-1, Anam-Dong 5 Ga, Seongbuk-Gu, Seoul 136-705, South Korea. Tel.: +82 2 920 6649; fax: +82 2 925 2472.
E-mail address: jungky@korea.ac.kr (K.-Y. Jung).

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electrophysiologic and neuroimaging studies have demonstrated cortical sensorimotor dysfunction in RLS [8–10] and that cortical excitability in RLS can be reduced by dopaminergic agents [11,12]. These findings suggest that intrinsic cortical abnormalities are present in RLS. Therefore, it could be hypothesized that cognitive dysfunction in RLS may be either secondary to excessive daytime sleepiness and/or due to an attention deficit caused by the symptoms of RLS, or primary due to intrinsic cerebral cortical dysfunction underlying RLS syndrome.

EEG allows the non-invasive monitoring of brain processes with excellent temporal resolution. EEG during relaxed wakefulness (the resting state) reflects a particularly important state of arousal, which can be characterized by frequency analysis [13]. In addition, event-related potentials (ERPs) provide a neurophysiologic index of a subject's cognitive function. In particular, P300 has been proposed as an index of multiple cognitive processes, including attention, context updating, and processing resource allocation [14]. Furthermore, P300 latency is believed to reflect the duration of the stimulus evaluation process, and its amplitude to represent processing capacity allocated for stimulus evaluation. Moreover, ERP measurements during tasks may provide a more sensitive means of objectively assessing cognitive function. Thus, EEG and ERP studies might be useful for exploring cognitive functions in RLS possibly associated with attention and/or arousal state dysfunctions. But few studies have addressed electrophysiologic disturbances in RLS [15].

In the present study, we performed EEG and ERP analysis during the daytime to find electrophysiologic correspondences with cognitive dysfunction in previously unmedicated RLS patients. We hypothesized that compared with age- and sex-matched healthy controls, RLS patients should have electrophysiologic abnormalities, particularly in the frontal region.

2. Methods

2.1. Subjects

Seventeen female RLS drug naive patients (53.7 ± 9.6 years) were enrolled in the present study. All patients underwent a standardized interview using a structured sleep questionnaire and clinical neurologic examinations. The structured sleep questionnaire included questions on sleep habits and medication history, the Global Sleep Assessment Questionnaire [16], the Pittsburgh Sleep Quality Index [17], the Epworth Sleepiness Scale [18], and the Insomnia Severity Index [19]. RLS was diagnosed according to the diagnostic criteria proposed by the International RLS Study Group [20]. Patients were excluded if they had a secondary cause of RLS, such as a history of taking drugs thought to cause RLS (e.g., neuroleptics, antidepressants, or antihistamines), a relevant neurologic or psychiatric disorder, or a history of sleep-related disorders other than RLS-related insomnia. In all patients, laboratory findings, which included blood glucose and serum levels of creatinine, iron/ferritin, and thyroid hormones were within normal limits. RLS severities were determined using the International RLS Severity Scale (IRLS) [21]. The mean IRLS score of patients in the RLS group was 21.1 ± 7.4 (range; 9–35). An age-matched group of 13 healthy female volunteers served as controls (mean age, 54.6 ± 7.6 years). Mean age, years in full-time education, and proportions in menopause (82.4% in RLS vs. 84.7% in controls) were no different in the RLS and control groups (Table 1). All subjects provided written informed consent, and the experimental protocol was approved by the Institutional Review Board of the Korea University Medical Center.

Table 1
Demographic data of subjects.

	RLS	Control	*P*
N	17	13	
Age (years)	53.7 ± 9.6	54.6 ± 7.6	NS
Education (years)	12.1 ± 3.3	9.8 ± 3.2	NS
Number of menopause (%)	14 (82.4%)	11 (84.7%)	NS
IRLS score	21.1 ± 7.4	–	

RLS, restless legs syndrome; IRLS, International RLS Severity Scale; NS, not significant.

2.2. EEG recording and stimulus presentation

EEG recordings were made at 10 am using a 32-channel digital EEG machine with 27 electrodes placed on the scalp in accord with the requirements of the international 10–20 system, with extended coverage of the lower temporal region (F9/10, T9/10, and P9/10). The reference electrode was set to linked-mastoid electrodes. Impedance was kept below 5 kΩ, and the bandpass filter was set at 0.1–100 Hz with a sampling rate of 400 Hz. Two electrooculogram (EOG) channels (placed on left and right outer canthi) were added to confirm eyeball movements and to remove EOG artifacts. EEGs were recorded under waking–rest conditions for about 5 min prior to ERP sessions and repeated six times with eyes closed (for 20 s) and eyes open (for 20 s) alternatively to ascertain alertness.

A visual oddball paradigm was used to determine ERPs. Stimuli consisted of a regular white triangle and a 50 × 50 mm white square on a black background. Commercial software (PRESENTATION; Neurobehavioral systems, Berkeley, CA) was used to present stimuli on a 17-inch LCD monitor. The distance between subjects' eyes and the monitor was approximately 75 cm, and the visual angle was 1.91°. Standard (triangle) and target (square) stimuli were presented for 200 ms in randomized order at a standard to target ratio of 4:1. Interstimulus intervals were fixed at 1200 ms. Black screens were presented elsewhere. Subjects were requested to respond only to target stimuli by pressing a button as quickly as possible. The overall experiment for each subject was divided into two blocks, and 400 stimuli were presented during each block. Subjects rested for 5 min between blocks. Experimental sessions usually took 25–30 min per subject. The Stanford sleepiness scale (SSS) [22] and the visual analog scale (VAS) for bothersomeness [23] (from 0 to 10 points) in relation to either RLS symptoms or experimental procedures were assessed immediately after ERP sessions.

EEG data were processed using EEGLAB version 6.03b [24] and Fieldtrip (available at http://fieldtrip.fcdonders.nl/) operated in the MATLAB environment (version 7.01, MathWorks, Natick, MA). After transforming EEG data to an average reference, it was digitally filtered using a 0.5–50 Hz band pass filter. Electrodes were grouped to frontal (F3, Fz, and F4), central (C3, Cz, and C4) and parietal (P3, Pz, and P4) brain regions.

2.3. Power spectral analysis of resting state EEG

The waking state EEG of each subject was reviewed, and 10 artifact-free 1.5-s epochs in the eyes-closed state were selected per patient. The conventional fast Fourier transformation method was used for power spectral analysis. Each epoch was fast Fourier transformed and then averaged to compute the power spectral density function for each subject. The relative powers of delta-, theta-, alpha-, beta1-, and beta2-frequency ranges were computed to be 0.67–3.34, 4.0–7.34, 8.0–12.67, 13.34–18.67, and 19.34–30.0 Hz, respectively.

2.4. Averaged ERP analysis

ERP epochs were extracted from −200 to +800 ms from stimulus onset. Baselines were corrected by subtracting the root mean

square of the pre-stimulus interval from whole epoch lengths. Only those trials with correct responses were included in the ERP analysis. EEG activities were averaged for target and standard stimuli separately over −200 to 800 ms poststimulus (1000 ms). Epochs exceeding ±100 μV in EEGs or in EOGs were not included in averaged waveforms. The mean number of epochs recorded per patient for standard and target stimuli were 485.2 ± 98.7 and 123.7 ± 22.8, respectively.

ERP latencies and amplitudes were measured relative to pre-stimulus baselines. The N100, P200, N200, and P300 components were defined as points with a negative peak amplitude between 125 and 185 ms, a positive peak amplitude between 185 and 250 ms, a negative peak amplitude between 230 and 330 ms, and a positive peak amplitude between 325 and 450 ms, respectively.

2.5. Statistical analysis

EEG and ERP data were analyzed by repeated measures analysis of variance (ANOVA). For EEG data, within-subject variables were frequency band (five levels: delta, theta, alpha, beta1, and beta2) and location (three levels: frontal, central, and parietal), whereas the between-subject variable was group (i.e., RLS vs. Control). For ERP data, within-subject variables were stimulus (two levels: standard and target), and location (three levels: frontal, central, and parietal), and again the between-subject variable was group (i.e., RLS vs. Control). The Greenhouse-Geisser correction was used to evaluate F ratios to control for Type 1 error in the repeated measures design. Bonferroni post hoc tests were used to identify the sources of significant ANOVA. Statistically significant EEG frequency bands and ERP components revealed by repeated measures ANOVA were subject to correlation analysis vs. IRLS and VAS scores.

EEG and ERP data from all electrodes and from each time frame or each frequency bin were subject to cluster-based nonparametric statistical tests using Fieldtrip [25]. In order to control for type I error rate in multiple comparisons, a nonparametric randomization test incorporating the cluster-level randomization method, which identifies electrodes at which differences between the RLS and control group exceed a significance level, was used [25]. This method takes the cluster showing the maximum difference between two groups to calculate a critical value for statistical significance, under the null distribution for this test statistic, using a permutation method (the Monte Carlo approximation). Statistical significance was accepted for p values of <0.05.

3. Results

3.1. EEG power spectra

For all frequency bands, ANOVA showed neither a between-group effect nor an interaction between group and location. Nevertheless, cluster-based nonparametric statistical analysis showed RLS patients had significantly greater beta activity in the 26–30 Hz range in frontal and central regions (Fig. 1).

3.2. ERP analysis

SSS scores were no different in the two groups (Table 2). But patients felt significantly more bothersomeness during the ERP test than controls (6.1 ± 3.2 vs. 0.2 ± 0.6, $t = -5.147$, $p < 0.001$). Hit rates for target stimuli were 98.2% in patients and 99.1% in controls, which was not significantly different. But mean reaction time to a target stimulus in controls was shorter than in patients (382.7 ms vs. 425.4 ms, respectively) ($t = -3.116$, $p = 0.004$).

ERP waveforms are shown in Fig. 2. P300 latency was significantly greater in patients than in controls. Repeated measures ANOVA revealed a significant main effect of group ($F_{1,28} = 14.375$, $p < 0.001$). P300 amplitude tended to be lower in RLS patients than in controls ($F_{1,28} = 3.468$, $p = 0.073$). Pairwise comparisons of P300

Table 2
Behavioral characteristics during ERP recording.

Group	RLS	Control	P
Stanford sleepiness scale	3.2 ± 1.6	2.2 ± 1.0	NS
Bothersomeness (VAS)	6.1 ± 3.2	0.2 ± 0.6	<0.001
Reaction time (ms)	425.4 ± 40.3	382.7 ± 32.6	0.004
Hit rate (%)	98.2 ± 2.1	99.1 ± 1.3	NS

RLS, restless legs syndrome; NS, not significant; VAS, visual analog scale.

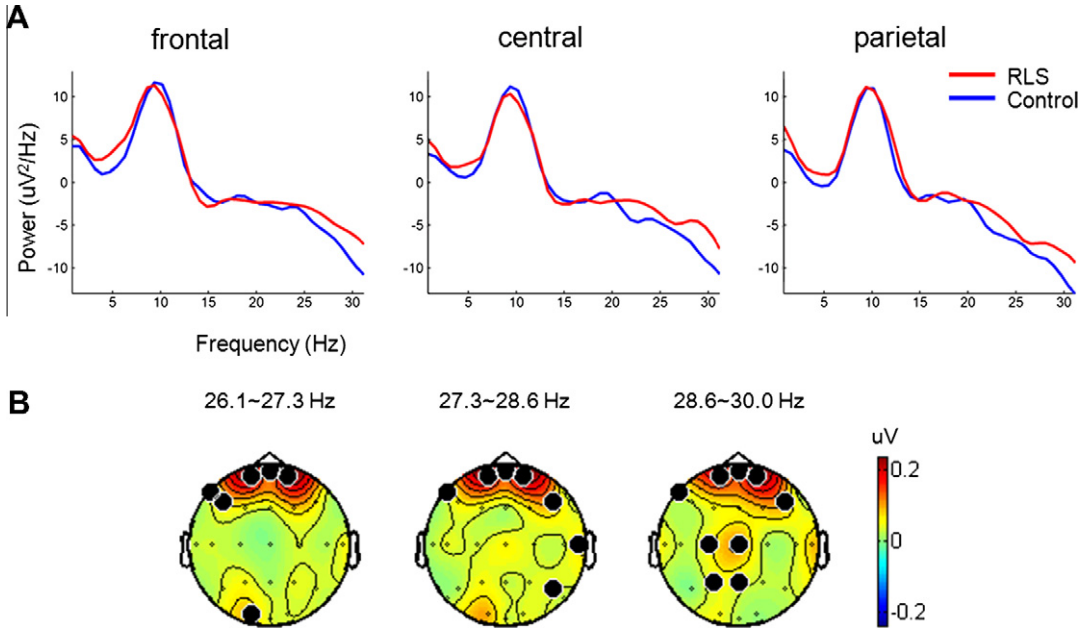

Fig. 1. (A) Averaged power spectra of patients and controls at different recording sites. (B) The topography of EEG spectral power differences (spectral power of RLS patients minus that of controls) in the high beta frequency band. Red denotes a positive and blue denotes a negative potential. Black dots indicate significant electrodes ($p < 0.05$).

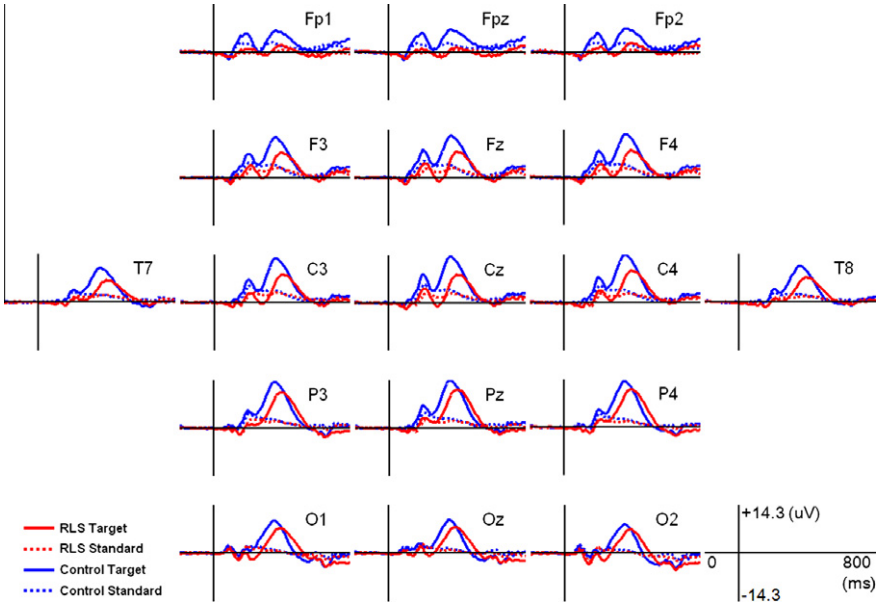

Fig. 2. Grand average ERP responses to standard and target visual stimuli.

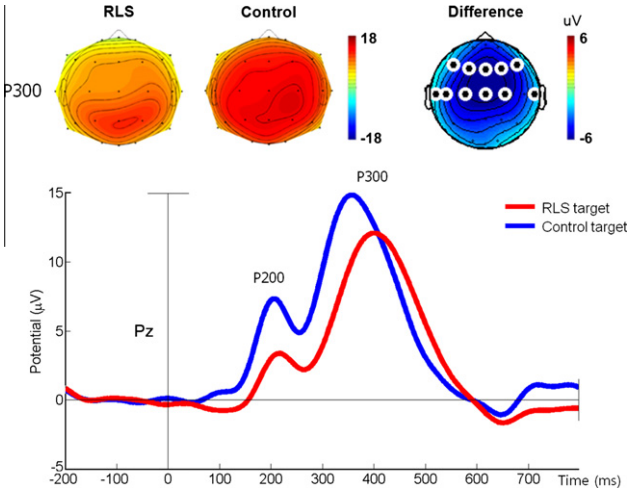

Fig. 3. Voltage topographic scalp maps of P300 (left and middle panels) and ERP differences (right panel) between groups (ERP of RLS patients minus that of controls). Red denotes a positive and blue denotes a negative potential. Significant electrodes are highlighted ($p < 0.05$).

amplitudes at different locations showed that RLS patients had significantly lower P300 amplitudes in frontal and central locations than controls, and cluster-based nonparametric statistical analysis showed significantly lower amplitude in RLS patients in the anterior head region at 300–350 ms (Fig. 3). P300 latency was found to be significantly correlated with bothersomeness during the ERP test at all three locations in patients ($r = 0.756$, $p < 0.001$ frontal; $r = 0.682$, $p = 0.003$ central; and $r = 0.857$, $p < 0.001$ parietal; Fig. 4). However, P300 amplitude showed no such tendency. IRLS did not show any significant correlation with either P300 amplitude or latency.

4. Discussion

In this study, we found that P300 had a significantly lower amplitude and greater latency, particularly in the frontocentral region in RLS patients than in age-matched controls. Mean reaction time was significantly longer in RLS patients, although correct response percentages were similar in patients and controls. Lower amplitude and greater latency P300 has been reported in patients with reduced cognitive ability, and for more difficult tasks. Thus, our P300 findings suggest that RLS patients have either cognitive dysfunction or experienced more difficulty performing the task. Accordingly, our results support those of previous studies [2], which concluded that RLS patients have cognitive dysfunction.

There are several possibilities for the cognitive dysfunction in RLS patients, although the mechanism involved is not understood. First, because sleep loss or sleep restriction is common in RLS, excessive daytime sleepiness may account for the cognitive deficit observed, although it does not cause the expected profound sleepiness [7]. On the other hand, inattention caused by the sensory symptoms of RLS [6] may lead to poor performance in response to target stimuli in the oddball task. Finally, as was demonstrated by a neuroimaging study, RLS patients may have intrinsic cortical dysfunction, particularly in the frontal lobe [26].

We performed ERP studies at 10 am on all subjects to avoid RLS symptoms and sleepiness during EEG and ERP recordings because alertness is highest and RLS symptoms are usually at a nadir at this time [27]. The SSS scores of RLS patients ranged 2–3 points, which was similar to that observed in controls. This finding concurs with that of a recent study, in which RLS subjects, despite greater sleep loss, displayed greater sustained alertness than sleep-restricted controls [7], which suggests that daytime sleepiness contributes to cognitive dysfunction in RLS patients.

Bothersomeness scores during the ERP test were significantly higher for RLS patients, which means that they had a greater subjective feeling of bothersomeness or troublesomeness during ERP testing, which requires considerable attention, although they did not complain of RLS symptoms at the time. Furthermore, delayed reaction times may reflect inattention in patients. In addition, VAS bothersomeness scores during the ERP study were found to be significantly correlated with P300 latency. This bothersomeness during the ERP test may have prevented patients concentrating on target stimuli and caused poor patient performance during the oddball task. It has been reported that ADHD is more common in adults with RLS than in controls [6,28,29]. RLS patients, even adults aged more than 60 years, frequently experience hyperactivity and inattention [6], and it has been suggested that RLS symptoms

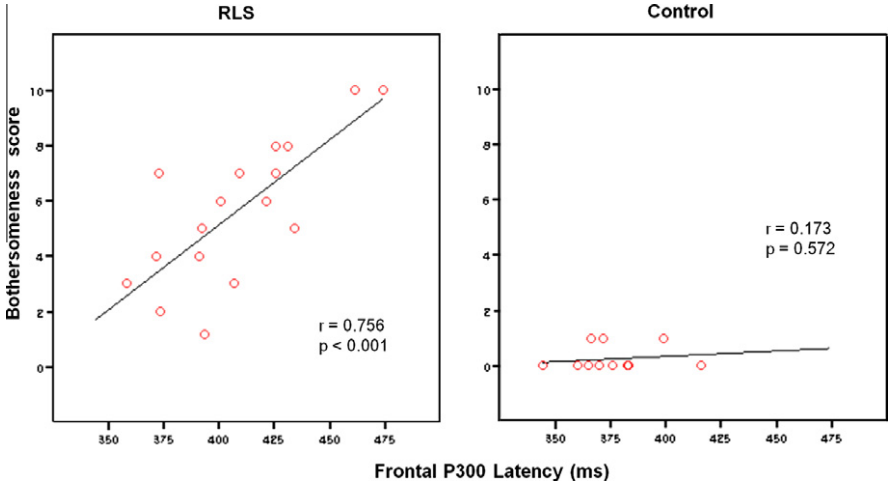

Fig. 4. Correlation between bothersomeness scores and frontal P300 latencies.

mimic those of ADHD, and even that RLS might be associated with ADHD [29]. P300 is believed to reflect context updating due to the renewal of the representation of current environment within working memory. Thus, the lower P300 amplitude and greater P300 latency observed in RLS patients appears to be due to the demands of attention and processing resources [30], and thus it could be speculated that inattention in relation to bothersomeness during the ERP test may have contributed to cognitive dysfunction in RLS patients.

In the present study, EEG spectral analysis of waking–rest conditions revealed that high beta band power was significantly higher (primarily in the anterior head region) in patients. High frequency activity in the beta band (16–32 Hz) is thought to reflect cortical activation that represents an analog of sensory processing, attention focusing, or working memory [13,31,32]. Moreover, increased beta activity during the sleep onset period and during NREM sleep has been repeatedly reported in patients with insomnia, indicating a cortical hyperarousal state [32]. The finding that RLS subjects have greater sustained alertness than sleep-restricted controls in daytime [7] also supports the presence of hyperarousal in RLS patients. Furthermore, it is believed that RLS patients have high demand for focused attention and sensory processing. Recently, Astrakas et al., in a functional MRI study, found that RLS patients show higher dorsolateral prefrontal cortex activation than controls [26], which is in accord with our results. Therefore, our EEG findings indicate the presence of cortical dysfunction in RLS patients, but it remains unclear whether this is a primary abnormality or an effect of the symptoms of RLS.

Taken together, we hypothesize that inattention and an underlying cortical dysfunction contribute to the cognitive deficit observed in RLS patients. In other words, RLS patients may have difficulty updating the contexts of incoming sensory stimuli due to cortical hyperarousal. In addition, decreased attention caused by the symptoms of RLS when patients are concentrating may further block performance during cognitive tasks.

Repeated measures ANOVA revealed a significant difference between patients and controls in terms of P300 amplitude and latency in the frontocentral region. Furthermore, cluster-based nonparametric statistical test covering all electrodes and time frames or all frequency bins corroborated this finding for both ERP and EEG data. Neuropsychological tests have revealed that RLS patients have cognitive dysfunction, particularly with respect to prefrontal functions such as the trail making test and verbal fluency [2], which is in accord with our results. Although the pathophysiology of RLS has not been elucidated, the subcortical dopaminergic system has been implicated [1,33]. Furthermore, a number of genetic and pharmacological studies have demonstrated that the dopaminergic system is associated with frontal P300 generation [34]. This encourages us to speculate that the smaller frontal P300 amplitude observed in RLS patients may be mediated by dopaminergic dysfunction, and that this is the underlying pathophysiology of RLS. This hypothesis would be supported if dopaminergic medication reverses observed P300 abnormalities in RLS patients.

The patients enrolled in the present study were relatively homogenous; all patients were middle-aged drug naive women, and ERP studies were performed at 10 am in all subjects. Thus, we believe that some factors that influence ERPs [14], such as gender, medication, and diurnal variation, were avoided. Nevertheless, some study limitations require consideration. Most obviously, only a small number of subjects were recruited. Furthermore, neuropsychological tests were not performed in parallel with ERP tests, and thus, we were unable to examine correlations between neuropsychological and ERP findings. Accordingly, we suggest that a larger-scale study, including men and other age groups, be conducted to substantiate our results. In addition, a study on the effect of dopaminergic drugs on P300 in RLS patients is required to explore the dopamine hypothesis of cognitive dysfunction in RLS.

P300 amplitudes and latencies can be affected by several factors including previous night's sleep quality, food, caffeine, and other biologic factors [14]. The major limitation of the present study is the lack of polysomnographic data, which would have allowed us to determine the possible presences of other sleep disorders, such as sleep apnea, since apneics have been reported to have similar P300 results [35] and the adequacy of nocturnal sleep prior to EEG and ERP [36].

Our results support the notion that RLS patients have cognitive dysfunction. The findings of significant correlations between P300 and bothersomeness and lack of sleepiness during the ERP test and of increased beta activity in the resting state EEG favor the hypothesis that a combination of inattention and cortical dysfunction underlie cognitive dysfunction in RLS.

Conflict of interest statement

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: doi: doi:10.1016/j.sleep.2010.08.018.

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