Table 2. Polysomnograhic variables before and after treatment with pramipexole.

| | before treatment | after treatment | $p$ |
|---|---|---|---|
| total sleep time (minutes) | 402.8 ± 63.4 | 409.0 ± 88.6 | n.s. |
| Sleep efficiency (%) | 82.5 ± 10.3 | 79.4 ± 14.1 | n.s. |
| Stage 1 (%SPT) | 6.8 ± 3.3 | 7.5 ± 3.4 | n.s. |
| Stage 2 (%SPT) | 51.8 ± 9.8 | 52.5 ± 12.3 | n.s. |
| Stage 3 + 4 (%SPT) | 5.0 ± 5.5 | 3.0 ± 2.8 | n.s. |
| Stage REM (%SPT) | 11.3 ± 4.9 | 14.7 ± 6.8 | n.s. |
| RWA (%SPT) | 7.7 ± 5.2 | 5.7 ± 3.8 | n.s. |
| RWA (%REM) | 39.2 ± 19.3 | 34.7 ± 21.6 | n.s. |
| tonic REM (%/REM) | 11.2 ± 8.7 | 9.8 ± 11.1 | n.s. |
| phasic REM (%REM) | 28.1 ± 18.9 | 24.5 ± 21.4 | n.s. |
| WASO (%SPT) | 17.4 ± 10.3 | 20.6 ± 14.2 | n.s. |
| REM density (%) | 23.3 ± 10.0 | 16.2 ± 8.4 | < 0.01 |
| PLMS index (events/hour) | 38.4 ± 17.9 | 19.2 ± 20.7 | < 0.01 |
| PLMS arousal index (events/hour) | 4.7 ± 5.4 | 1.5 ± 2.2 | < 0.01 |
| PLMS index during NREM sleep (events/hour) | 36.0 ± 16.7 | 11.1 ± 16.4 | < 0.01 |
| PLMS index during REM sleep (events/hour) | 39.4 ± 31.6 | 33.5 ± 35.1 | n.s. |

Values are expressed as mean ± S.D.

SPT, sleep period time; REM, rapid eye movement; RWA, REM sleep without atonia; WASO, wake after sleep onset; PLMS, periodic leg movements during sleep.

$p < 0.01$). All the patient subjects complained of frequent nightmares before treatment. After pramipexole treatment, five patients (33.3%) reported complete disappearance of nightmares, the number of patients having nightmares decreased to six patients (40.0%). Consequently, among the 12 patients who achieved clear improvement of RBD symptoms, 10 patients (83.3%) reported disappearance or improvement of nightmares.

Regarding n-PSG measures, no significant differences in the sleep stage variables, including the amount of RWA, were found between those assessed before and after treatment with pramipexole. However, the REM density after the treatment was significantly lower than the value before the treatment ($Z = -2.556$, $p < 0.01$). Among PLMS measures, the PLMS index during the sleep period as a whole ($Z = -3.238$, $p < 0.01$), the index during NREM sleep period ($Z = -3.351$, $p < 0.01$), and the PLMS arousal index ($Z = -3.297$, $p < 0.01$) decreased significantly after the treatment. Nevertheless, no significant change in PLMS index was observed during the REM sleep period (Table 2).

Regarding the relation between the RBD symptoms and the REM density, positive correlation was found between the reduction rate of RBD symptoms and that of REM density with pramipexole treatment ($rs = 0.785$, $p < 0.01$) (Fig. 1).

## Discussion

According to a recent review of the effectiveness of interventions in RBD (Aurora et al. 2010), only two reports have described published studies that evaluated the effectiveness of pramipexole treatment on idiopathic RBD (Fantini et al. 2003; Schmidt et al. 2006). Fantini et al. (2003) reported that 7 of 8 patients reported reduced RBD clinical manifestations after pramipexole treatment. Schmidt et al. (2006) also reported that pramipexole mitigated the RBD symptom severity. However, to date, the mechanism of action of pramipexole on RBD symptoms remains unclear.

This study is the first to investigate the influence of pramipexole on RBD symptoms, PLMS-related variables, and REM-related PSG variables simultaneously. The results of our study show that pramipexole treatment improved RBD symptoms in 80.0% patients, suggesting that pramipexole is effective for the treatment of idiopathic RBD. Fantini et al. (2003) reported that pramipexole treatment decreased neither the amount of phasic EMG activity nor the REM density. Consistent with their finding, the amount of RWA did not decrease in this study. Zhang et al. (2008) reported that RBD episodes do not occur commonly during one-night PSG monitoring and reported that the occurrence tends to show high night-to-night variation. In the present study, however, RBD symptoms examined before and after treatment were evaluated according to reports about RBD symptoms obtained from the patients or their family members. The severity was rated according to the revised edition of ICSD-1. Therefore, the improvement of RBD symptoms after treatment was not explained by the night-to-night variation of the occurrence of RBD episodes. Regarding EMG activity, Zhang et al. reported high correlations in both tonic and phasic EMG activities between night 1 and night 2 (tonic, $r = 0.82$; phasic, $r = 0.83$). Accordingly, no difference in the amount of RWA between

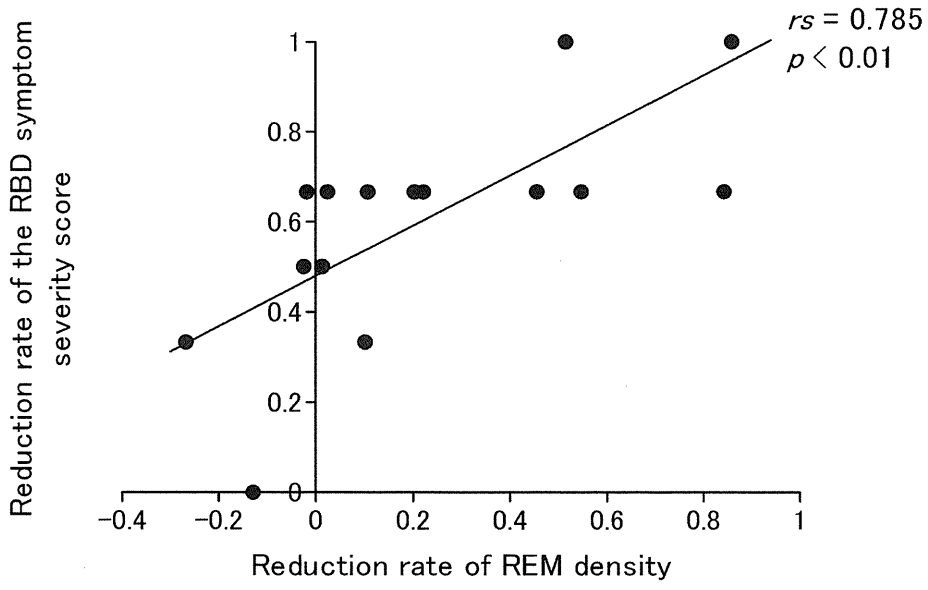


Fig. 1. Correlation between the rate of reduction of RBD symptom scores and REM density following treatment with pramipexole.
REM, rapid eye movement; RBD, REM sleep behavior disorder.

those measured before and after treatment was thought to depend on the night-to-night variation of the amount of RWA; pramipexole cannot influence RWA.

Inconsistent with Fantini's report, a significant decrease in REM density after treatment with pramipexole was observed in this study. The reason for the inconsistency in REM density findings remains unknown. Nevertheless, it is noteworthy that in the present study, the changes in RBD symptoms with pramipexole treatment were associated significantly with the reduction of REM density. This study lacked data related to comparison between RBD patients and the control group. However, Tachibana et al. reported previously that RBD patients showed a significantly higher REM density than that of control subjects (Tachibana et al. 1994). Reportedly, neural activity in the parieto-occipital visual cortex after the appearance of REMs during the REM sleep period can trigger dream imagery (Ogawa et al. 2005; Miyauchi et al. 2009). Based on these earlier reports and the results of the present study, the improvement in RBD symptoms associated with the reduction of REM density indicates that the effectiveness of pramipexole on RBD symptoms depends on a decrease in the vividness or the number of dreams linked closely with REM density. This idea is supported by the fact that 83.3% of patients with clear improvement of RBD symptoms showed the reduction or disappearance of nightmares after pramipexole treatment.

High doses of dopaminergic drugs are known to induce vivid dreams, nightmares, and RBD in PD patients (Kulisevsky and Roldan 2004; Gjerstad et al. 2008). In contrast, consistent with previous studies (Fantini et al. 2003; Schmidt et al. 2006), the results of our study suggest that a low dose of pramipexole can be effective for reducing nightmares, engendering improvement in RBD symptoms in patients with idiopathic RBD. In this regard, the effect of pramipexole on idiopathic RBD might differ from that on secondary RBD in PD patients who are already taking high-dosage dopaminergic medication (Kumru et al. 2008). Effects of pramipexole might differ depending on differences in the dosage of dopaminergic medication or in the presence or absence of neurodegenerative disorders (Aurora et al. 2010). Further study is necessary to clarify this issue.

It remains unclear whether dopaminergic dysregulation is involved in PLMS in RBD. Fantini et al. (2003) reported no change in the PLMS index in patients with RBD after pramipexole treatment. However, no report in the relevant literature describes the influence of pramipexole on PLMS in RBD during NREM and REM sleep periods. The results of the present study demonstrated that selective improvement of PLMS during NREM sleep period occurs in patients with idiopathic RBD. Bliwise and Rye (2008) reported that, in comparison with healthy controls, higher EMG activity detected by the phasic electromyographic metric (PEM) rate was observed in patients with RBD, especially during REM sleep. In addition, Huang et al. (2011) reported that excessive electromyographic activities in RBD patients might ameliorate the severity of OSA, especially during REM sleep, possibly because of activation of upper airway dilator muscles. These increased muscle activities during REM sleep might also be associated with the increased PLMS and its weak responsiveness to pramipexole treatment during REM sleep in RBD patients. Consequently, the difference in the effectiveness of pramipexole treatment might indicate that PLMS during REM sleep period has a pathology associated

with a lack of REM sleep motor inhibition probably because of brainstem dysfunction (Fantini et al. 2002) rather than dopaminergic dysfunction.

However, this study presents some limitations. First, this study was not a randomized controlled investigation. Second, the participating subjects were enrolled from one institute and the number of study subjects was small. A future double-blind placebo-controlled trial of pramipexole treatment on numerous RBD patients is desirable for confirming our results. Third, the evaluation of RBD symptom severity was made according to the criteria set in the revised edition of ICSD-1. More comprehensive rating scales for RBD severity that have been published more recently must be used to evaluate RBD symptoms (Boeve et al. 2007; Stiasny-Kolster et al. 2007; Li et al. 2010).

This study shows that treatment with pramipexole improves RBD symptoms, possibly via a mechanism involving a reduction in the REM density. Pramipexole decreases PLMS only during the NREM sleep period, suggesting that other factors affect the pathophysiology of PLMS during the REM sleep period in RBD. Additional double-blind, randomized, controlled trials must be conducted to provide new insights into the effectiveness and mechanism of action of pramipexole on idiopathic RBD.

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## Conflict of Interest

We declare no conflict of interest.

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# Mismatch negativity for speech sounds in temporal lobe epilepsy

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ABSTRACT

The mismatch negativity (MMN) is an electrophysiological trace of change detection, measured by electroencephalography (EEG), and is a reliable marker for pre-attentive auditory sensory memory. We used a phonetic oddball paradigm in patients with temporal lobe epilepsy (TLE) to elicit the MMN response at fronto-central sites and the mismatch positivity (MMP) response at mastoid sites. The MMN in 26 patients was compared with that of 26 age- and gender-matched healthy control participants. Electroencephalography responses were recorded during the presentation of speech sounds: the vowels 'a' and 'o' in alternation. Average waveforms were obtained for standard and deviant trials. We found that the MMP response at bilateral mastoid sites was reduced, whereas the MMN response at fronto-central sites did not change significantly. These results support the view that the MMN is generated by separable sources in the frontal and temporal lobes and that these sources are differentially affected by TLE.



## 1. Introduction

Epilepsy is a major chronic neurological disorder, involving a range of seizure types. Epileptic seizures often occur sporadically, and, in most cases, little evidence of neurological impairment is apparent during the interictal period. Electroencephalography (EEG) recording of electrical activity of the brain is standard practice in patients with epilepsy. The EEG signature of epilepsy patients shows abnormalities both during and between seizures. Temporal lobe epilepsy (TLE) often develops a prolonged and intractable course [1–3]. The cognitive profile of TLE patients is typically characterized by memory impairments, along with other neuropsychological difficulties [4].

Tying EEG measurements to behavior, event-related potentials (ERPs) represent the average EEG signal time-locked to a particular set of trials. As such, they allow clinicians and neuroscientists to investigate the ways in which neurological disorders affect electrical activity in the brain during the performance of different cognitive tasks. Event-related potential abnormalities have been described in the context of epilepsy, in particular, in the vicinity of seizure foci [5–8].

The mismatch negativity (MMN) is a component of the ERP elicited by a discriminable (deviant) change in some regular (standard) aspect of the auditory environment. It reflects a pre-attentive cognitive function that performs automatic comparisons between consecutively presented stimuli [9]. The MMN, calculated as the deviant–standard difference, is considered a reliable index of auditory pre-attentive sensory memory. Although the MMN has been used extensively in studies of patients with neurological disorders affecting the temporal lobe [10–13], such as Landau–Kleffner syndrome [14] and benign childhood epilepsy with centro-temporal spikes with atypical features and learning difficulties [15], few studies have focused exclusively on patients with TLE [16–18]. Previous studies of the MMN in patients with TLE have focused on changes in the frequency of an auditory stimulus (pure tone) [16–18]. Lin et al. reported that TLE patients showed longer latencies in the magnetically measured MMN (MMNm) in response to tone changes [16]. Miyajima et al. found that there was a delayed latency to the MMN peak in TLE patients compared with healthy controls. In addition, they reported an increase in MMN amplitude at fronto-central sites in patients with TLE, but no significant changes at mastoid sites

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[17,18]. On the other hand, Mets-Luts et al. [15] reported that the MMN was absent or prolonged for speech but not for tones in patients with benign rolandic epilepsy compared with controls. These findings suggest that MMN abnormalities for phonetic changes may differ from those for the tonal changes in TLE. To address this issue, we used an adapted version of the phonetic oddball paradigm to investigate the MMN and evaluate pre-sensory memory function in patients with TLE. In addition, previous observations have led to the view that electrodes at mastoid sites mainly detect mismatch sources in the superior temporal lobe, perhaps including its lateral surface, while electrodes on the frontal scalp reflect function from frontal generators [20,21]. Mismatch potential abnormalities in TLE patients may be observed at mastoid sites.

There is now a wealth of evidence suggesting that the source of the MMN is largely in the superior temporal cortex [19–22]. Some studies have also pointed to the frontal lobe as another possible source [19,23,24]. Magnetoencephalography (MEG) and EEG studies have shown that the MMN generated by the frontal source has a greater peak latency than the response generated by the temporal source [25]. It has also been questioned as to what extent the MMN and the N1 component can be separated. In a previous study examining the temporal and frontal MMNs, the frontal and temporal source activations could not be spatially separated from one another [25]. Furthermore, some scientists argue that the deviant–standard difference wave might simply reflect the difference in the N1 response on standard and deviant trials [26].

To shed light on these issues, we used an adapted version of the phonetic oddball paradigm to investigate the MMN in a group of patients with TLE. If the MMN is generated by sources in both frontal and temporal regions, we predicted that the source closer to the seizure focus, in this case the temporal lobe, would have a greater impact on the MMN than the frontal source, which is presumably less affected by the disease. To that end, we compared the MMN at fronto-central and mastoid sites during the presentation of speech sounds in TLE patients and their healthy counterparts.

## 2. Methods

### 2.1. Participants

Twenty-six patients with TLE (10 females; age range: 20–50 years, with mean age 32.7 ± 9.8 [SD] years) and 26 age- and gender-matched healthy control participants (10 females; age range: 20–50 years, mean age 32.9 ± 9.0 years) were recruited. The data of 7 patients with TLE and 5 controls were discarded for further analysis because of excessive artifacts [27]. In total, data from 19 TLE patients (7 females; mean age 33.6 ± 10.1 [SD] years) and 22 healthy participants (8 females; mean age 33.6 ± 9.3 [SD] years) were included for further analysis.

Table 1 summarizes the clinical characteristics of the participants included for further analysis. All healthy control participants were right-handed (determined using the Edinburgh Handedness Inventory [28]; we used a laterality index of 0.8 or more as the cutoff for right-handedness). Three of the 19 TLE patients were ambidextrous, while the remaining 16 patients were right-handed. Seven patients had been seizure-free for more than 1 year, nine patients had a low frequency of seizures (at least one seizure but fewer than four per month in the year preceding the study), and three were classified as having a high seizure frequency (four or more seizures per month in the year preceding the study). All patients were treated with at least one antiepileptic drug (AED) for seizure control. The TLE diagnoses were based on a combination of clinical symptoms, EEG findings, and structural/functional imaging data, and were made by at least two certified epileptologists for each patient. Epilepsy patients were recruited from two medical facilities, which were certified as training facilities by the Japan Epilepsy Society. All patients suffered from partial seizures with features that were strongly suggestive of TLE. These seizures included simple partial seizures characterized by nausea, déjà-vu, a strange sensation, auditory or olfactory phenomena, or sensory aphasia, and complex partial seizures such as oral automatisms, or speech/motion arrest followed by automatisms [57]. The details of the imaging observations are listed in Table 1.

Exclusion criteria for TLE groups included comorbid psychiatric disease, substance abuse or dependence, reports of hearing or vision problems at the time of the experiment, and a history of psychiatric disease. Participants as controls with history of traumatic brain injury with any known cognitive consequences or loss of consciousness, history of convulsions other than simple febrile seizures, and psychiatric disease or epileptic disorder in first-degree relatives were excluded. Two experienced psychiatrists certified by the Ministry of Health, Labour and Welfare of Japan did the interviews of all participants.

The study was approved by the Ethics Committee at Tokyo Medical and Dental University. Written informed consent was obtained from each participant after an experimenter thoroughly described the study.

### 2.2. Stimulus presentation

Stimuli were made using a natural adult male voice [29], slightly modified to create uniform mean intensity, formant 0 (F0), and duration. While undergoing EEG, participants were randomly presented with auditory stimuli consisting of standard and deviant items. Stimuli were presented binaurally at a 90 dB sound pressure level via headphones that was the dynamic type, which covered frequencies between 20 and 20,000 Hz. Trials were presented in three blocks, with 200 standard and 50 deviant items in each block, i.e. 80% of trials were standard, and 20% were deviant. This procedure was designed to elicit the MMN in response to changes in a sequence of Japanese vowel speech sounds [30]. Stimuli consisted of vowel speech sounds presented for 100 ms each, with a rise/fall time of 10 ms and a stimulus onset asynchrony (SOA) of 500 ms. Each participant was seated comfortably in a sound-attenuated room. Participants were specifically instructed to watch silent cartoon films displayed on a TV monitor in front of them. They were allowed to take 2- to 3-minute breaks between blocks, resulting in a total completion time of 8 to 12 min for all three blocks.

### 2.3. ERP recording

Event-related potentials were recorded from electrodes applied to four midline sites (Fz, Cz, Pz, and Oz) and two bilateral mastoid sites, and referenced to the electrode at the nose. A ground electrode was attached to the forehead. Vertical and horizontal electro-oculographic (EOG) activity was recorded with an electrode placed above the left eye and another below the right eye. All electrode impedances were kept below 5 kΩ. A portable bio-amplifier recording device (Polymate AP, TEAC Corporation, Japan) was used. The signal was band-pass filtered at 0.05–300 Hz, sampled at 1 kHz, and stored on disk for off-line analysis.

### 2.4. Data analysis

Event-related potential data were band-pass filtered offline at 0.5–45 Hz. Data analysis focused on a 600 ms time window ranging from 100 ms before stimulus onset to 500 ms post-stimulus. The pre-stimulus baseline was normalized separately for each channel using the mean EEG amplitude over the 100 ms period. Averaging and artifact rejection were performed offline. All trials with amplitudes exceeding 100 μV in any of the EOG or EEG electrodes were excluded from the analysis. Average waveforms were obtained separately for deviant and standard stimuli, with a minimum of 95 deviant trials for each participant.

**Table 1**
Characteristics of participants.

| Patients | Age at time of study (years) | Gender | Education (years) | Handedness | Seizure frequency | Age at seizure onset (years) | Laterality of epileptic focus | Lesion | AEDs (mg/day) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 22 | F | 15 | Right | High | 17 | Right | Cavernous angioma in the right lateral temporal lobe[a] | ZNS200, CLB20 |
| 2 | 23 | M | 16 | Right | Low | 15 | Left | None | PB90, TPM75 |
| 3 | 34 | M | 16 | Right | Low | 28 | Right | Right hippocampal sclerosis [a] | CBZ1000, VPA1200, CLB10 |
| 4 | 20 | M | 16 | Right | Low | 15 | Not clear | – | CBZ300 |
| 5 | 50 | F | 12 | Ambidextrous | None | 43 | Not clear | None | CBZ500 |
| 6 | 47 | M | 14 | Right | None | 13.5 | Not clear | None | VPA1200, CBZ700, TPM100 |
| 7 | 27 | F | 16 | Right | None | 12 | Not clear | – | VPA1000 |
| 8 | 44 | M | 16 | Right | None | 41 | Bilateral | None | PHT175 |
| 9 | 37 | M | 14 | Ambidextrous | None | 14 | Not clear | None | CBZ150, CLB10 |
| 10 | 36 | M | 9 | Right | High | 21 | Left | DNT in the left temporal base[a] | CBZ800, CLB40, VPA200 |
| 11 | 20 | F | 12 | Right | Low | 0.8 | Left | Left hippocampal atrophy[a] | CZP2.0, CBZ300 |
| 12 | 40 | M | 16 | Ambidextrous | None | 30 | Left | None | CBZ500 |
| 13 | 48 | F | 12 | Right | None | 15.5 | Not clear | None | CBZ200 |
| 14 | 31 | M | 12 | Right | None | 7 | Not clear | None | CBZ500, VPA1200 |
| 15 | 32 | F | 16 | Right | None | 30 | Right | None | CLB10 |
| 16 | 46 | F | 12 | Right | Low | 23 | Right | None | ZNS200, PHT200, CBZ400, CLB10 |
| 17 | 20 | M | 12 | Right | High | 3 | Right | None | CBZ400, CZP1 |
| 18 | 30 | M | 16 | Right | Low | 28 | Left | Chronic hemorrhage in the left medial temporal lobe[a] | CBZ400, CLB20, |
| 19 | 31 | M | 14 | Right | Low | 14 | Left | DNT in the left medial temporal lobe[a] | ZNS200, CZP1.5 |
| Patients' summary | $33.6 \pm 10.1$[b] | Male, 12 and female, 7 | $14.1 \pm 2.1$[b] | Right, 16 and ambidextrous, 3 | None, 9; low, 7; high, 3 | $19.1 \pm 11.1$[b] | Right, 5; left, 6; others, 8 | | AEDs $1.8 \pm 0.8$[b] |
| Healthy subjects | $33.6 \pm 9.3$[b] | Male, 14 and female, 8 | $17.2 \pm 2.6$[b] | Right, 21 | N/A | N/A | N/A | | N/A |

None, no seizure – patients who were seizure-free for 1 year or more prior to the experiment.
Low, low seizure frequency, patients who experienced <4 seizures/month.
High, high seizure frequency – patients who experienced ≧4 seizures/month.
Right-handed, Edinburgh Handedness Inventory ≥ 0.8; ambidextrous, −0.8 < Edinburgh Handedness Inventory < 0.8.
DNT, dysembryoplastic neuroepithelial tumor; N/A, not available; M, male; F, female.
ZNS, zonisamide; CLB, clobazam; PB, phenobarbital; TPM, topiramate; CBZ, carbamazepine; VPA, valproate; PHT, phenytoin; CZP, clonazepam.
[a] Based on MRI and pathology after surgery.
[b] Average ± SD.

Mismatch difference waveforms were obtained by subtracting ERP waveforms elicited by the deviant stimuli from those elicited by the standard stimuli to evaluate peak latency. Because MMN is known to show inverted polarity at mastoid locations, we adopted the term 'mismatch positivity' (MMP) to describe the mismatch component at this location [31]. For this reason, we use the term MMP when describing mastoid findings and MMN for findings at midline electrodes.

Mean amplitudes between 150 and 180 ms were also calculated, because inspection of ERPs [14,32] revealed a clear separation between the waveforms for deviant and standard stimuli. This began nearly 80 ms after stimulus onset and reached a maximum at about 150–180 ms. The MMN/P peak latency was defined as the latency to the maximal negativity/positivity between 100 and 200 ms after stimulus onset [33,34]. The averaged waveforms for the electrode sites with negative polarity (MMN; Fz and Cz) and positive polarity (MMP; left and right mastoids) were evaluated separately.

### 2.5. Statistical analyses

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows, version 19 (SPSS, Chicago, IL). A $2 \times 2 \times 2$ repeated measures analysis of variance (ANOVA) was performed on ERP amplitudes with Group (TLE patients or controls) as the between-subjects factor and Stimulus type (standard or deviant) and Electrode site (Fz or Cz) as within-subjects factors. In addition, when there were significant results in the three-way ANOVA, separate $2 \times 2$ repeated measures ANOVAs of the mean amplitudes were performed with Group (TLE patients or controls) as the between-subjects factor and Electrode site as the within-subjects factor for standard trials and deviant trials. A $2 \times 2$ repeated measures ANOVA on the peak latency of MMN was also performed with Group (TLE patients or controls) as the between-subjects factor and Electrode site as the within-subjects factor.

Finally, in order to examine the effect of seizure frequency on ERP parameters, we divided the epilepsy patients into three groups: patients who had been seizure-free for >1 year ('none'), patients with low seizure frequency (<4 seizures/month; 'low'), and patients with high seizure frequency (≥4 seizures/month; 'high') [35]. Because of the small number of patients in each group, the Kruskal–Wallis test was used. Other correlations between clinical factors in TLE patients (age at time of study, handedness, seizure duration, the number of AEDs) and ERP parameters were examined using the Pearson's coefficient correlation method. We considered a P value of <0.05 to be statistically significant for the ANOVAs and Pearson's coefficient correlations.

## 3. Results

We examined group differences in ERP-averaged waveforms to standard and deviant stimuli (Fig. 1A, B). Although statistical analyses for mean amplitude were performed based upon standard and deviant waveforms, we also present grand-averaged MMN/P waveforms

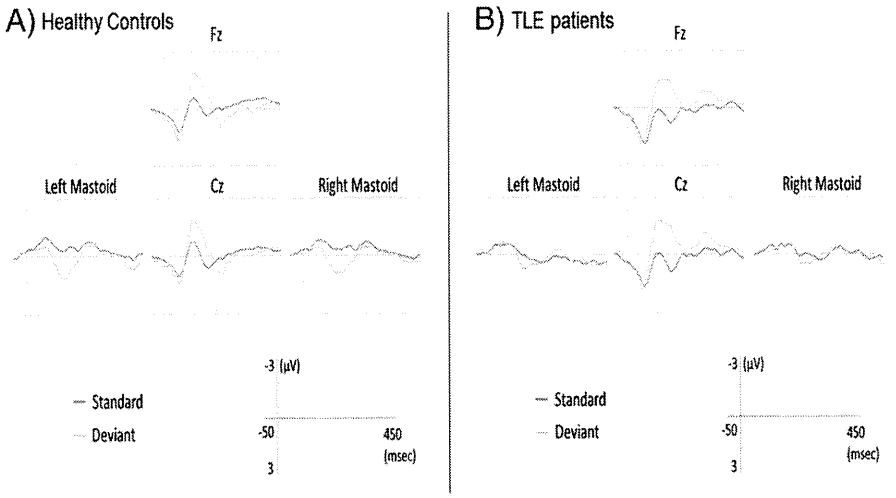


**Fig. 1.** Grand-averaged ERPs elicited by deviant stimuli (probability = 0.20) and standard stimuli in the auditory oddball paradigm in control group (1A, left) and the TLE group (1B, right). Black line: responses to standard stimuli; gray line: responses to deviant stimuli. Stimulus onset occurred at 0 ms, and positivity is indicated by a downward deflection. N100 responses to standard stimuli were smaller in the TLE group compared with the healthy controls at Fz and Cz. Responses around 100 and 200 ms at mastoids were less positive in the TLE group than in the healthy controls.

(difference waveforms) in Fig. 2 for ease of comparing mismatch signals across groups. MMN parameters at fronto-central sites are presented in Table 2. MMP parameters at mastoid sites are presented in Table 3. Both standard and deviant stimuli elicited pronounced N1 potentials at Fz and Cz in healthy control participants, around 120 ms after stimulus onset, and MMN peaks obtained by subtraction of standard from deviant responses were observed between 150 and 180 ms.

### 3.1. Mean amplitudes and peak latency

#### 3.1.1. Fronto-central site

A three-way repeated measures ANOVA examining mean amplitudes at 150–180 ms after stimulus onset revealed a significant main effect of Stimulus type ($F1,41 = 39.29$, $P<0.001$), such that amplitudes were greater for the deviant stimulus than for the standard stimulus. There were also a significant main effect of Electrode site ($F1,41 = 5.04$, $P<0.05$) and a significant Group by Electrode site interaction ($F1,41 = 4.69$, $P<0.05$). Fz dominance was diminished in the TLE group. There was no significant main effect of Group.

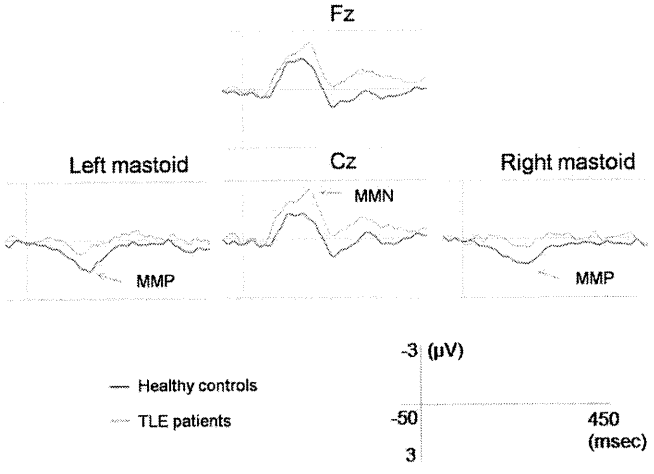


**Fig. 2.** Grand-averaged MMN/P (deviant minus standard difference waveforms) in controls and TLE patients. Solid line: control group; gray line: TLE group. The MMN at Fz and Cz was larger in the TLE group than in healthy controls, whereas the MMP at mastoids was smaller in the TLE group than in healthy controls.

There were no other significant main effects or interactions in the mean amplitude or peak latency in the two-way ANOVAs.

#### 3.1.2. Mastoid sites

A three-way repeated measures ANOVA examining mean amplitudes for standard and deviant stimuli revealed a significant main effect of Stimulus type ($F1,41 = 19.4$, $P<0.001$). Collapsed across groups and electrode sites, deviant amplitudes were greater than standard amplitudes. A significant interaction between Stimulus type and Group was also found ($F1,41 = 6.44$, $P<0.05$), indicating that the difference between deviant and standard amplitudes in patients with TLE was smaller than in controls. There were no other significant interactions.

To investigate the source of the significant interaction between Group and Stimulus type, we ran separate post-hoc t-tests for amplitudes for deviant and standard stimuli in each group. A two-way ANOVA for standard stimuli also revealed a significant main effect of Group ($F1,41 = 4.7$, $P<0.05$) with less negative amplitudes exhibited by TLE patients compared with healthy controls (Fig. 1 and Table 3). In addition, a two-way ANOVA for deviant stimuli did not reveal any significant main effects or interactions.

### 3.2. MMN/P and clinical factors

The results of the Kruskal–Wallis test indicated that patients with frequent seizures showed smaller deviant amplitudes at Fz ($P<0.05$) (Fig. 3). Other clinical factors (age at the time of study, seizure

**Table 2**
MMN mean amplitudes and peak latency in the TLE group and HC group at Fz and Cz.

| | | TLE group | | HC group | |
|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD |
| *Amplitude (μV)* | | | | | |
| Standard | Fz | 0.71 | 1.58 | 0.29 | 1.33 |
| | Cz | 0.77 | 1.48 | 0.53 | 1.16 |
| Deviant | Fz | −1.28 | 2.31 | −0.87 | 2.03 |
| | Cz | −1.33 | 2.19 | −0.47 | 1.77 |
| MMN | Fz | −2.19 | 1.86 | −1.23 | 1.6 |
| | Cz | −2.33 | 1.6 | −0.96 | 1.42 |
| *Latency (ms)* | | | | | |
| MMN | Fz | 150.1 | 26.7 | 144.1 | 28.5 |
| | Cz | 143.3 | 28 | 138 | 29.6 |

**Table 3**
MMP mean amplitudes and peak latency in the TLE group and HC group at mastoids.

| | | TLE group | | HC group | |
|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD |
| *Amplitude (μV)* | | | | | |
| Standard | Left mastoid | 0.23 | 0.83 | −0.43 | 0.89 |
| | Right mastoid | 0.05 | 0.64 | −0.38 | 0.88 |
| Deviant | Left mastoid | 0.5 | 1.56 | 0.82 | 1.08 |
| | Right mastoid | 0.4 | 1.69 | 0.69 | 0.97 |
| MMN | Left mastoid | 0.26 | 1.32 | 1.36 | 1.2 |
| | Right mastoid | 0.32 | 1.38 | 1.19 | 1.11 |
| *Latency (ms)* | | | | | |
| MMN | Left mastoid | 141.5 | 36.9 | 149.5 | 36.7 |
| | Right mastoid | 130.7 | 35.6 | 139.9 | 30.5 |

duration, number of antiepileptic drugs, or handedness) did not correlate significantly with MMN/P parameters.

## 4. Discussion

Several key findings were obtained in this study. First, the effect of TLE on the MMN at fronto-central sites was different from the effect at mastoid sites. There was a significant Group by Stimulus type interaction at mastoid sites in a three-way ANOVA, indicating that the difference between standard and deviant mean ERP amplitudes was smaller in TLE patients compared with controls. In contrast, the MMN at fronto-central sites did not show a significant interaction between Group and Stimulus type.

It has been argued that MMN has at least two main sources [23]: the first source is located in the bilateral auditory cortex [36] and underlies pre-perceptual sound change detection in the auditory cortex. This likely triggers the second source, the frontal-cortex MMN generator, which is associated with the initiation of the attention switch to sound change [25,36,37]. A growing body of studies investigating patients with neurological and psychiatric diseases has shown that the effects of disease on mismatch potentials are different in fronto-central compared with mastoid sites [17,20,31,38]. Taken together, the findings from non-invasive scalp recordings and previous reports of intracranial recordings not only confirm the hypothesis that the MMN is generated in the temporal lobe but also provide additional evidence of a frontal MMN component [24,39]. Our findings raise the possibility that the two generators are impaired to different extents in patients with TLE. Specifically, one of the components may cause the dysfunction of pre-attentive sensory memory, which has been observed in patients with TLE. In addition, these changes might be markers of neuroplasticity that accompany seizure control.

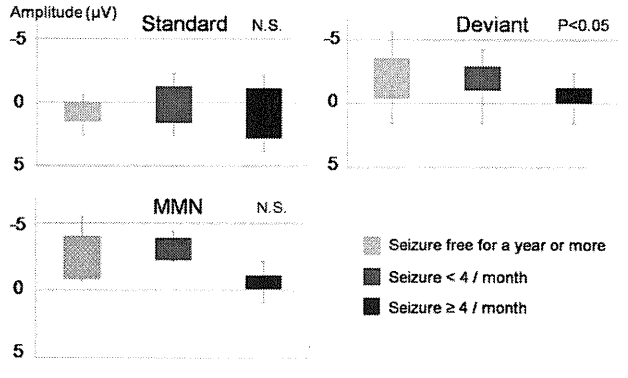


**Fig. 3.** Box plot of mean amplitude for each waveform for each group divided according to seizure frequency. Dark gray: Fz; light gray: Cz. Sz-free: patients who had been seizure-free for 1 year prior to this experiment; low: patients who had <4 seizures/month; high: patients who had ≥4 seizures/month.

They might also reflect impaired corticocortical connectivity or dysfunction of the neurons in the vicinity of the seizure focus in patients with TLE [40].

Miyajima et al. [16] reported the difference between deviant and standard ERP amplitudes measured during frequency changes in sinusoidal tones. While mastoid sites in the current paper showed significantly reduced amplitudes, Miyajima et al. did not see significant changes. In the current study, we used the oddball paradigm with Japanese vowel speech sounds as stimuli, whereas in the previous study, pure tones were used. Generators of the MMNm elicited by changes in more complex sounds, including phonetic stimuli, have been localized to the supra-temporal auditory cortex [22]. This differed from the region in which activity was elicited by an identical frequency change in a simple tone [41]. A recent study of spoken language processing has demonstrated that the acoustic change detection MMN may have its cortical generators in the superior temporal lobe [42]. Neuroimaging studies during speech perception have consistently shown activation not only in the primary auditory cortex but also in the posterior superior temporal region, the anterior superior temporal gyrus, and the middle temporal gyrus [43]. MMN at mastoid sites is thought to reflect the activity of the generator in the temporal lobe [19,36]. Based on these previous reports, the temporal lobe MMN generators appear to be more involved when MMN is elicited by vowel changes than when it is elicited by pure-tone frequency changes. Vowel stimuli contain more complex sound waves compared with pure tone stimuli. Given the complexity of speech sounds, it is likely that a broader area of the temporal lobe is activated by the vowel stimuli, facilitating the detection of differences in MMN at mastoid sites in patients with TLE [17], while there were no significant changes in fronto-central sites.

The detection of MMN differences in clinical populations appears to depend on which feature of a sound is changed. Schulte-Korne et al. [44,45] investigated patients with dyslexia for tone and speech stimuli and found no group differences (dyslexia group vs. controls) for tone stimuli in spite of a significant group difference for speech stimuli. Similarly, the MMN in response to change in a phoneme was not seen in aphasic patients with temporal-parietal lesions, while a prominent MMN was elicited in the same patients by a frequency change in a simple tone [46]. Honbolygo et al. [14] reported a case of a patient with Landau–Kleffner syndrome in which the MMN was elicited by a phonetic change cue but not by a stress change cue. In patients with BRE, Boatman et al. found that the MMN was absent or prolonged for speech but not for tones [45]. The MMN for phonetic change as well as the MMN for frequency change that is more common would be useful to evaluate patients who are suspected with abnormal function in temporal lobe at both fronto-central and mastoid sites.

The MMN findings in epilepsy patients remain controversial. In the current study, the MMN at fronto-central site in TLE did not reach any significance in TLE. Some prior reports have shown that MMN amplitudes tend to be larger in patients with epilepsy than in healthy controls [12,17]. The enhanced MMN was interpreted by authors [17] as reflecting frontal lobe hyperexcitability to compensate for temporal lobe dysfunction indexed, according to the authors, by prolonged MMN peak latencies in patients relative to controls at both fronto-central and mastoid sites, consistent with previous reports [16,47]. In contrast, several studies revealed diminished MMN. Krostenskaja et al. [11] found attenuated MMNs in pediatric intractable epilepsy patients. In another study of patients with epilepsy, Borghettiet et al. [10] reported changes in only two of 12 patients, and those patients showed diminished MMN before vagus nerve stimulation (VNS) and a return to normal after VNS. Patients with benign rolandic epilepsy (BRE) with impaired speech recognition abilities have showed smaller MMN [48]. Taken together, these studies demonstrate the complexity of the changes that have been observed in the MMN in patients with epilepsy.

We suspect that seizure frequency might be one of possible reasons why MMN can be both diminished and enhanced in the setting of epilepsy. For example, postictal ERPs in an oddball paradigm have been shown to be significantly reduced compared with pre-ictal ERPs recorded from electrodes placed ipsilateral to the epileptogenic focus [49,50]. In these previous studies [10,11,14], attenuated MMN was observed in patients with intractable epilepsy. In contrast, the current study that did not show significant change at fronto-central sites included patients with a wide range of seizure frequencies, from those with daily seizures to patients who had been seizure-free for more than a decade. Our finding that patients with more frequent seizures showed smaller deviant stimulus amplitudes is in line with previous results.

One limitation of our study is the inclusion of patients with both medial and lateral temporal lobe epilepsy. More than half of our patients showed no abnormal MRI findings, making it difficult to separate the TLE patients into medial and lateral temporal lobe subcategories. Interictal EEG discharges seen in the patients with medial TLE, however, demonstrated that epileptic discharges propagated to the lateral temporal lobe [51] where the main generator of MMN is thought to be located. Follow-up studies separating patients with medial and temporal lobe seizure foci are needed to clarify this issue.

As is well known, MMN/P is based on the difference waveform between responses to standard and deviant stimuli. Our results indicate that at mastoid sites, the standard stimuli elicited less negative amplitudes in TLE patients compared with healthy controls, while deviant stimuli elicited similar responses in both groups. No such differences were detected at fronto-central sites. These results are consistent with findings in a previous study of MMN in TLE patients [17]. Our results demonstrate that standard stimuli in TLE patients may elicit deviant-like responses even to repetitive stimuli.

The effects of epilepsy on the N1 ERP component are also varied [11,40,52]. Boutros et al. [52] investigated the N1 using repetitive stimuli in patients with focal epilepsy and healthy controls and found no significant differences between patients and controls. Korostenskaja et al. [11], however, observed diminished N1 in pediatric patients with intractable epilepsy, whereas Usui et al. [40] revealed markedly increased magnetically measured N1 (N1m) potentials in patients with autosomal dominant lateral temporal lobe epilepsy. These previous reports typically compared waveforms at fronto-central sites between two groups, ignoring waveforms at mastoid sites on EEG [52] or MEG [11,40]. Our results suggest that waveforms at mastoid sites on EEG should not be ignored because they can provide further insights into the electrophysiological changes that accompany TLE.

Both ERPs and performance on psychophysical tasks have been used to study auditory function in patients with epilepsy. Despite fairly uniform auditory ERP methodology across research groups (oddball paradigm, pure tone stimuli, target stimuli of 20–25% of the total), results have been inconsistent [53]. Studies of TLE patients typically report trends toward lower P3 amplitudes relative to controls [49]. These results are important to consider because the middle and late components of the ERP, such as P3a, may also affect the baseline of MMN/P. Because we chose a short SOA (500 ms) in this study, standard trials preceded by a deviant trial may have had different pre-stimulus baseline potentials than those preceded by another standard trial. To avoid potential confounding effects of changes in P3a, future studies should exclude standard trials preceded by deviant trials.

We also found that seizure frequency affected deviant amplitudes at Fz with greater attenuation in patients with frequent seizures. These results should be interpreted with caution, however, because our measure of seizure frequency was based on self-report, and some patients might not have reported seizures that were too numerous to count or those that were undetected by the patients themselves, causing an underestimation of seizure frequency. In addition, the small number of patients with high seizure frequency in this study limits our ability to draw conclusions about the effect of seizure frequency on MMN. Another limitation was the small number of patients with clearly lateralized epileptic foci, with only five patients with a focus in the right hemisphere and six patients with a left focus, including one ambidextrous person.

MMN amplitudes have been reported to be affected by aging [54]. In our study, we did not find any significant correlation between MMN/P amplitudes and age. Generally, effects of aging on amplitudes are observed only in participants who are over the age of 60, while middle-aged and young adults do not differ [55]. In addition, oddball paradigms with long ISIs are more likely to reveal age-related differences than those with short ISI, such as ours [56]. Therefore, with respect to age, our results are consistent with previous findings.

## 5. Conclusion

The present results provided evidence for the view that the MMN is generated by separable sources in the frontal and temporal lobes and that these sources are differentially affected by TLE. Thus, in the evaluation of pre-attentive cognitive function in TLE patients, MMP should be recorded at mastoid sites in addition to the conventional fronto-central sites. In addition, MMN for phonetic change as well as MMN for frequency change could be a useful tool to evaluate temporal function.

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ORIGINAL COMMUNICATION

# Clinical significance of periodic leg movements during sleep in rapid eye movement sleep behavior disorder

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**Abstract** The aim of the study was to explore the clinical significance of periodic leg movements during sleep (PLMS) in rapid eye movement sleep behavior disorder (RBD) and the pathological relation between these two disorders. Eighty-one consecutive idiopathic RBD (iRBD) patients, classified into two groups—27 patients with PLMS (iRBD–PLMS) and 54 patients without PLMS (iRBD w/o PLMS), and 31 patients with idiopathic PLMS (iPLMS)—were enrolled in this study. Descriptive variables including Epworth Sleepiness Scale (ESS) scores and polysomnography measures were compared among the three patient groups. Correlation analysis between the ratio of PLMS-related arousal index to PLMS index (PLMAI/PLMI) and sleep stage-related variables or clinically descriptive RBD variables was performed in the iRBD–PLMS group. Associated factors indicating the existence of PLMS during both stages NREM and REM were investigated in this group with clinically descriptive RBD variables. The iRBD–PLMS group showed a significantly lower ESS score and PLMAI/PLMI than the iPLMS group. The PLMAI/PLMI value negatively correlated with RWA/REM. RWA/REM was extracted as a factor that was significantly associated with the existence of PLMS during both stages NREM and REM. The RBD morbidity duration appeared as an associated factor for PLMS only during stage REM among the iRBD patients. In iRBD patients, daytime sleepiness remains modest probably because of suppressed cortical reactivity to PLMS. Increased PLMS activity during both stages NREM and REM is related to the mechanism of REM atonia loss caused by brainstem dysfunction. Especially, PLMS during stage REM might reflect the length of RBD morbidity.

**Keywords** REM sleep behavior disorder · REM sleep without atonia · Parasomnia · Periodic leg movements · Epworth Sleepiness Scale · α-Synucleinopathy

## Introduction

Rapid eye movement sleep behavior disorder (RBD) occurs idiopathically (iRBD) or secondarily to neurodegenerative diseases [23, 28] and frequently represents a prodromal phase of α-synucleinopathies [16, 26]. This important issue has recently encouraged many researchers to investigate predictive factors associated with development of α-synucleinopathies among iRBD patients [15, 25].

Periodic leg movements during sleep (PLMS) are extremely common among patients with restless legs syndrome (RLS) [22], and has been regarded to relate with dopaminergic dysfunction [21]. Furthermore, PLMS is frequently observed in patients with RBD [12, 23], suggesting that PLMS and RBD partly share a common pathogenesis: impairment of central dopaminergic transmission [12]. Some previous reports have suggested the

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possibility of dysfunction of the nigrostriatal dopaminergic system as an important cause of RBD [5, 11, 29]. However, the results of neuropathological studies of the relation between the presence of RBD and dopaminergic dysfunction remain controversial [7, 8, 18].

The characteristics of PLMS in RBD patients have been compared to those in RLS patients [12, 20]. Nevertheless, to our knowledge, the clinical significance and underlying mechanism of the presence of PLMS in iRBD have not been conclusive. To clarify these issues, we investigated the influence of PLMS on subjective daytime sleepiness and the relation between clinical RBD variables and PLMS in patients with iRBD.

## Methods

The Ethical Committee of the Neuropsychiatric Research Institute approved this retrospective study; informed consent was obtained from all participants. From consecutive patients who visited the outpatient clinic of the Japan Somnology Center during May 2003–August 2008, we enrolled 81 patients with iRBD and 31 patients with PLMS not showing symptoms suggesting RBD for this study (PLMS group). Diagnoses were made by at least two sleep-disorder expert physicians based on results of both nocturnal polysomnography (n-PSG) findings and clinical interviews according to the International Classification of Sleep Disorders, 2nd edition (ICSD-2) [4]. PLMS was found incidentally in the patients of the PLMS group, who had the following subjective complaints at their first visit: excessive daytime sleepiness ($n = 11$), habitual snoring ($n = 13$), and difficulty in initiating maintenance of sleep ($n = 7$). The enrolled patients took no medication both at the first visit and at the time of n-PSG, and had no symptom indicating the possible existence of RLS or any dementia. None had any abnormal neurological finding. For the apnea–hypopnea index on n-PSG, none showed 15 or more per hour. Patients with iRBD were classified into two groups: patients with PLMS index $\geq$15 events/hour [4] (iRBD–PLMS) and those without (iRBD w/o PLMS).

For iRBD groups with and without PLMS, and the PLMS group, we compared diagnostic n-PSG variables and the Epworth Sleepiness Scale (ESS) [17] scores at the first visit to the clinic. Among the n-PSG variables, we specifically calculated the common PLMS-related variables including PLMS index, mean duration of PLMS, and the inter-PLMS interval for stage NREM and for stage REM including stage REM without atonia (RWA) [20]. These variables were compared between the iRBD–PLMS group and the PLMS group.

For iRBD patients, clinically descriptive RBD variables were evaluated, including the duration of RBD morbidity reported by patients themselves or their bed partners, proportion of stage RWA—an important physiological background of RBD [10]—to total stage REM (RWA/REM), and severity of RBD symptoms. As in a prior study [30], the iRBD severity was classified mainly based on the frequency of dream enactment behavior according to the revised ICSD [3].

Especially in the iRBD–PLMS group, correlation between the ratio of the number of PLMS-related arousal to the total number of PLMS and the n-PSG variables was investigated in addition to the clinically descriptive RBD variables. Moreover, for all enrolled iRBD patients, we investigated the associated factors for the existence of PLMS during both stage NREM and REM among the demographic variables and the clinically descriptive RBD variables indicated above.

### Nocturnal polysomnography

Using a standard system (Alice 5; Respironics Inc., Murrysville, PA, USA) with video monitoring of patient behavior, diagnostic n-PSG recordings and measurements including four channels of the scalp EEG (C3/A2, C4/A1, O1/A2, O2/A1), two electrooculograms (EOG), submental electromyogram (EMG), electrocardiogram, nasal/oral airflow, oximetry sensor for $SpO_2$ recording, a microphone for snoring sounds, chest/abdominal respiratory effort, and anterior tibialis electromyogram for leg movements (bipolar derivations with two electrodes placed 3 cm apart on the belly of the anterior tibialis muscle of right and left legs) were taken.

### Scoring of PSG measures

Sleep stages were scored according to the criteria set by Rechtschaffen and Kales [27]. Since RBD patients lack muscle atonia, REM sleep was scored without submental EMG atonia. The onset and the termination of REM sleep were determined according to the method of Lapierre et al. [19]. EEG arousal was evaluated according to the criteria set by the American Sleep Disorders Association [6]. Respiratory events were assessed according to the diagnostic criteria of the American Academy of Sleep Medicine Task Force [1]. As described in earlier reports [10, 19], RWA was scored based on the following criteria: (1) tonic REM sleep—submentalis muscle EMG activity was present for more than 50% of a 30-s epoch; (2) phasic REM sleep—3-s epoch showing bursts of EMG activity of the submentalis muscle and anterior tibialis muscle, with an amplitude that is at least four times greater than that of background EMG, and 0.1–5.0 s in duration. Then PLMS was scored according to criteria set by the American Academy of Sleep Medicine [2]. PLMS were carefully

distinguished from phasic EMG activity on anterior tibialis muscle during stage REM in the anterior tibialis based upon their regular periodicity [14].

### Statistical analyses

The chi-square test followed by residual analysis was used to compare the differences in gender distribution among the groups of iRBD w/o PLMS, iRBD-PLMS, and PLMS. Comparisons of age and ESS scores among the three groups were conducted using a Kruskal–Wallis test followed by Mann–Whitney's $U$ test with Bonferroni correction as post hoc analysis. The estimated duration of RBD morbidity, RWA/REM, and the PLMS-related variables during stage REM were compared between the iRBD groups with and without PLMS using Mann–Whitney's U test. Regarding PLMS-related variables during stage NREM and the other polysomnographic variables, comparisons were made among the iRBD–PLMS group, the iRBD w/o PLMS group, and the PLMS group using a Kruskal–Wallis test followed by a Mann–Whitney's U test with Bonferroni correction as post hoc analysis. Moreover, in the group with iRBD–PLMS and that with PLMS, the PLMS-related variables during stage NREM and stage REM were compared using Wilcoxon's signed rank test.

In the iRBD–PLMS patients, correlation was calculated between the ratio of the number of PLMS-related arousal to the total number of PLMS and the n-PSG measures including PLMS-related variables or clinically descriptive RBD variables using Spearman's rank correlation coefficient. The associated factors for the existence of PLMS during both stage NREM and stage REM were also investigated using univariate and multivariate logistic regression analyses with the clinically descriptive RBD variables and demographic variables described above as independent variables among all subject iRBD patients.

## Results

### Demographic characteristics, ESS scores, and clinically descriptive variables of subject patient groups

As shown in Table 1, a significant difference was found among the ESS scores of the three patient groups ($H = 9.969$, $df = 2$, $p < 0.01$). Post hoc tests revealed that the scores in the group with iRBD w/o PLMS ($p < 0.01$) and those in the group with iRBD–PLMS were significantly lower than those in PLMS ($p < 0.05$), but no significant difference was found between the former two groups. Among the clinically descriptive RBD variables, neither the severity of iRBD nor the estimated duration of RBD morbidity showed significant differences between the two iRBD groups.

### Comparison of polysomnographic variables among the groups of iRBD-PLMS, iRBD w/o PLMS, and PLMS

As shown in Table 2, the RWA/REM in the iRBD–PLMS group was significantly higher than that in the iRBD w/o PLMS group ($U = 399.0$, $p < 0.01$). The proportions of stage-atonic REM were significantly different among the three patient groups ($H = 12.115$, $df = 2$, $p < 0.01$). Post hoc tests revealed that the iRBD–PLMS group showed a significantly lower proportion of stage-atonic REM than either the iRBD w/o PLMS group or the PLMS group did ($p < 0.01$ respectively). The proportions of total stage

**Table 1** Demographic characteristics, scores of ESS, and clinical descriptive RBD variables of subjects

| | Total with iRBD | iRBD w/o PLMS | iRBD–PLMS | PLMS |
|---|---|---|---|---|
| No. of subjects | 81 | 54 (68.6) | 27 (31.4) | 31 |
| Sex (M:F) | 52:29 | 37:17 | 15:12 | 19:12 |
| Age, years | 66.5 ± 7.0 | 65.9 ± 6.9 | 67.7 ± 7.1 | 63.5 ± 5.9 |
| Score of ESS | 6.0 ± 4.3 | 6.0 ± 4.2** | 6.5 ± 4.7* | 9.3 ± 5.3 |
| Severity of iRBD[a] | 2.6 ± 0.7 | 2.6 ± 0.7 | 2.5 ± 0.6 | 0 |
| Estimated duration of iRBD, years | 4.5 ± 3.3 | 4.0 ± 2.6 | 5.5 ± 6.2 | 0 |

Parenthesis indicates percentage of patients with or without PLMS in total iRBD patients

*PLMS* periodic leg movements during sleep, *iRBD* idiopathic rapid eye movement sleep behavior disorder, *iRBD w/o PLMS* iRBD without PLMS, *iRBD–PLMS* iRBD with PLMS

* $p < 0.05$, ** $p < 0.01$, compared to the PLMS group

[a] Severity of iRBD was scored according to the revised edition of *ICSD*; (1) mild, less than once per month with only mild discomfort; (2) moderate, more than once per month but less than once per week associated with physical discomfort; (3) severe, more than once per week associated with physical injury

**Table 2** Comparison of polysomnograhic variables among iRBD with and without PLMS, and PLMS

| | iRBD w/o PLMS ($n = 54$) | iRBD–PLMS ($n = 27$) | PLMS ($n = 31$) |
|---|---|---|---|
| PSG measures | | | |
| Sleep efficiency, % | 85.2 ± 9.6 | 83.7 ± 9.2 | 82.5 ± 10.9 |
| Stage 1, %SPT | 10.0 ± 8.4 | 8.1 ± 4.1 | 7.2 ± 4.1 |
| Stage 2, %SPT | 54.3 ± 9.1 | 52.2 ± 9.0 | 54.9 ± 10.1 |
| Stage 3 + 4, %SPT | 4.5 ± 6.0 | 4.2 ± 4.8 | 5.6 ± 5.0 |
| Stage atonic REM, %SPT | 16.3 ± 6.0 | 12.0 ± 6.2**,a,**,b | 14.7 ± 6.8 |
| Stage RWA, %SPT | 5.5 ± 4.4 | 7.2 ± 4.8 | 0.0 |
| Stage RWA, %REM | 19.7 ± 19.7 | 36.5 ± 19.4**,a | 0.0 |
| PLMS index, events/h[e] | 3.0 ± 4.3 | 54.2 ± 27.4**,a | 47.7 ± 23.9**,a |
| Ratio of PLMS related arousal to PLMS%[d,e] | 7.1 ± 7.0*,b | 8.2 ± 4.4*,b | 16.6 ± 16.5 |
| Index, duration and interval of PLMS during stage NREM[e] | | | |
| PLMS index, events/h | 2.4 ± 3.4 | 53.9 ± 30.1*,a | 53.8 ± 23.9*,a |
| Mean duration of PLMS, s | 1.9 ± 0.4 | 1.8 ± 0.6 | 1.9 ± 0.6 |
| Inter-PLMS interval, s | 29.4 ± 3.1 | 29.0 ± 4.7 | 31.5 ± 5.7 |
| Index, duration and interval of PLMS during stage REM[f] | | | |
| PLMS index, events/h | – | 47.0 ± 33.8**,b | 10.3 ± 32.6*,c |
| Mean duration of PLMS, s | – | 2.6 ± 0.9**,b,*,c | 1.5 ± 0.9[c] |
| Inter-PLMS interval, s | – | 28.2 ± 4.8**,b | 37.9 ± 7.8*,c |

*PSG* polysomnography, *SPT* sleep period time, *REM* rapid eye movement, *RWA* REM sleep without atonia; *PLMS* periodic leg movements during sleep, *NREM* non REM, *iRBD–PLMS* idiopathic rapid eye movement sleep behavior disorder with PLMS

* $p < 0.05$, ** $p < 0.01$

[a] Compared to iRBD w/o PLMS group

[b] Compared to PLMS group

[c] Compared to stage NREM. Values are expressed as mean ± SD

[d] PLMS related arousal index/PLMS index

[e] $n = 25$ in the iRBD w/o PLMS group

[f] $n = 18$ in the PLMS group

REM were also significantly different among the three patient groups ($H = 18.803$, $df = 2$, $p < 0.01$). Post hoc tests revealed that the compared to the PLMS group, the iRBD–PLMS group and the iRBD without PLMS group showed a significantly higher proportion of total stage REM ($p < 0.05$ and $p < 0.01$, respectively).

As for PLMS-related variables, significant differences were found in the PLMS index ($H = 84.938$, $df = 2$, $p < 0.01$) and the ratio of PLMS-related arousal to PLMS ($H = 9.545$, $df = 2$, $p < 0.01$) among the three patient groups during the total sleep period. No significant difference in the PLMS index was observed between the iRBD–PLMS group and the PLMS group. With respect to the ratio of PLMS-related arousal to PLMS, the iRBD–PLMS group and the iRBD w/o PLMS group showed a significantly lower value than the PLMS group did ($p < 0.05$, respectively). No significant difference in the ratio was observed between the iRBD–PLMS group and the iRBD w/o PLMS group.

During stage NREM, there were significant differences in the PLMS index ($H = 84.552$, $df = 2$, $p < 0.01$) among the three patient groups. Post hoc tests revealed that the iRBD–PLMS group and the PLMS group each showed a significantly higher PLMS index than the iRBD w/o PLMS group did ($p < 0.01$). However, no significant difference in the index was observed between the iRBD–PLMS group and the PLMS group. Moreover, no significant difference in either the duration or the interval of PLMS was observed among the three patient groups.

During stage REM, the iRBD–PLMS group showed a significantly higher PLMS index than the PLMS group did ($U = 67.0$, $p < 0.01$). Furthermore, the PLMS duration was significantly longer ($U = 58.5$, $p < 0.01$) and the interval of PLMS was significantly shorter in the iRBD–PLMS group ($U = 58.5$, $p < 0.01$) than in the PLMS group ($U = 57.5$, $p < 0.01$).

In the PLMS group, the PLMS index was significantly higher ($Z = -3.978$, $p < 0.05$), the duration of PLMS was significantly longer ($Z = -2.592$, $p < 0.05$), and the inter-PLMS interval was significantly shorter ($Z = -1.940$, $p < 0.05$) during stage NREM than during stage REM. However, in the iRBD–PLMS group, only the PLMS

duration was significantly longer during stage REM than during stage NREM ($Z = -3.697$, $p < 0.01$).

Factors correlated with the ratio of the number of PLMS-related arousals to the total number of PLMS in each sleep stage

To clarify the mechanism of low ratio of PLMS-related arousal to the total number of PLMS, we conducted correlation analyses between the ratio and either the n-PSG variables or clinically descriptive RBD variables. In the iRBD–PLMS group, among the studied variables, only RWA/REM showed significant and negative correlation with the ratio ($r_s = -0.375$, $p < 0.05$) (Fig. 1).

Factors associated with the existence of PLMS during stage NREM in iRBD patients

Among all iRBD patients, 27 patients (31.4%) who showed a PLMS index of more than 15 events/h during stage NREM were designated as the group with the existence of PLMS during stage NREM (mean PLMS index during NREM [SD]; 53.9 [30.0] in iRBD-PLMS, 2.4 [3.4] in iRBD w/o PLMS).

Univariate logistic regression analyses were performed to ascertain the associated factor for the existence of PLMS during stage NREM with the following five independent variables: gender, age, severity of iRBD, estimated duration of RBD morbidity, and RWA/REM. Among these variables, RWA/REM was significantly associated with the existence of PLMS during stage NREM in the univariate model (10% increase in RWA/REM: OR = 1.42, 95%CI 1.12–1.81). Multivariate logistic regression analysis also revealed that the existence of PLMS during this sleep stage was significantly associated only with a 10% increase in RWA/REM (OR = 1.45, 95%CI 1.12–1.89) (Table 3).

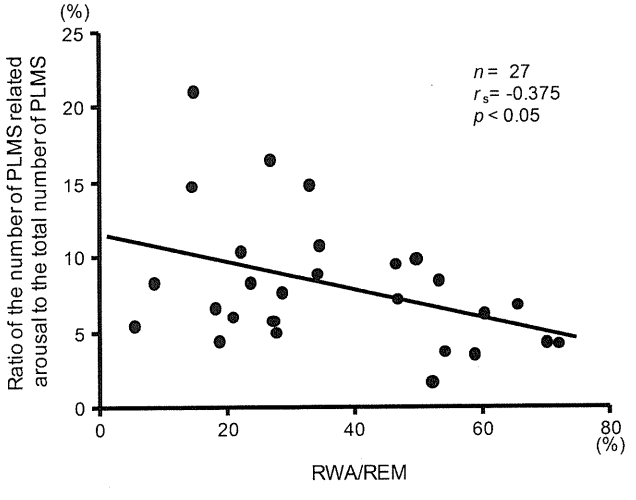


**Fig. 1** Correlation between RWA/REM and ratio of PLMS-related arousal index to PLMS index in patients with iRBD-PLMS. *PLMS* periodic leg movement during sleep, *REM* rapid eye movement, *iRBD–PLMS* idiopathic rapid eye movement sleep behavior disorder with PLMS, *RWA/REM* proportion of stage REM without atonia to total stage REM (atonic REM and RWA)

Factors associated with the existence of PLMS during stage REM in iRBD patients

Twenty-five patients (30.9%) who showed a PLMS index of more than 15 events/h during stage REM were designated as the group with the existence of PLMS during stage REM (mean PLMS index during REM [SD]; 47.0 [33.8] in iRBD-PLMS, 0.1 [0.6] in iRBD w/o PLMS).

Univariate logistic regression analyses were performed to ascertain the factors associated with the existence of PLMS during stage REM with the five independent variables indicated above. Among these variables, two items (estimated duration of RBD morbidity and RWA/REM) were significantly associated with the existence of PLMS during stage REM in the univariate model (estimated duration of RBD morbidity: OR = 1.18, 95%CI 1.01–1.38, 10% increase in RWA/REM: OR = 1.44, 95%CI 1.13–1.83). Multivariate logistic regression analysis also revealed that the existence of PLMS during stage REM was significantly associated with the estimated duration of RBD morbidity (OR = 1.19, 95%CI 1.00–1.41) and a 10% increase in RWA/REM (OR = 1.45, 95%CI 1.11–1.88) (Table 4).

## Discussion

This is the first study to elucidate both the influence of PLMS on the level of subjective daytime sleepiness manifested on ESS in patients with iRBD and the relation between PLMS measures and clinical iRBD variables. Reportedly, the existence of PLMS contributes to the occurrence of excessive daytime sleepiness [24]. However, the ESS score in the iRBD–PLMS group was remarkably lower than the value in the PLMS group despite a similar value of PLMS index between these two groups. The value in the iRBD–PLMS group was similar to that in the iRBD w/o PLMS group. Moreover, the iRBD–PLMS group showed a significantly lower ratio of PLMS-related arousal index to the total PLMS index than the PLMS group did, which is quite compatible with the report by Fantini et al., in which RBD patients had smaller EEG activation associated with PLMS than in RLS patients [12].

In the present study, the two iRBD groups showed a higher proportion of stage REM than the PLMS group, and the iRBD–PLMS group showed a higher proportion of RWA to total stage REM than the PLMS group. The reason

**Table 3** Factors associated with the existence of PLMS during stage NREM in iRBD patients

| Predictor | Total | PLMS index during stage NREM ≥ 15 events/h | | Univariate model | *p* | Multivariate model | *p* |
|---|---|---|---|---|---|---|---|
| | *n* | *n* | % | Odds ratio (95%CI) | | Adjusted odds ratio (95%CI) | |
| Gender | | | | | | | |
| Female | 29 | 12 | 41.3 | 1.00 (ref) | | | |
| Male | 52 | 15 | 28.8 | 0.57 (0.22–1.49) | 0.25 | | |
| Age, years | 81 | | | 1.74 (0.67–1.51) | 0.25 | | |
| Severity of RBD[a] | | | | | | | |
| Mild | 7 | 2 | 28.6 | 1.00 (ref) | | | |
| Moderate | 21 | 9 | 42.9 | 1.88 (0.29–11.97) | 0.51 | | |
| Severe | 53 | 16 | 30.2 | 1.08 (0.19–6.17) | 0.93 | | |
| Duration of RBD, years | 81 | | | 1.15 (0.99–1.33) | 0.07 | | |
| RWA/REM, 10%[b] | 81 | | | 1.42 (1.12–1.81) | <0.01 | 1.45 (1.12–1.89) | <0.01 |

*CI* confidence interval, *iRBD* idiopathic rapid eye movement sleep behavior disorder, *PLMS* periodic leg movements during sleep, *RWA* rapid eye movement sleep without atonia, *NREM* non rapid eye movement, *RWA/REM* proportion of stage RWA to total stage REM (atonic REM and RWA)

[a] Severity of RBD was classified according to the revised edition of *ICSD*; (1) mild, less than once per month with only mild discomfort; (2) moderate, more than once per month but less than once per week associated with physical discomfort; (3) severe, more than once per week associated with physical injury

[b] Odds ratio was expressed as the ratio for 10% increase in RWA/REM

**Table 4** Factors associated with the existence of PLMS during stage REM in iRBD patients

| Predictor | Total | PLMS index during stage NREM ≥ 15 events/h | | Univariate model | *p* | Multivariate model | *p* |
|---|---|---|---|---|---|---|---|
| | *n* | *n* | % | Odds ratio (95%CI) | | Adjusted odds ratio (95%CI) | |
| Gender | | | | | | | |
| Female | 29 | 11 | 37.9 | 1.00 (ref) | | | |
| Male | 52 | 14 | 26.9 | 0.60 (0.23–1.59) | 0.31 | | |
| Age, years | 81 | | | 1.04 (0.97–1.12) | 0.25 | | |
| Severity of RBD[a] | | | | | | | |
| Mild | 7 | 1 | 14.3 | 1.00 (ref) | | | |
| Moderate | 21 | 9 | 42.9 | 4.50 (0.46–14.29) | 0.20 | | |
| Severe | 53 | 15 | 28.3 | 2.37 (0.26–21.37) | 0.44 | | |
| Duration of RBD, years | 81 | | | 1.18 (1.01–1.38) | <0.05 | 1.19 (1.00–1.41) | <0.05 |
| RWA/REM, 10%[b] | 81 | | | 1.44 (1.13–1.83) | <0.01 | 1.45 (1.11–1.88) | <0.01 |

*CI* confidence interval, *iRBD* idiopathic rapid eye movement sleep behavior disorder, *PLMS* periodic leg movements during sleep, *REM* rapid eye movement, *RWA* REM sleep without atonia, *RWA/REM* proportion of stage RWA to total stage REM (atonic REM and RWA)

[a] Severity of RBD was classified according to the revised edition of *ICSD*; (1) mild, less than once per month with only mild discomfort; (2) moderate, more than once per month but less than once per week associated with physical discomfort; (3) severe, more than once per week associated with physical injury

[b] Odds ratio was expressed as the ratio for 10% increase in RWA/REM

for the higher proportion of stage REM in iRBD patients was unclear; however, this finding was consistent with that of a previous study in which a trend toward an increased REM sleep percentage was found among RBD patients [13]. It is particularly interesting that the increased amount of RWA was proven to be associated with the lower arousal response to PLMS in the iRBD–PLMS group, although the negative correlation between these two variables was considered to be weak. Considering those facts, it is possible that the impairment of cortical reactivity to

PLMS becomes more pronounced along with the progression of RWA in patients with iRBD, probably engendering the absence of daytime sleepiness in this patient group.

Comparison of PLMS-related variables in stage NREM and stage REM revealed that the PLMS group had higher activity of PLMS manifested as the significantly higher PLMS index, shorter inter-PLMS interval, and longer mean duration of PLMS in stage NREM than in stage REM, which is consistent with results of previous studies of RLS patients [12, 20]. The characteristics of PLMS in the iRBD–PLMS group differed from those in the PLMS group in that the PLMS index and the inter-PLMS interval did not differ between stages REM and NREM; the mean duration of PLMS during stage REM was longer than that during stage NREM in this group. As Fantini et al. [12] reported, increased activity of PLMS during stage REM could arise from the disinhibition of motor control during this sleep stage associated with the disorder. The disinhibition explains the high PLMS index during stage REM in the iRBD group. However, considering the longer duration and the shorter interval of PLMS during stage REM, the PLMS rhythm formation process occurring during this sleep stage in the iRBD patient group might be associated not only with the disinhibition of motor control, but also with other RBD-associated mechanisms.

The most noteworthy finding in this study was that a 10% increase in the proportion of stage RWA to stage REM was revealed to be associated with the existence of PLMS during both stage REM and stage NREM among the subject iRBD patients. In addition, the estimated duration of iRBD morbidity was associated with the existence of PLMS only during stage REM. In summary, in iRBD patients, the process of RWA formation was thought to be associated with the process of PLMS formation during both stage NREM and stage REM. Moreover, given the relation to the length of morbidity of RBD, the mechanism of PLMS—especially during stage REM—might be reflected in the RBD disease process.

This study has some limitations. First, daytime sleepiness was evaluated only with the self-checked ESS score, but not with multiple sleep latency test, an objective measure for daytime sleepiness [9]. Future studies should objectively evaluate the influence of PLMS on daytime sleepiness in patients with RBD. Second, the present study was conducted with the retrospective design. Iranzo et al. [15] reported that excessive EMG activity increases with time course suggesting a progressive dysfunction of brainstem structures that modulate REM sleep atonia in idiopathic RBD. Further study would be necessary to investigate the changes in the amount of PLMS prospectively to support the possibility of the presence of PLMS as a biological marker of RBD. Third, the PLMS group did not consist of homogenous subjects, e.g. PLM disorder and incidental PLMS found in sleep onset insomnia and habitual snorer.

In conclusion, the influence of PLMS on daytime sleepiness is modest in iRBD patients, probably because of the impaired cortical reactivity to PLMS. In iRBD patients, PLMS occurs more frequently during stage REM. Disinhibition of motor control in stage REM underlying the process of RWA formation might be related with the presence of PLMS not only during stage REM but also during stage NREM. Moreover, PLMS especially during stage REM might reflect the length of RBD morbidity, probably related to the RBD disease process.

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**Conflict of interest** None.

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