



ORIGINAL ARTICLE

Abnormal activation of motor cortical network during phasic REM sleep in idiopathic REM sleep behavior disorder

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Abstract

Study Objectives: We investigated electroencephalography (EEG) power spectral density and functional connectivity during phasic and tonic rapid eye movement (REM) sleep, and examined any differences between patients with idiopathic REM sleep behavior disorder (iRBD) and controls.

Methods: EEG data from 13 people with iRBD (mean age, 66.3 years; men, 84.6%) and 10 controls (mean age, 62.3 years; men, 70%) were analyzed. We selected thirty 3 s miniepochs of both tonic and phasic REM sleep. We estimated relative power for six frequency bands. For functional connectivity analysis, we calculated weighted phase lag index (wPLI) and conducted pairwise comparisons between the two groups.

Results: EEG power spectral analysis revealed significant interactions between the REM sleep state (phasic vs. tonic) and group at sigma ($p = 0.009$) and beta ($p = 0.002$) bands. Sigma- and beta-power decrease during phasic REM sleep was more pronounced and extensive in people with iRBD than in controls. Regarding functional connectivity, there were significant interactions between the REM sleep state and group at alpha ($p = 0.029$), sigma ($p = 0.047$), beta ($p = 0.015$), and gamma ($p = 0.046$) bands. The average wPLI was significantly higher during phasic REM sleep than during tonic REM sleep, which was observed in people with iRBD but not in controls. The altered functional connections mainly involved the frontal and parietal regions at beta and gamma bands.

Conclusions: Our findings provide neurophysiological evidence for pathological motor cortex activation during phasic REM sleep which may be associated with generation of dream-enacting behaviors in iRBD.

Statement of Significance

Idiopathic REM sleep behavior disorder (iRBD) is characterized by loss of REM sleep atonia with dream-enacting behaviors in people without neurological disorders. Rapid eye movement (REM) sleep is categorized into two different microstates based on the presence or absence of REMs: phasic and tonic REM sleep. People with iRBD demonstrated more pronounced sigma- and beta-band power decrease during phasic REM sleep compared with controls. Furthermore, people with iRBD showed significantly enhanced functional connectivity exclusively during phasic REM sleep. Functional connectivity during tonic REM sleep did not differ between the two groups. This is the first electrophysiological evidence of increased motor cortex activation during phasic REM sleep in people with iRBD, which might be associated with dream-enacting behaviors in iRBD.

Key words: rapid eye movement; tonic and phasic motor activity; idiopathic REM sleep behavior disorder; EEG; functional connectivity

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Introduction

Rapid eye movement (REM) sleep is characterized by low-amplitude desynchronized brain activity on electroencephalography (EEG), physiological loss of muscle tone, dream imagery, and spontaneous REMs [1, 2]. REM sleep is categorized into two different states based on the presence or absence of REMs: phasic REM sleep, characterized by REMs and tonic REM sleep, containing no REMs. Accumulating evidence suggests that phasic and tonic REM states are functionally distinct from each other. A functional MRI (fMRI) study demonstrated that the thalamocortical network is activated during phasic REM sleep while brain reactivity to acoustic stimuli is more preserved during tonic REM sleep [3]. Additionally, the arousal threshold to external auditory stimuli is higher in phasic REM sleep than in tonic REM sleep [4]. Furthermore, studies have shown a clear difference in EEG spectral power between phasic and tonic REM sleep [5, 6]. Increased alpha and beta power in tonic REM sleep was interpreted as being close to wakefulness, whereas increased gamma power during phasic REM sleep might indicate enhanced cognitive processing [7]. In addition, brain activity time-locked to REMs was generated by the premotor, primary sensorimotor, inferior parietal, and occipital areas, suggesting a possible association of phasic REM sleep with visuomotor processing [8]. Considering that the brain activity time-locked to REMs is not reproduced by voluntary saccades, cognitive processes during phasic REM sleep are likely to involve dream-related visual imagery [9, 10].

REM sleep behavior disorder (RBD) is a parasomnia characterized by the loss of the physiological atonia during REM sleep with dream-enacting behaviors [11]. The REM sleep behaviors range from minor limb jerking and twitching, and a range of sleep talking and shouting, to complex and violent movements such as punching and kicking [12]. The violent behaviors during REM sleep can result in physical injury to the patients and/or their bed-partners. Idiopathic RBD (iRBD) refers to RBD without any associated neurological disorder or other trigger, such as antidepressant use. However, iRBD is considered a strong predictor of neurodegenerative synucleinopathy, including Parkinson's disease, multiple systemic atrophy, and dementia with Lewy bodies [13–17]. Neurodegeneration of the REM sleep generating brainstem circuit and consequent loss of inhibitory signals to spinal motor neurons are considered key pathomechanisms of REM sleep without atonia and dream-enacting behaviors in people with iRBD [18].

REM sleep behaviors occur more frequently during phasic REM sleep than during tonic REM sleep in people with iRBD [19, 20]. In addition, the association of active dreams with phasic REM sleep is higher than that with tonic REM sleep [21]. The saccades during phasic REM sleep are considered to imitate the dream imagery [22]. More importantly, an intracranial EEG study reported that during phasic REM sleep, the motor cortex exhibits decreased power at alpha and beta frequencies, which is similar to spectral power patterns observed for voluntary movements [23]. This finding provides direct evidence of motor cortex activation during phasic REM sleep. Taken together, dream-enactment behaviors of people with iRBD could be associated with motor cortex activation during phasic REM sleep rather than during tonic REM sleep. This is consistent with the observations in previous studies that motor behaviors during REM sleep are accompanied by supplementary motor area activation [24, 25].

Functional interactions between brain structures are crucial for normal brain functioning, including motor performance [26, 27]. Functional connectivity, defined as a temporal correlation between spatially remote oscillatory activities, is a measure of the functional integration of the brain network [28]. Previous studies have shown that synchronized oscillatory activities represent the neural mechanisms for motor control and sensorimotor integration [27, 29, 30]. Recently, Simor et al. reported that long-range alpha/beta synchronization was increased during tonic REM sleep compared with phasic REM sleep in healthy adults, suggesting that environmental awareness and attentional processes are enhanced during tonic REM sleep [31]. However, little is known about the functional connectivity during tonic and phasic REM sleep in people with iRBD.

In this study, we analyzed differences in EEG power spectral density between phasic and tonic REM sleep and examined any distinctive pattern between people with iRBD and controls. We hypothesize that people with iRBD demonstrate enhanced EEG power decrease during phasic REM sleep compared with controls, suggesting motor cortex activation associated with dream-enacting behaviors in iRBD. We additionally conducted functional connectivity analysis to determine the brain network associated with the spectral power changes in people with iRBD.

Methods

Participants

We prospectively recruited 21 drug-naïve people with iRBD and 16 age- and sex-matched controls from October 2014 to April 2016 at the Department of Neurology of the Seoul National University Hospital. All patients visited our clinic with complaints of complex motor behaviors while asleep and were subsequently diagnosed with iRBD. A neurologist (K.-Y.J.) who specializes in sleep medicine examined all participants to rule out individuals with overt manifestations of neurodegenerative disease, such as parkinsonism and dementia. All participants underwent overnight video-polysomnography (vPSG) and a diagnosis of iRBD was confirmed according to the third edition of the International Classification of Sleep Disorders (ICSD-3) criteria [32]. We excluded 14 participants (8 people with iRBD, 6 controls) whose apnea-hypopnea index was greater than 15 events/hr, because obstructive sleep apnea during REM sleep might have affected EEG activities and also made it difficult to sufficiently obtain noise-free EEG epochs. Finally, data from 13 people with iRBD and 10 controls were analyzed in this study. All participants provided written informed consent before enrollment in the study. This study was approved by the institutional review board of the Seoul National University Hospital (1406100589) and was performed in compliance with the Declaration of Helsinki and the Good Clinical Practice guidelines.

Clinical investigations

Detailed information on the clinical investigations has been described elsewhere [33]. Briefly, we used the Korean version of the RBD questionnaire-Hong Kong (RBDQ-KR) as a measure of RBD symptom severity, which was validated in Korean adults [34]. We investigated sleep quality and excessive daytime sleepiness by using the Pittsburgh Sleep Quality Index (PSQI) and Epworth

Sleepiness Scale (ESS), respectively [35, 36]. Neurocognitive tests included the Montreal Cognitive Assessment (MoCA) and the Korean version of the Consortium to Establish a Registry for Alzheimer's disease (CERAD-K) [37, 38]. Olfactory function was tested by the Korean version of Sniffin' sticks (KVSS) [39], whereas clinical symptoms of autonomic dysfunction were evaluated using the Scales for Outcomes in Parkinson's disease for Autonomic Symptoms (SCOPA-AUT) [40]. We used the Korean version of the Geriatric Depression Scale (GDS-K) for screening depression [41].

Video-polysomnography recording

Single-night vPSG recording was performed in a laboratory using a 64-channel Embla RemLogic PSG system (Natus, Pleasanton, CA). The recording system consisted of 21-channel EEG, two-channel electrooculogram (EOG), EMG for the submentalis and tibialis anterior muscles, and an electrocardiogram. In addition, a thermistor, nasal pressure-monitoring cannula, finger pulse oximetry, and thoracic and abdominal piezoelectric bands were applied for respiratory monitoring. A body position sensor and snore sensor were also employed. All participants had time-synchronized audio-visual recording during the PSG. Sleep stages were scored in 30 s epochs according to the American Academy of Sleep Medicine (AASM) manual for the scoring of sleep and associated events [42]. In addition, we calculated the REM sleep atonia index as described previously [43].

Selection of phasic and tonic REM sleep epochs

We segmented 30 s REM sleep epochs into 3 s miniepochs. REM sleep miniepochs were scored as phasic or tonic based on the presence of REMs, which were defined as sharply peaked eye movements with initial deflections on EOG lasting less than 500 ms. Phasic REM sleep was defined when there were at least two consecutive REMs within a 3 s miniepoch, which mostly occur in the middle of REM bursts. Tonic REM sleep was defined when REM or any eye movement was not detected within a 3 s miniepoch. A miniepoch including only one REM, which usually occurs at the beginning and the end of REM bursts, was discarded to exclude intermediate states between phasic and tonic REM states. In addition, EEG segments contaminated by limb and facial movements or electrode artifacts were selected by visual inspection and excluded from the analysis. According to this definition, we selected 30 miniepochs of both tonic and phasic REM sleep from at least three sleep cycles throughout the night to include early, middle, and late REM sleep. Two electroencephalographers (J.S.S. and K.-Y.J.) independently reviewed and verified all the selected epochs.

EEG recording and preprocessing

Twenty-one scalp EEG electrodes were placed according to the international 10–20 system and sleep EEG was recorded during the overnight vPSG. We used linked ear electrodes as a reference and the ground electrode was placed on the forehead. EEG data were sampled at 400 Hz and bandpass filtered between 0.1 and 70 Hz. A 60 Hz notch filter was also applied. Impedances of all EEG electrodes were kept below 10 kΩ.

EEG preprocessing and power spectral analysis were conducted using MATLAB (MathWorks, Natick, MA). EEG data were re-referenced to the average reference and resampled to 200 Hz. Then, a 1 Hz high pass filter was applied to remove low-frequency artifacts. REMs during phasic REM sleep inevitably contaminate EEG signals and produce large-amplitude delta waves especially in the frontal region. Therefore, we conducted independent component analysis decomposition and removed eye movement artifacts before analyzing EEG data [44]. Thereafter, the current source density (CSD) transformation was applied to minimize the volume conduction and improve spatial resolution of EEG data [45].

Power spectral density

The power spectral density was calculated using Welch's method with 1 s windows and a 50% overlap [46]. Then, we estimated the relative power by normalizing to the total power (0.5–50 Hz) for between-participants and within-participants comparisons. Relative power was expressed in dB for six frequency bands as follows: delta (2–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), sigma (12–15 Hz), beta (15–30 Hz), and gamma (30–50 Hz). Scalp electrodes were grouped into four regions of interest (ROIs), including the frontal (F3, Fz, F4), central (C3, Cz, C4), parietal (P3, Pz, P4), and occipital (O1, Oz, O2) regions.

Functional connectivity analysis

We calculated weighted phase lag index (wPLI) for measuring phase synchronization between different brain regions as described previously [33, 47]. Briefly, we applied Hilbert transform to the raw signal to determine the instantaneous phase for each time point. After calculating the wPLI between all 210 electrode pairs, we generated a connectivity matrix for each frequency band per epoch. Then, by averaging the wPLI values over 30 epochs, we obtained the connectivity matrix for each participant. For measuring overall connectivity strength, the wPLI was averaged over all electrode pairs. In addition, we conducted pairwise comparisons to identify topographical distribution of significantly altered functional connectivity by the REM sleep states (phasic vs. tonic) or participant groups (iRBD vs. control).

Statistical analysis

Data are presented as mean ± standard deviation or number (%). Considering the small sample size, clinical and PSG findings were compared using nonparametric tests, such as the Wilcoxon rank-sum test or Fisher's exact test as applicable. For the power spectral density, the assumption of normality was verified using the Kolmogorov-Smirnov test. Then, we performed repeated-measures ANOVA for each frequency band. Within-participants variables included the REM sleep states (tonic and phasic) and ROIs (frontal, central, parietal, and occipital). A between-participants variable was participant groups (iRBD and control). The Bonferroni method was used to correct multiple testing problems with the six frequency bands ($\alpha = 0.05/6$). In addition, post hoc comparisons between the two REM sleep states for each ROI were performed using the paired sample t-test. Comparisons

for each ROI were adjusted using the Bonferroni method ($\alpha = 0.05/4$). In repeated-measures ANOVA for the overall connectivity strength, ROIs were not included as a within-participant variable because the overall connectivity strength was measured by averaging wPLI over all brain regions. For correlation analysis, we estimated partial correlation coefficients while adjusting for age. Furthermore, we employed the false discovery rate (FDR) when conducting pairwise comparisons of the wPLI. A two-tailed $p < 0.05$ after the multiple testing correction was considered statistically significant and all statistical analyses were conducted using SPSS version 18 (SPSS Inc., Chicago, IL).

Results

Clinical findings

The mean age of the people with iRBD was 66.3 ± 6.5 years and 11 (84.6%) were men. The mean duration of RBD symptoms was 4.0 ± 2.1 years. The total and factor 2 (behavioral manifestations) scores of RBDQ-KR were 52.3 ± 19.5 and 37.1 ± 14.6 , respectively (Table 1). Although no patient was clinically diagnosed with dementia, the average MoCA score of the iRBD group was lower than that of controls ($p < 0.015$). Neurocognitive tests with CERAD-K revealed that cognitive subscales did not significantly differ between the two groups, although the iRBD group tended to have decreased verbal fluency (Supplementary Table S1). In addition, significant differences in the KVSS and SCOPA-AUT scores suggested impaired olfactory and autonomic functions of the people with iRBD compared with the controls. However, ESS, PSQI, and GDS-K scores did not significantly differ between the two groups.

Polysomnographic data revealed that REM sleep accounted for 24.5% of the total sleep time in the people with iRBD and 19.9% in the control group ($p = 0.077$). There was no significant difference in total sleep time, sleep latency, REM latency, wakefulness after sleep onset, sleep efficiency, or % sleep stages between the two groups (Supplementary Table S2). However, as expected, REM atonia index of the people with iRBD was significantly lower than that of the controls (0.73 ± 0.23 vs. 0.94 ± 0.14 , $p < 0.001$).

Table 1. Clinical characteristics of the study participants

Variables	iRBD (n = 13)	Control (n = 10)	P
Age, yr	66.3 ± 6.5	62.3 ± 7.5	0.186
Sex, male	11 (84.6)	7 (70.0)	0.618
BMI, kg/m ²	23.5 ± 3.1	24.6 ± 2.0	0.343
Education, yr	12.2 ± 3.5	12.0 ± 3.4	0.927
RBD duration, yr	4.0 ± 2.1		
RBDQ-KR, total	52.3 ± 19.5	6.1 ± 4.8	<0.001
Factor 1	15.2 ± 7.4	3.5 ± 2.8	<0.001
Factor 2	37.1 ± 14.6	2.6 ± 3.0	<0.001
MoCA	24.8 ± 3.1	27.9 ± 1.8	0.015
ESS	5.5 ± 3.1	4.0 ± 1.4	0.131
PSQI	4.4 ± 1.7	3.9 ± 1.9	0.693
KVSS	4.8 ± 1.2	5.9 ± 0.9	0.042
SCOPA-AUT	11.5 ± 4.9	7.7 ± 4.2	0.049
GDS-K	12.3 ± 5.1	8.1 ± 8.8	0.148

Data are presented as mean \pm standard deviation or number (%).

BMI = body mass index

Power spectral density between phasic and tonic REM sleep

There was no main effect of group in all frequency bands. However, we found significant main effects of the REM sleep state on EEG spectral power at delta, alpha, sigma, and beta bands (Table 2). Both groups showed that phasic REM sleep was characterized by decreased alpha, sigma, and beta power compared with tonic REM sleep (Figure 1A). By contrast, the delta-band power increased during phasic REM sleep compared with tonic REM sleep. When comparing the relative power between phasic and tonic REM sleep for each group, a significant decrease in alpha, sigma, and beta power during phasic REM sleep was found only in the iRBD group ($p < 0.001$, Figure 1B). In line with this, repeated-measures ANOVA revealed significant interactions between the REM sleep state and group in sigma ($F_{1,21} = 13.424$, $p = 0.009$) and beta ($F_{1,21} = 17.864$, $p = 0.002$) bands (Table 2). The result for alpha-band power ($F_{1,21} = 7.970$, $p = 0.061$) revealed a similar trend although it did not reach statistical significance after the multiple testing correction. Please see Supplementary Table S3 for the ROI results of repeated-measures ANOVA.

Differential patterns of EEG power changes by the REM sleep state were most pronounced in beta-power topography (Figure 2A). Post hoc comparisons per ROI revealed that beta-power decrease during phasic REM sleep was only significant in the central region among the controls, but was prominent in the whole brain among the people with iRBD (Figure 2B). Comparisons for sigma-band power yielded similar results that EEG power decrease during the phasic REM state was more remarkable and extensive in people with iRBD than in controls (Supplementary Figure S1). By contrast, there was no significant interaction between the REM sleep state and group in relative power of delta ($F_{1,21} = 0.030$, $p = 1$), theta ($F_{1,21} = 4.067$, $p = 0.340$), and gamma ($F_{1,21} = 0.012$, $p = 1$) frequencies.

Correlation between sigma power decrease and behavioral symptoms

Next, we evaluated the correlation of EEG power differences between phasic and tonic REM sleep with RBD symptom severity measured by RBDQ-KR. We analyzed the factor 1 and 2 scores separately, because they have different clinical significance; factor 1 is associated with dreams, whereas factor 2 reflects behavioral manifestation of RBD [48]. We found that, in the central region, sigma-band power differences were significantly correlated with the RBDQ-KR factor 2 score ($r = 0.427$, $p = 0.047$; Figure 3), but not with the factor 1 ($r = 0.081$, $p = 0.720$) or total ($r = 0.343$, $p = 0.119$) score. Beta-band power differences also revealed a similar trend towards a positive correlation with the factor 2 score ($r = 0.374$, $p = 0.086$). Apart from the central region, no significant correlation between EEG power decrease and RBD symptom severity was found in other brain regions. Additionally, we examined the relationship between power differences and REM atonia index. However, there was no significant correlation in sigma ($r = -0.045$, $p = 0.841$) or beta ($r = 0.039$, $p = 0.862$) band.

Functional connectivity analysis

The results of repeated-measures ANOVA for the overall connectivity strength are summarized in Table 3. We found a significant effect of the REM sleep state at all frequencies except

Table 2. Repeated-measures ANOVA for power spectral density

Frequency	REM sleep state		REM sleep state \times group		Group	
	F _{1,21}	P*	F _{1,21}	P*	F _{1,21}	P*
Delta	10.966	0.020	0.030	1	1.391	1
Theta	6.588	0.108	4.067	0.340	0.703	1
Alpha	29.944	<0.001	7.970	0.061	1.761	1
Sigma	18.681	0.002	13.424	0.009	7.218	0.083
Beta	52.916	<0.001	17.864	0.002	0.607	1
Gamma	2.126	0.958	0.012	1	1.379	1

REM sleep states consist of phasic and tonic REM sleep, and groups consist of idiopathic REM sleep behavior disorder and control.

*P corrected for six frequency bands with Bonferroni method ($\alpha = 0.05/6$). Please see [Supplementary Table S3](#) for the remaining results of the repeated-measures ANOVA.

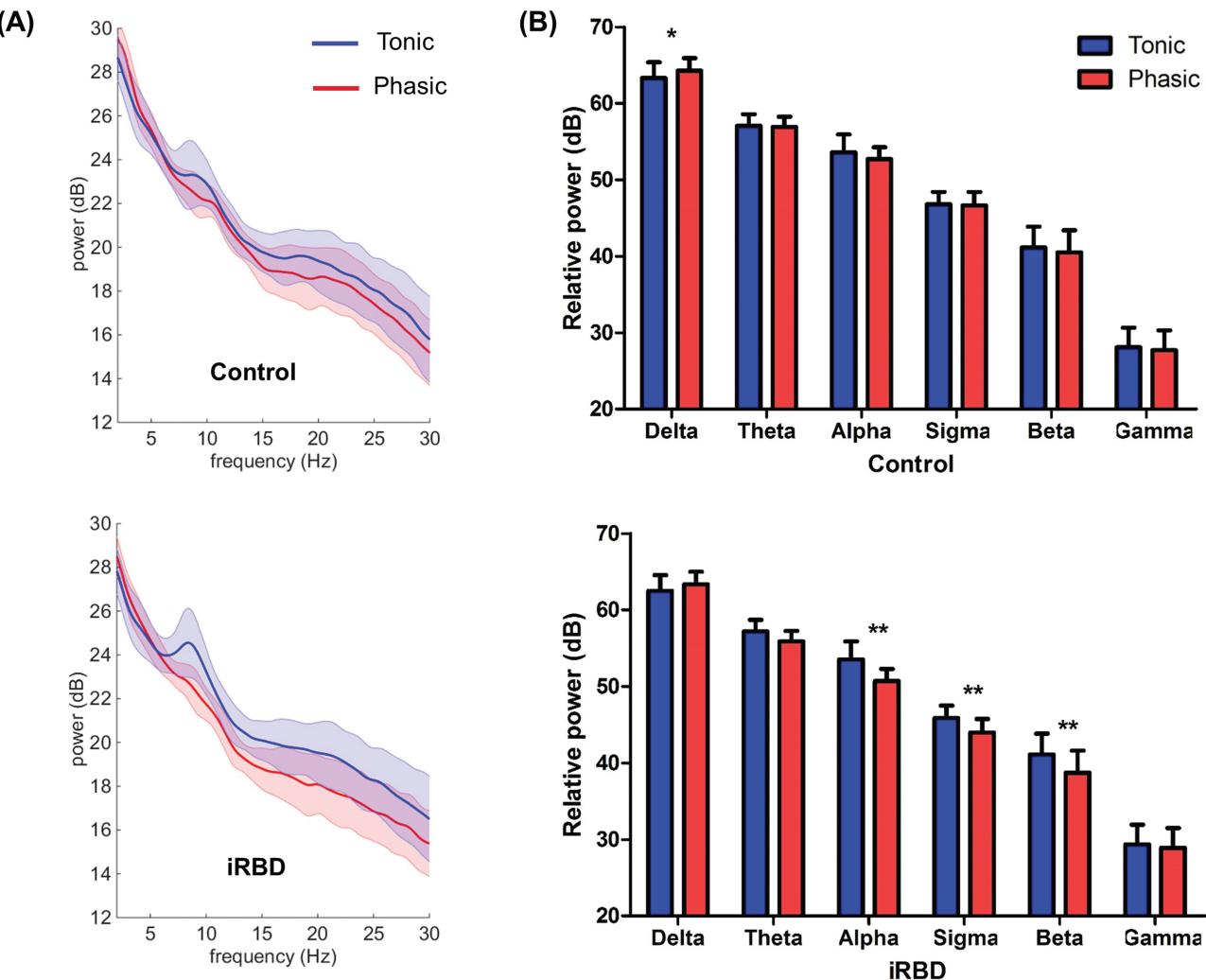


Figure 1. Power spectral density of controls ($n = 10$, upper panel) and people with iRBD ($n = 13$, lower panel). (A) The red line and area indicate the average and standard deviation for phasic REM sleep, and the blue line and area indicate the average and standard deviation for tonic REM sleep. (B) Comparisons of relative power between phasic and tonic REM sleep by paired sample t-tests for each frequency band. Error bars indicate standard deviation. * $p < 0.05$, ** $p < 0.01$ after the Bonferroni correction.

for alpha. A significant effect of the group on the average wPLI was also noted at sigma, beta, and gamma frequencies. More importantly, there was a significant interaction between the REM sleep state and group at alpha ($p = 0.029$), sigma ($p = 0.047$), beta ($p = 0.015$), and gamma ($p = 0.046$) bands. Post hoc comparisons in the iRBD group revealed that the average wPLI during phasic REM sleep was significantly higher than that during tonic REM

sleep at alpha ($p = 0.015$), sigma ($p = 0.019$), beta ($p = 0.007$), and gamma ($p = 0.012$) bands ([Figure 4A](#)). However, the controls showed no difference in the average wPLI between phasic and tonic REM sleep ([Figure 4B](#)). When comparing the wPLI between the two groups, the iRBD group had a higher wPLI value than the controls during the phasic REM state at sigma ($p = 0.040$), beta ($p = 0.003$), and gamma ($p = 0.005$) frequencies. However, a

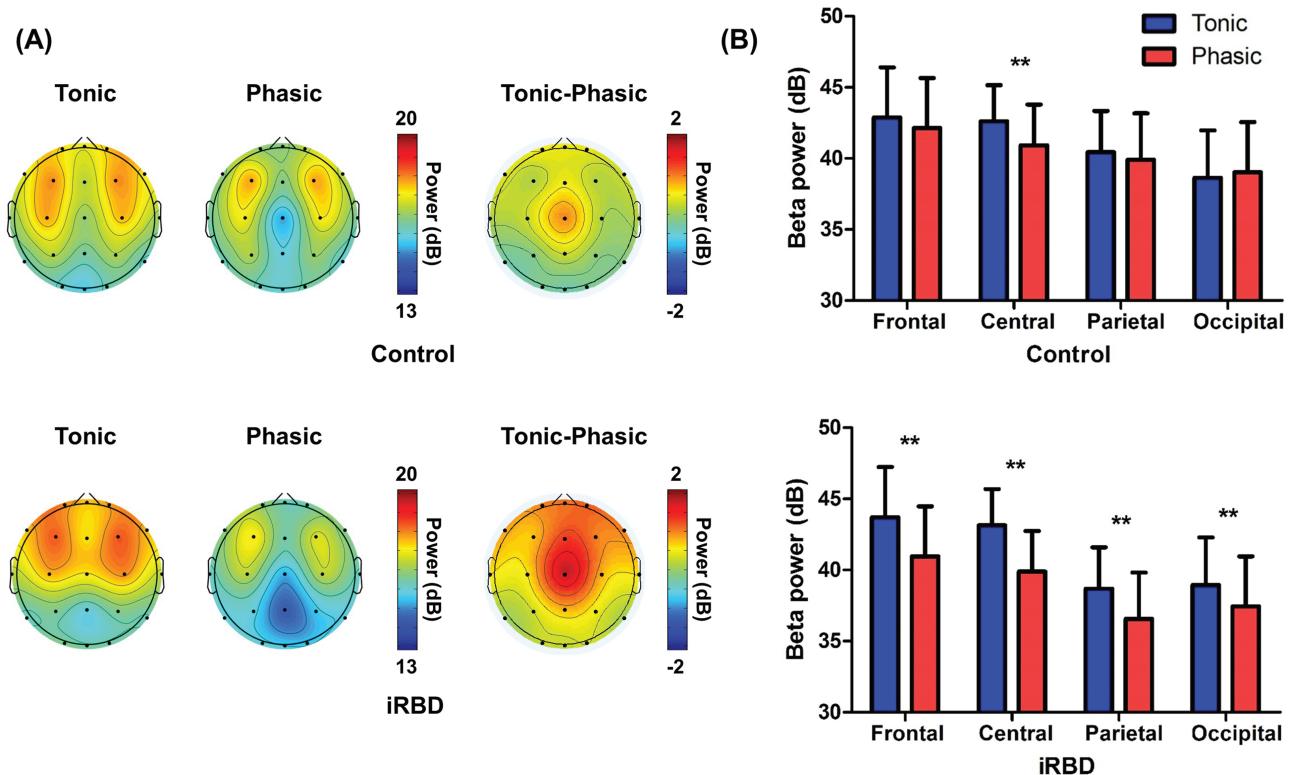


Figure 2. Beta (15–30 Hz) power during tonic and phasic REM sleep. (A) Topographical distribution of beta power in controls ($n = 10$, upper panel) and people with iRBD ($n = 13$, lower panel). (B) Comparisons of beta-band power between the two REM sleep states for each brain region. Error bars indicate standard deviation. * $p < 0.05$, ** $p < 0.01$ after the Bonferroni correction.

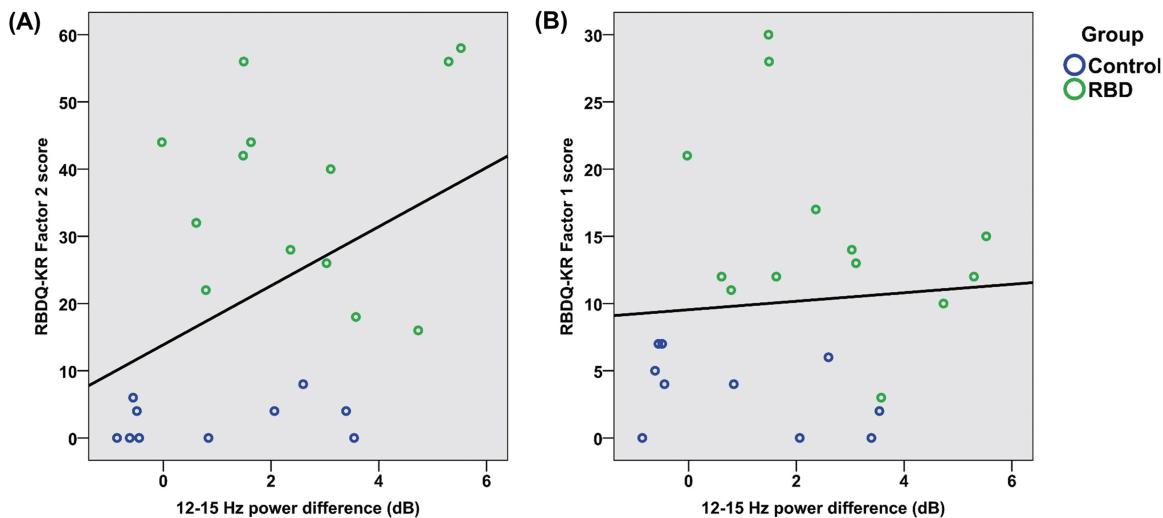


Figure 3. Correlation between sigma (12–15 Hz) desynchronization in the central region and RBD symptom score. Sigma-power differences between phasic and tonic REM sleep are significantly correlated with RBDQ-KR factor 2 scores ($r = 0.427$, $p = 0.047$; A), but not with factor 1 scores ($r = 0.081$, $p = 0.720$; B). The correlations were adjusted for age.

significant group difference was not observed during tonic REM sleep (Supplementary Figure S2).

Next, we performed pairwise comparisons of the wPLI to localize different functional connections between the iRBD and control groups. During phasic REM sleep, we found significantly increased functional connections in the iRBD group than in the controls, which was most prominent at beta frequency and mainly

involved the fronto-parietal connections (Figure 5A). By contrast, no significantly different connection was detected during tonic REM sleep (Figure 5B). Pairwise comparisons between the two REM sleep states also yielded similar findings. Beta-band fronto-parietal connections were significantly enhanced during phasic REM sleep in the iRBD group, whereas gamma-band connections were more diffusely increased (Supplementary Figure S3).

Table 3. Repeated-measures ANOVA for the average weighted phase lag index

Frequency	REM sleep state		REM sleep state × group		Group	
	F _{1,21}	P*	F _{1,21}	P*	F _{1,21}	P*
Delta	20.449	0.001	5.298	0.190	6.408	0.116
Theta	2.993	0.041	3.331	0.493	4.239	0.313
Alpha	8.209	0.056	9.894	0.029	6.402	0.117
Sigma	10.964	0.020	8.626	0.047	10.761	0.021
Beta	12.183	0.013	11.879	0.015	14.486	0.006
Gamma	15.754	0.004	8.676	0.046	11.956	0.014

REM sleep states consist of phasic and tonic REM sleep, and groups consist of idiopathic REM sleep behavior disorder and control.

*P corrected for six frequency bands with Bonferroni method ($\alpha = 0.05/6$).

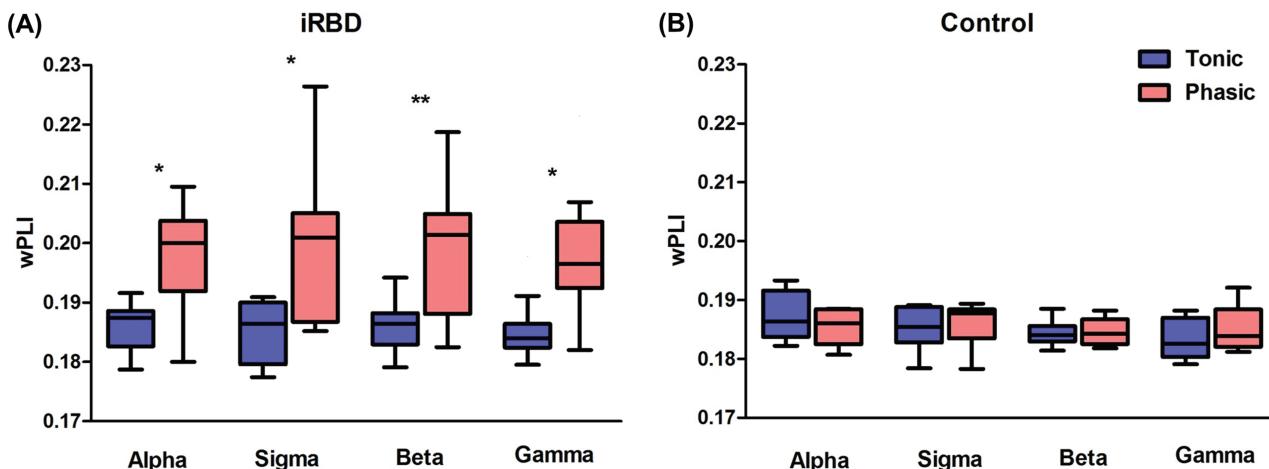


Figure 4. Comparisons of the average wPLI between phasic and tonic REM sleep. (A) In people with iRBD ($n = 13$), the wPLI during phasic REM sleep was higher than during tonic REM sleep at alpha ($p = 0.015$), sigma ($p = 0.019$), beta ($p = 0.007$), and gamma ($p = 0.012$) bands. (B) No significant difference was found in the control group ($n = 10$, $p = 1$ for all). The box represents the 25th and 75th percentiles and the line inside the box is the median. The whisker indicates 1.5 times the interquartile range. The Wilcoxon signed-rank test was used for statistical comparisons. * $p < 0.05$, ** $p < 0.01$ after the Bonferroni correction.

Discussion

In this study, we found that people with iRBD are characterized by more pronounced EEG power decrease at sigma and beta bands during phasic REM sleep compared with controls. In addition, decrease in sigma power was significantly correlated with the RBD behavioral symptom severity. These findings support the notion that pathological motor cortex activation may exist during phasic REM sleep in people with iRBD. People with iRBD also showed significantly enhanced functional connectivity particularly during phasic REM sleep compared with controls. The functional connectivity changes mainly involved the frontal and parietal regions at beta and gamma bands, which might reflect abnormal activation of the motor cortical network during phasic REM sleep in people with iRBD.

EEG beta power decrease and motor cortex activation during phasic REM sleep

Distinct EEG power spectral density between phasic and tonic REM sleep in healthy participants has been established in previous studies [5–7]. Consistent with results from previous studies, we found that alpha and beta power decreased and delta power increased during phasic REM sleep compared with tonic REM sleep in both iRBD and control groups. Notably, we identified

that decrease of the beta (12–30 Hz) band activities during phasic REM sleep occurred more markedly and extensively in people with iRBD than in the controls. A possible explanation for this phenomenon is that iRBD is associated with abnormal motor cortex activation especially during phasic REM sleep. Previous studies showed that motor preparation and execution are associated with event-related beta desynchronization in the periorolandic cortex [49–51]. This is consistent with a concept that movement-related attenuation of the Rolandic mu rhythm represents the activation of the motor-related cortical areas [52]. It is also in line with our results obtained from controls that beta-power decrease during phasic REM sleep was only evident in the central region. Additionally, the fact that low-beta (12–15 Hz) power decrease in the central region was correlated with the behavioral symptom score supports the notion that the motor-related neural activities aberrantly increased during phasic REM sleep rather than during tonic REM sleep in iRBD. However, REM atonia index was not significantly correlated with beta power difference. We speculate that the degree of REM sleep without atonia is mainly affected by the loss of inhibitory signals to spinal motor neurons rather than by the activity of the motor cortex. In addition, both tonic and phasic muscle activities are included in the calculation of REM atonia index. Collectively, considering the major role of beta oscillations in motor control, it is conceivable that enhanced beta-power decrease during phasic REM sleep

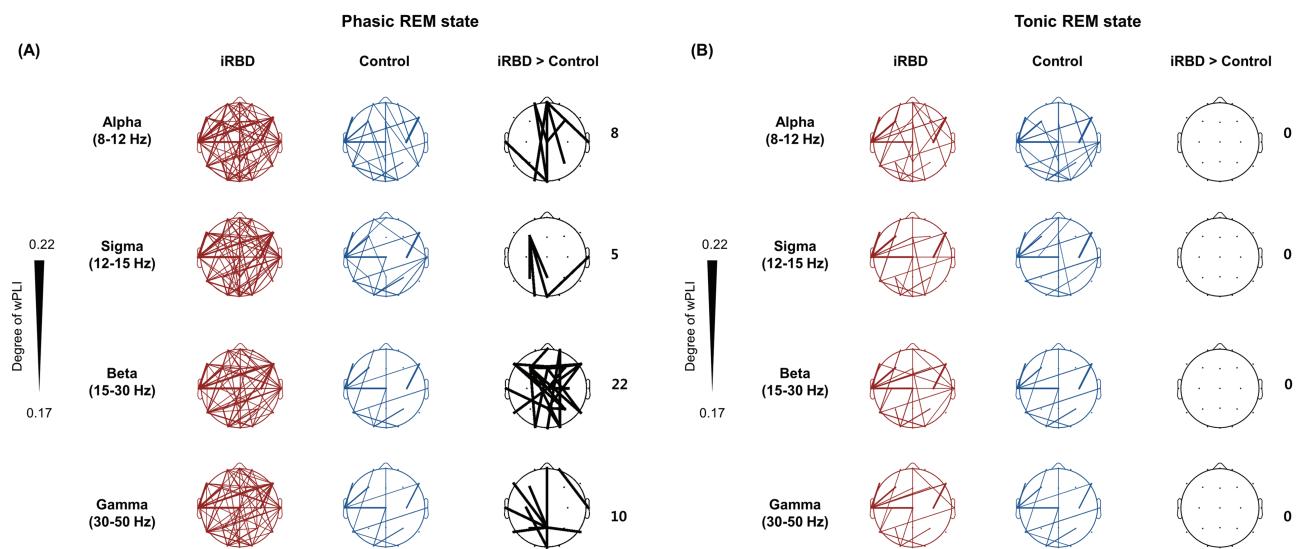


Figure 5. Functional connectivity maps of the iRBD ($n = 13$) and control ($n = 10$) groups. (A) Phasic REM sleep. (B) Tonic REM sleep. Left and middle panels indicate channel pairs with the wPLI value of >0.17 in the iRBD and control groups, respectively. Right panels indicate functional connections in which the wPLI of the people with iRBD was significantly higher than that of the controls. Numbers indicate the number of significantly different functional connections. Pairwise comparisons were conducted by the Student's t-test and FDR-corrected $p < 0.05$ was considered significant.

might suggest increased activation of the motor cortex in people with iRBD. We previously found that during REM sleep, beta-band corticomuscular coherence in people with iRBD was higher than in controls [53]. This finding suggests that cortical locomotor drive is increased during REM sleep in iRBD, which is in close agreement with the hypothesis of motor cortex activation in the current study. Further research on spectral power changes with respect to motor behaviors during REM sleep will provide convincing evidence to confirm this hypothesis.

Cortical network changes during phasic REM sleep in iRBD

In the healthy controls, there was no significant difference in EEG functional connectivity between phasic and tonic REM sleep. However, iRBD was characterized by an enhanced functional connectivity particularly during phasic REM sleep.

Based on the power spectral density results, this phenomenon can be interpreted as neural correlates of the motor cortex activation during phasic REM sleep in iRBD. Although previous imaging studies reported cortical activation associated with REM sleep behaviors [24, 25], this is the first study to demonstrate electrophysiological evidence of increased motor cortex activation during REM sleep in people with iRBD. It should be noted that, among six frequency bands, beta-band connectivity was most affected by the REM sleep state (phasic vs. tonic). Given the significant implication of beta oscillations in motor control as mentioned earlier, increased functional connectivity during phasic REM sleep might represent recruitment of the motor network. In agreement with this, a recent study reported that increased beta-band connectivity from the parietal to motor cortex is important for sensorimotor integration and modulation of motor performance [30]. Furthermore, it has been hypothesized that during REM sleep, movements are generated via activation of the motor cortex and they descend through the alternative motor pathway bypassing the extrapyramidal system [24, 54, 55]. Ictal single photon emission tomography at

the onset of REM sleep behaviors confirmed the activation of the bilateral premotor and supplementary cortex [24]. In this context, excessive beta connectivity between the frontal and parietal regions during phasic REM sleep observed in our study might reflect increased activation of the cortical motor network in people with iRBD.

It has been suggested that tonic and phasic muscle activities during REM sleep have different neural mechanisms. Phasic EMG activity is considered to originate from the glutamatergic pyramidal cells of the motor cortex, whereas tonic EMG activity depends on REM-on neurons of the sublaterodorsal tegmental nucleus [56]. In agreement with this, phenoconversion to PD was associated with increased tonic EMG activity but not with phasic EMG activity during REM sleep [57]. Dream-enacting behaviors during REM sleep was found to have a directional coherence with saccadic eye movements in people with RBD, indicating that phasic REM sleep is associated with visual scanning of the dream scene [22]. Furthermore, phasic REM sleep is characterized by ponto-geniculo-occipital waves time-locked to the REMs [58]. Activation of the visual cortex and geniculate body in direct temporal relationship to REMs suggests that phasic REM sleep is implicated in visual information processing, which is associated with dream content [9, 59]. A previous study showed that visuomotor integrative behavior is associated with increased beta connectivity between the visual and motor cortex [60]. Gamma-band synchronization was also reported to be involved in transmission of visual information and visuomotor integration [61]. Collectively, our results showing the increased functional connectivity within the frontal, parietal, and occipital cortex during phasic REM sleep might represent an inter-regional brain communication for dream-related visual information and subsequent visuomotor integration.

This study has several limitations. First, the number of study participants as well as the number of REM sleep epochs selected per participant is small. Another limitation is that we could not determine the contribution of the subcortical structures to the neural activities by scalp EEG. Therefore, the

neural pathway from the sublaterodorsal tegmental nucleus to the motor cortex during phasic REM sleep remains uncertain. Animal models in which intracranial EEG is performed may provide more direct evidence of the involvement of the motor cortex in iRBD. Furthermore, phasic muscle activities during REM sleep are not limited to the oculomotor system but associated with noneye movements, such as middle ear motor activities and twitches in laryngeal, neck, and limb muscles [62]. Therefore, phasic REM sleep, defined by REMs in this study, may not represent the entire phasic activities during REM sleep. However, the nonoculomotor phasic activities do not necessarily coincide with REMs. Most of the previous studies also divided REM sleep into the phasic and tonic states solely based on the eye movements [3, 7, 23]. Further studies will be needed to characterize phasic REM sleep with both REMs and nonoculomotor muscle activities. In addition, variability of REM sleep spectral power or functional connectivity across the night was not investigated in this study, which will be an interesting topic to explore in the future.

In summary, people with iRBD showed more decrease in sigma and beta power during phasic REM sleep than controls. Moreover, the overall connectivity strength was significantly higher during phasic REM sleep than during tonic REM sleep in people with iRBD, whereas these functional connectivity changes were not observed in controls. Taken together, our results reflect abnormally increased motor cortex activation during phasic REM sleep in people with iRBD, which might be associated with generation of dream-enacting behaviors in iRBD.

Supplementary Material

Supplementary material is available at SLEEP online.

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