

# Generalized EEG Slowing Across Phasic REM Sleep, Not Subjective RBD Severity, Predicts Neurodegeneration in Idiopathic RBD

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**Purpose:** Idiopathic rapid eye movement sleep behavior disorder (iRBD) is the prodromal marker of  $\alpha$ -synuclein degeneration with markedly high predictive value. We aim to evaluate the value of electroencephalography (EEG) data during rapid eye movement (REM) sleep and subjective RBD severity in predicting the conversion to neurodegenerative diseases in iRBD patients.

**Methods:** At the baseline, iRBD patients underwent clinical assessment and video-polysomnography (PSG). Relative spectral power for nine frequency bands during phasic and tonic REM sleep in three regions of interest, slow-to-fast ratios, clinical and PSG variables were estimated and compared between iRBD patients who converted to neurodegenerative diseases (iRBD-C) and iRBD patients who remained disease-free (iRBD-NC). Receiver operating characteristic (ROC) curves evaluated the predictive performance of slow-to-fast ratios, and subjective RBD severity as assessed with RBD Questionnaire-Hong Kong.

**Results:** Twenty-two (33.8%) patients eventually developed neurodegenerative diseases. The iRBD-C group showed shorter total sleep time ( $p < 0.001$ ), lower stage 2 sleep percentage ( $p = 0.044$ ), more periodic leg-movement-related arousal index ( $p = 0.004$ ), increased tonic chin electromyographic activity ( $p = 0.040$ ) and higher REM density in the third REM episode ( $p = 0.034$ ) than the iRBD-NC group. EEG spectral power analyses revealed that iRBD phenoconverters showed significantly higher delta and lower alpha power, especially in central and occipital regions during the phasic REM state compared to the iRBD-NC group. Significantly higher slow-to-fast ratios were observed in a more generalized way during the phasic state in the iRBD-C group compared to the iRBD-NC group. ROC analyses of the slowing ratio in occipital areas during phasic REM sleep yielded an area under the curve of 0.749 ( $p = 0.001$ ), while no significant predictive value of subjective RBD severity was observed.

**Conclusion:** Our study shows that EEG slowing, especially in a more generalized manner during the phasic period, may be a promising marker in predicting phenoconversion in iRBD, rather than subjective RBD severity.

**Keywords:** idiopathic rapid eye movement sleep behavior disorder, neurodegenerative diseases, EEG slowing, RBD severity, phenoconversion, neuroprotective therapy

## Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) refers to a type of parasomnia that is featured by increased muscle tone and dream enactment behaviors,<sup>1</sup> which usually cause injury to themselves or the bed partner.<sup>2</sup> Mounting evidence showed that approximately 35–45% of the patients with idiopathic RBD (iRBD) will develop neurodegenerative diseases in five years after the diagnosis of iRBD, including Parkinson's disease (PD), dementia with Lewy bodies, multiple system atrophy (MSA), mild cognitive impairment (MCI), and Alzheimer's disease (AD).<sup>3–6</sup> The conversion rate will rise to approximately 91% after 14

years post-diagnosis.<sup>7</sup> Meanwhile, iRBD tends to precede neurodegenerative diseases for about 13 years on average,<sup>5</sup> providing an optimal opportunity to conduct neuroprotective therapies. However, the question of when to suggest that patients undertake neuroprotective trials remains controversial. Therefore, identifying sensitive markers in iRBD patients for phenoconversion is of the utmost importance.

Previous longitudinal and multicenter studies have revealed that predictors of parkinsonism and dementia included abnormal quantitative motor testing, olfactory deficit, MCI, erectile dysfunction, constipation, REM sleep without atonia (RWA), acoustic speech impairment and so on.<sup>8,9</sup> Researchers further evaluated the role of RWA in predicting phenoconversion and concluded that severity of RWA,<sup>10</sup> tonic electromyography (EMG) activities,<sup>11</sup> and mixed RWA<sup>12</sup> could serve as the markers for prediction. Additionally, a recent study showed that iRBD patients who had phenoconverted exhibited specific electroencephalography (EEG) abnormalities during wakefulness, compared to those who did not, remained disease-free.<sup>13</sup> More electrophysiological markers of neurodegeneration in iRBD have been thoroughly reviewed by Figorilli and Ferini-Strambi et al.<sup>14,15</sup> However, few studies have demonstrated the role of EEG data recorded during REM sleep and RBD severity as assessed with the RBD questionnaire—Hong Kong (RBD-HK) to predict phenoconversion in iRBD.

In brief, the REM-sleep state comprises two distinct sleep states (ie, tonic and phasic periods) based on the presence of REM, which display functional disparity from each other in terms of arousal thresholds,<sup>16</sup> information processing,<sup>17</sup> and synchronized oscillatory activities.<sup>18</sup> Studies showed that motor activities mostly occur during the phasic REM-sleep state,<sup>19</sup> and behavioral arousal thresholds were relatively higher in phasic REM sleep than tonic REM sleep.<sup>16</sup> Hence, accumulating evidence suggests that REM sleep should not be assumed to be a uniform state.<sup>16,19–21</sup> A recent study further corroborated this notion by stating that the blunted difference regarding EEG spectral power between the sub-stages of REM sleep may be a biomarker of RBD.<sup>22</sup> However, no studies to date are available to determine the usefulness of EEG data during sub-stages of REM sleep and RBD severity as biomarkers of neurodegeneration in iRBD.

Therefore, we hypothesized that if EEG data during REM sleep, especially during phasic and tonic sleep states, and RBD severity could identify iRBD patients at an elevated risk of developing neurodegenerative diseases. To test the hypothesis, we compared EEG spectral power during phasic and tonic REM sleep states and RBD severity as assessed with RBD-HK between iRBD patients who developed neurodegenerative diseases and those who remained disease-free.

## Materials and Methods

### Participants

Seventy-one iRBD patients were recruited at the Sleep Center of the Second Affiliated Hospital of Soochow University from July 2010 to July 2019 and were followed for at least two years. The diagnosis of iRBD was based primarily on the *International Classification of Sleep Disorders, 2nd edition* (ICSD-2).<sup>23</sup> Six iRBD patients were excluded due to invalid EEG data at the baseline. Finally, sixty-five iRBD patients were included in this study. All the patients were free of medications that might affect sleep, including antidepressants, benzodiazepine, and melatonin.<sup>24–26</sup> This study complied with the Declaration of Helsinki. Ethics approval was obtained from the Research Ethics Committee of the Second Affiliated Hospital of Soochow University, and all the written informed consents were provided.

### Neurophysiological Assessment

Patients were routinely followed up every 0.5–1 year by the treating neurologists. If the patients were unable to present to the clinic due to severe disability or refusal of in-person assessments, telephone interviews were conducted by their previous treating neurologists. At the baseline, eligible iRBD patients completed the Mini-Mental State Examination (MMSE),<sup>27</sup> Montreal Cognitive Assessment (MoCA, Beijing version),<sup>28</sup> Epworth Sleepiness Scale (ESS),<sup>29</sup> RBD Screening Questionnaire (RBDSQ) and RBD-HK.<sup>30,31</sup> RBD-HK comprises 13 questions about the presence and severity of RBD itself. It also can be classified into factors I and II, with factor I related to dreaming content (Q1-5 and Q13) and factor II related to behavioral manifestation (Q6-12).<sup>32</sup> Subjective RBD severity was assessed with RBD-HK. During follow-up, iRBD patients were diagnosed by specialists as PD,<sup>33,34</sup> MSA,<sup>35</sup> AD,<sup>36,37</sup> or MCI,<sup>38</sup> according to their respective diagnostic criteria. Follow-up duration was defined as the interval from the time of RBD diagnosis to the time of the last visit or to the time of neurological-disease diagnosis.

## Polysomnography (PSG) Recording

At the baseline, eligible iRBD patients underwent video-PSG using an E-Series System digital polygraph (Compumedics Company, Abbotsford, Victoria, Australia) after comprehensive neurophysiological assessments. Scalp EEG montages, including frontal (F3, F4), central (C3, C4) and occipital (O1, O2), with A1, A2 being the linked mastoid references, were placed based on the 10–20 international system. The EEG impedances were kept below 10k $\Omega$ . All the EEG data were sampled at 256Hz and recorded with a bandpass filter of 0.5–35Hz. EMG activities were recorded for submental and both anterior tibialis muscles. A bilateral electrooculogram (EOG) was recorded with two electrodes placed at the outer canthi of both eyes, either below or above each eye. Respirations were monitored with the nasal cannula, thermistor, and thoracic and abdominal piezoelectric belts. Registered sleep technicians reclassified sleep stages based on the American Academy of Sleep Medicine (AASM)'s scoring manual. Polysomnographic variables included total sleep time (TST); sleep efficiency; sleep latency; sleep stages 1, 2 (N1, N2), and REM sleep; percentage of slow-wave sleep; REM-sleep latency; arousal index (ArI); wake-after-sleep onset (WASO); periodic limb movements during sleep; REM and non-REM sleep (PLMS, PLM-REM, PLM-NREM); periodic leg-movement-related arousal index (PLMARi); and apnea-hypopnea index (AHI).

## RWA and Rapid Eye Movement Density (REMD) Scoring

RWA and REMD scoring was performed by the same registered sleep technicians, who were blinded to the patients' diagnoses, according to the methods reported by previous literature.<sup>39</sup> EMG activity scored from submental muscles was analyzed. "Percent phasic EMG activity" refers to the percentage of 3-second mini-epochs, containing intermittent bursts of EMG activity lasting 0.1–5.0 seconds with amplitudes of at least twice the background, divided by all the 3-second mini-epochs. "Percent tonic EMG activity" is identified as the percentage of the epochs in which a persistent increase occurs in EMG activity for at least half of a 30-second epoch with amplitudes of more than twice that of the baseline signals, in all the 30-second epochs across REM sleep. Any epoch containing arousals or related respiratory events was excluded. "REMD" was defined as the number of ocular movements divided by the length of REM sleep in minutes. Only continuous REM sleep lasting for at least 3 minutes was included for analysis. The REMD for each REM-sleep episode and total REM sleep throughout the night was calculated. Any epoch contaminated by movements was selected by visual inspections and excluded from this study.

## EEG Preprocessing and Power-Spectral Analysis

EEG data preprocessing and power-spectral analyses were performed utilizing *Matlab* R2013b (*Mathworks*, Natick, MA, USA). Phasic or tonic REM sleep was visually selected throughout the whole-night REM sleep. Segments were defined as phasic REM sleep when at least two eye movements (EMs) occurred in adjacent 2s mini-epochs. Tonic REM-sleep segments were detected when there were no EMs (amplitude <25 $\mu$ V)<sup>40</sup> in consecutive 2s windows. Segments of less than 8s between phasic and tonic REM-sleep epochs were discarded to avoid contamination from intermediate stages. Transition stages around 30s, either from non-REM (NREM) to REM or REM to NREM, were removed from further analysis. EEG epochs contaminated by movement-related artifacts were excluded from this study.

Absolute spectral power in the delta (2.0–3.9Hz), theta (4.0–7.9Hz), alpha (8.0–12.9Hz), alpha1 (8.0–9.9Hz), alpha2 (10–12.9Hz), beta (13.0–32.0Hz), beta1 (13.0–21.9Hz), beta2 (22.0–32.0Hz), and sigma (12.0–14.9Hz) was calculated using Fast Fourier transform (FFT) and averaged over each region of interest (ROI), including frontal, central and occipital regions. Relative power was obtained by normalizing to the total absolute power (2.0–32.0Hz). Several ratios reflecting EEG slowing were calculated in each ROI as follows:

$$ratio1 = (\delta + \theta) / (\alpha + \beta)$$

$$ratio2 = (\delta + \theta) / (\alpha1 + \alpha2 + \beta)$$

$$ratio3 = (\delta + \theta) / (\beta1 + \beta2)$$

$$\text{ratio4} = \delta/\alpha$$

## Statistical Analysis

Normality tests were verified using the Shapiro–Wilk normality test. Data were presented as mean with standard deviations when they passed the normality tests; otherwise, data were reported as median with quartiles. For the demographic, clinical, and PSG variables, Mann–Whitney *U*-tests or independent sample *t*-tests were used to analyze quantitative data, and categorical data were compared with Chi-square tests. For the power-spectral analysis, relative power data for each frequency band in each ROI were log-transformed to normalize the data distribution. Repeated measures of analysis of variance (ANOVA) were applied with the group as the independent factor and ROIs as the repeated measures. Additional analyses for the ratios (log-transformed) applied the same ANOVA design. The *p* values were adjusted using the Huynh-Feldt correction of sphericity. Simple effect analyses were conducted for decomposing significant interactions. ROC curves were calculated to evaluate the sensitivity and specificity of the ratios in predicting the phenoconversion of iRBD patients. Optimal cutoff values were yielded when the largest Youden index was achieved. Additionally, ROC analysis was performed to assess the predictive ability of RBD severity, as assessed with RBD-HK and RWA. All the statistical analyses were performed with IBM SPSS Statistics, version 24.0, 64-bit (IBM Corporation, Armonk, NY, USA), and *p* < 0.05 was regarded statistically significant.

## Results

### Demographics and Polysomnographic Variables

In total, 65 iRBD patients were included in this study. At follow-ups, 22 patients eventually developed a neurodegenerative disease. Of the 22 patients, 15 were diagnosed as PD, 1 developed MSA, 2 developed AD, and 4 developed MCI. The average age at RBD diagnosis was  $67.64 \pm 8.27$  years old, and 17 (77.27%) were male. The mean follow-up duration was  $6.64 \pm 2.48$  years, and RBD symptoms preceded the onset of the neurologic symptoms at approximately five years. At the baseline, no significant difference was observed in body mass index (BMI), RBD-HK and its subfactors, RBDSQ, MMSE, MoCA, or ESS between the iRBD-C and iRBD-NC groups (Table 1).

iRBD phenoconverters had a shorter total sleep time (TST, *p* < 0.001), lower stage 2 sleep percentage (*p* = 0.044), more PLM-NREM (*p* = 0.032), and more PLMArI (*p* = 0.004) compared to the iRBD-NC group (Table 2). Moreover, the iRBD-C group exhibited significantly increased chin %tonic EMG activity (*p* = 0.040), and higher REM density during the third REM episode (*p* = 0.034) compared to the iRBD-NC group (Table 3).

Additionally, ROC analyses revealed that RBD severity, as assessed with RBD-HK (Area Under the Curve, AUC = 0.555, *p* = 0.471), was not the predictor of neurodegeneration in iRBD.

### EEG Power-Spectral Analysis

#### Relative Power

A significant group-by-REM sleep-state interaction was found in the alpha, alpha2, and delta bands. Further simple effect analyses demonstrated a significant decrease in alpha, alpha1, alpha2, beta, beta1, and sigma and increased delta power in phasic REM sleep in the iRBD-C group (Figure 1).

During phasic REM sleep, the iRBD-C group showed lower alpha, alpha1, and alpha2 and higher delta power in the central and occipital regions compared to the iRBD-NC group. Additionally, the iRBD-C group exhibited lower frontal alpha, alpha1 power, occipital beta, and sigma power than the iRBD-NC group. During tonic REM sleep, iRBD phenoconverters exhibited lower alpha, beta1, and sigma power in occipital areas (Figure 2).

#### Slow-to-Fast Frequency Ratios

More generalized EEG slowing was observed during the phasic period in iRBD phenoconverters compared to the iRBD-NC group. Specifically, the iRBD-C group exhibited a higher ratio1, ratio2, and ratio4 in central and occipital regions during phasic REM sleep and a higher ratio1, ratio3 and ratio4 only in occipital regions during tonic REM sleep than the nonconverted group (Figure 3).

**Table 1** Demographic and Clinical Characteristics

	iRBD-C (n=22)	iRBD-NC (n=43)	p value
Age at RBD diagnosis, y	67.64±8.27	65.05±9.56	0.284
Age at RBD symptoms onset, y	62.14±9.42	60.08±10.91	0.455
Age at neurologic symptoms onset, y	69.80±8.51	—	—
Age at neurologic disease diagnosis, y	70.82±8.70	—	—
Follow-up duration from RBD diagnosis, y	6.64±2.48	5.42±2.33	0.056
Duration from RBD symptoms to neurologic symptoms onset, y	5.00 (2.50–8.25)	—	—
Duration of RBD symptoms at RBD diagnosis, y	2.75 (1.00–5.00)	4.50 (1.50–6.63)	0.362
Education, y	8.50±3.22	10.05±3.89	0.114
BMI	24.58±2.94	22.13±6.98	0.120
Gender, % male	77.27	74.42	0.802
ESS	5.50 (4.00–9.25)	6.00 (2.00–9.00)	0.457
RBD-HK	35.50 (25.50–43.50)	32 (23.00–38.00)	0.470
Factor I	18.00 (14.00–20.00)	16.00 (11.00–21.00)	0.744
Factor II	17.50 (12.25–22.25)	16.00 (8.00–20.00)	0.486
RBDSQ	6.00 (4.50–8.00)	6.00 (3.00–8.00)	0.618
MMSE	28.00±1.27	28.12±1.53	0.761
MoCA	24.18±2.38	24.53±2.07	0.539

**Notes:** iRBD-C refers to the group of patients with idiopathic rapid eye movement sleep behavior disorder (iRBD) who have converted to neurodegenerative diseases. iRBD-NC refers to the group of iRBD patients who remained disease-free.

**Abbreviations:** iRBD, idiopathic rapid eye movement sleep behavior disorder; BMI, body mass index; ESS, Epworth Sleepiness Scale; RBD-HK, rapid eye movement sleep behavior disorder questionnaire—Hong Kong; RBDSQ, rapid eye movement sleep behavior disorder Screening Questionnaire; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

**Table 2** Comparisons of Polysomnographic Variables Between iRBD Patients Who Have Converted and Those Who Remained Disease Free

	iRBD-C (n=22)	iRBD-NC (n=43)	p value
TST, min	313.57±81.99	397.19±84.18	<b>&lt;0.001</b>
Sleep latency, min	21.50 (4.50–32.00)	9.50 (2.50–28.50)	0.194
REM sleep, min	50.00 (38.75–76.75)	71.50 (42.00–105.75)	0.118
REM sleep latency, min	115.25 (83.75–160.75)	131.50 (65.25–177.50)	0.972
N1, min	63.00 (36.75–117.13)	64.50 (39.00–91.25)	0.450
N2, min	125.96±44.25	193.91±78.37	<b>&lt;0.001</b>
N1, %	26.15 (12.55–36.13)	15.80 (11.10–23.15)	0.074
N2, %	40.14±11.34	47.94±15.77	<b>0.044</b>
REM sleep, %	15.90 (12.40–23.83)	17.10 (10.80–24.65)	0.750
Sleep efficiency, %	66.07±18.13	74.49±15.04	0.134
Slow wave sleep, %	17.20 (10.95–22.48)	13.80 (7.35–23.95)	0.358
AHI	1.60 (0.00–8.78)	2.60 (0.00–19.00)	0.187
Arl	5.55 (3.23–10.18)	6.60 (2.65–10.35)	0.972
WASO	21.00 (14.75–29.00)	31.00 (16.00–38.50)	0.097
PLMS	9.00 (0.00–40.53)	0.00 (0.00–16.30)	0.063
PLM-NREM	17.95 (0.00–52.20)	0.00 (0.00–15.55)	<b>0.032</b>
PLM-REM	0.00 (0.00–19.10)	0.00 (0.00–7.15)	0.250
PLMArl	0.20 (0.00–1.43)	0.00 (0.00–0.00)	<b>0.004</b>

**Notes:** iRBD-C refers to the group of patients with idiopathic rapid eye movement sleep behavior disorder (iRBD) who have converted to neurodegenerative diseases. iRBD-NC refers to the group of iRBD patients who remained disease-free. Bold values denote statistically significant difference ( $p < 0.05$ ).

**Abbreviations:** iRBD, idiopathic rapid eye movement sleep behavior disorder; TST, total sleep time; REM, rapid eye movement; WASO, wake-after-sleep onset; N1, non-REM stage 1; N2, non-REM stage 2; AHI, apnea-hypopnea index; ArI, arousal index; PLMS, periodic limb movements during sleep; PLM-NREM, periodic limb movements during non-REM sleep; PLM-REM, periodic limb movements during REM sleep; PLMArI, periodic leg movement related arousal index.

**Table 3** Comparisons of RWA and REMD Variables Between iRBD Patients Who Have Converted and Those Who Remained Disease Free

	iRBD-C (n=22)	iRBD-NC (n=43)	p value
Phasic REM, %	38.39 (29.74–57.32)	34.92 (28.48–48.30)	0.233
Tonic REM, %	41.98 (24.64–61.43)	36.01 (15.41–55.56)	<b>0.040</b>
REM density	5.75 (3.33–7.30)	5.10 (3.63–8.28)	0.734
REM density in 1st REM period	3.78 (3.03–8.13)	4.65 (3.40–7.83)	0.519
REM density in 2nd REM period	5.73 (2.08–8.20)	4.45 (1.62–6.40)	0.321
REM density in 3rd REM period	5.36 (1.27–7.85)	3.00 (0.00–4.32)	<b>0.034</b>
REM density in 4th REM period	1.65 (0.00–4.43)	0.00 (0.00–3.00)	0.220
REM density in 5th REM period	0.00 (0.00–4.31)	0.00 (0.00–1.27)	0.461
REM density in 6th REM period	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.308

**Notes:** iRBD-C refers to the group of patients with idiopathic rapid eye movement sleep behavior disorder (iRBD) who have converted to neurodegenerative diseases. iRBD-NC refers to the group of iRBD patients who remained disease-free. Bold values denote statistically significant difference ( $p < 0.05$ ).

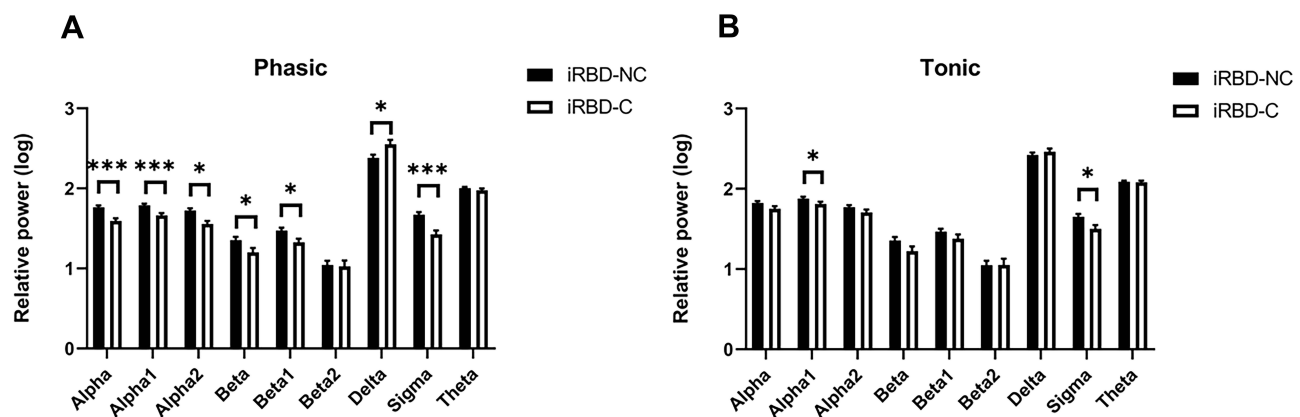
**Abbreviations:** RWA, rapid eye movement sleep without atonia; REMD, rapid eye movement density; iRBD, idiopathic rapid eye movement sleep behavior disorder; REM, rapid eye movement.

ROC analyses revealed that ratio1 ( $((\delta + \theta)/(\alpha + \beta))$ ) in the occipital areas during phasic REM sleep turned out to be the best predictor of iRBD phenoconversion, yielding an AUC of 0.749 (95% CI 0.625 to 0.874), with the optimal cutoff value of 2.204 (Figure 4). Further details of other predictors are included in Table 4.

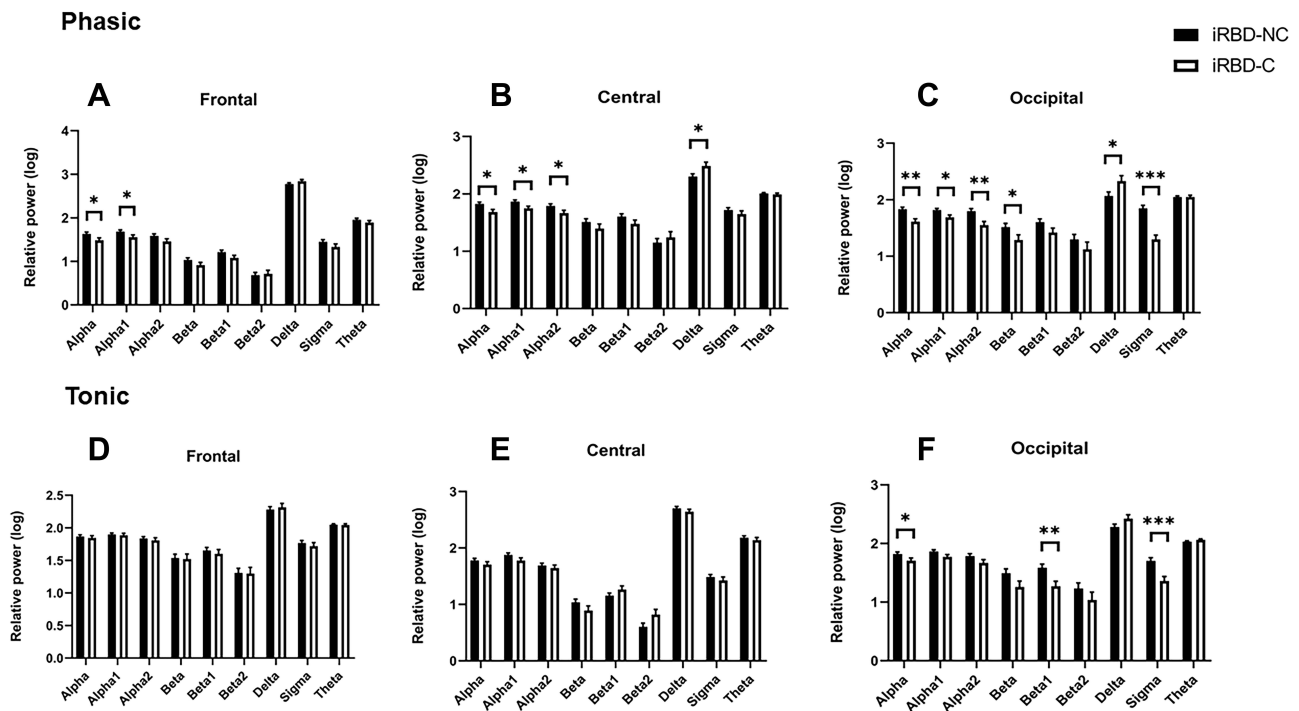
## Discussion

In this retro-prospective study, iRBD patients characterized by EEG slowing, especially in a more generalized, slowing manner during phasic REM sleep, were more likely to develop neurodegenerative diseases. This study provided evidence that generalized EEG slowing during phasic REM sleep, instead of RBD severity assessed with RBD-HK, in iRBD patients may potentially be the early marker of neurodegeneration in iRBD.

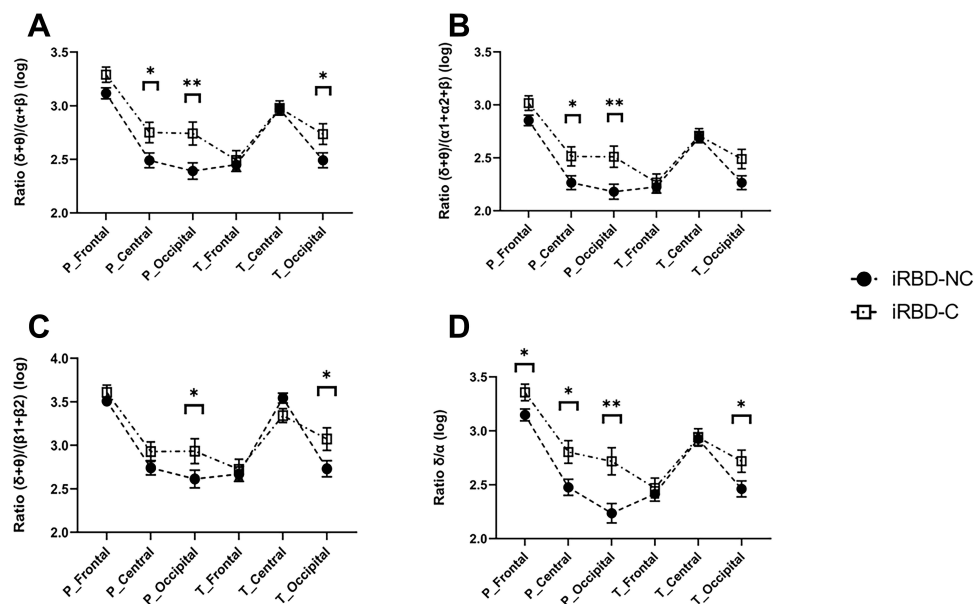
Consistent with results from previous longitudinal studies, EEG slowing was found in iRBD patients with later development of cognitive declines<sup>41</sup> and in PD patients with progression into PD with dementia.<sup>42</sup> This was further supported by a recent study showing that parameters of transcranial magnetic stimulation were positively correlated with cognitive functions in patients with parkinsonian syndrome.<sup>43</sup> Additionally, waking EEG slowing was also proved as the biomarker of neurodegeneration in iRBD.<sup>13</sup> In this study, generalized EEG slowing also was observed in iRBD phenoconverters. However, our study also indicated that EEG slowing was demonstrated in a more generalized way during the phasic period. The plausible reasons for this phenomenon are twofold. Firstly, the widely distributed slow oscillations during phasic periods may assist in the disconnection from the external environment.<sup>44</sup> A second factor is



**Figure 1** Comparisons of the relative power between the iRBD-C and the iRBD-NC group during (A) phasic REM sleep and (B) tonic REM sleep. Results are stated as mean  $\pm$  standard error of the mean. \*Denotes  $p < 0.05$ ; \*\*\*Denotes  $p < 0.001$ .



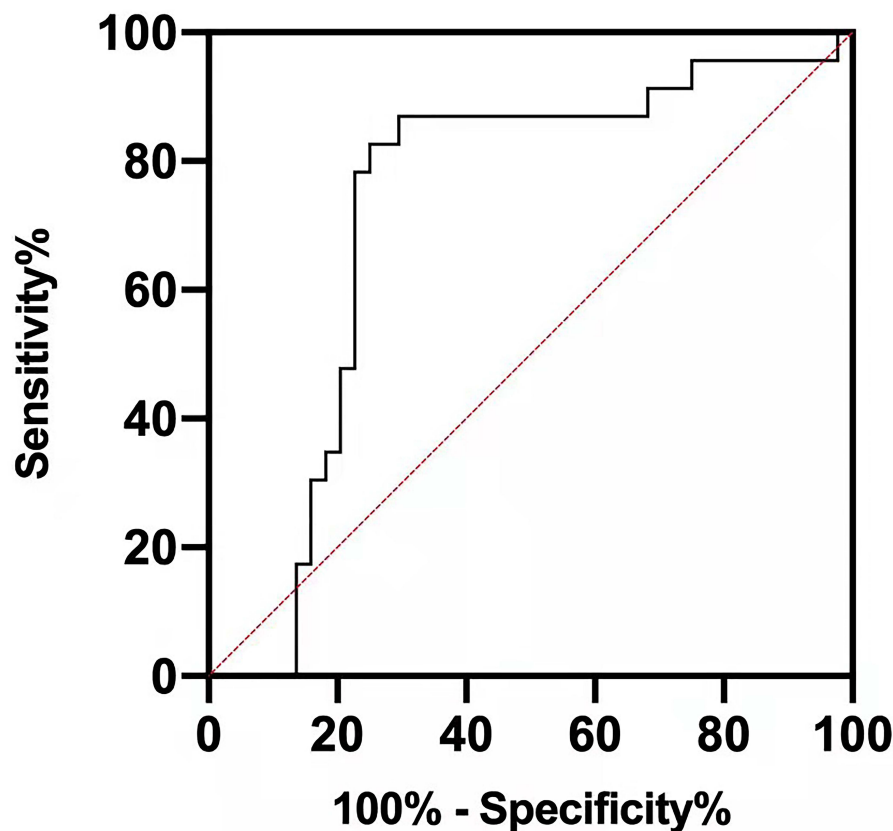
**Figure 2** Comparisons of the relative power between the iRBD-C and the iRBD-NC group during (A–C) phasic REM sleep and (D–F) tonic REM sleep in three regions of interest (frontal, central and occipital) respectively. Results are stated as mean  $\pm$  standard error of the mean. \*Denotes  $p < 0.05$ ; \*\*Denotes  $p < 0.01$ ; \*\*\*Denotes  $p < 0.001$ .



**Figure 3** Comparisons between the iRBD-C and the iRBD-NC group on four slow-to-fast ratios (A–D). Results are stated as mean  $\pm$  standard error of the mean. \*Denotes  $p < 0.05$ ; \*\*Denotes  $p < 0.01$ .

**Notes:** P\_Frontal refers to the ratio in frontal regions during the phasic REM sleep, P\_Central refers to the ratio in central regions during the phasic REM sleep, P\_Occipital refers to the ratio in occipital regions during the phasic REM sleep, T\_Frontal refers to the ratio in frontal regions during the tonic REM sleep, T\_Central refers to the ratio in central regions during the tonic REM sleep, T\_Occipital refers to the ratio in occipital regions during the tonic REM sleep.

that this pattern of slow oscillations may reflect Ponto-Geniculo-Occipital waves,<sup>45</sup> which are closely related to the dreaming experience in the phasic state.<sup>46</sup> Further studies to delve into the microarchitecture of REM sleep may provide novel insight into the underlying mechanisms of neurodegeneration in iRBD.



**Figure 4** ROC curves of ratio I in the occipital regions during phasic REM sleep.

In alignment with previous studies,<sup>13,41,42,47–49</sup> the EEG slowing pattern demonstrated increased delta power and decreased alpha and beta power. Further research<sup>49</sup> showed that decreased beta power during phasic periods indicated abnormal motor-cortex activation. Therefore, it is conceivable that iRBD patients with abnormal motor-cortex activation are more likely to develop neurodegeneration, which is supported by the study demonstrated that iRBD patients exhibited changes of motor evoked potential markers of inhibition and facilitation.<sup>50</sup> Moreover, our results showed that the iRBD-C group exhibited a decrement in frontal, central, and occipital alpha power during the phasic period, resembling the

**Table 4** Results of ROC Curves of Candidate Biomarkers

	Cut-off Value	AUC	Sensitivity	Specificity	95% CI	p value
P_F_I	3.157	0.651	0.864	0.535	0.520–0.782	0.047
P_F_4	3.083	0.659	0.909	0.419	0.529–0.788	0.038
P_C_4	3.011	0.654	0.455	0.837	0.510–0.798	0.043
P_O_I	2.204	<b>0.749</b>	0.864	0.744	0.625–0.874	0.001
P_O_2	1.991	0.744	0.909	0.698	0.616–0.872	0.001
P_O_4	2.019	0.727	0.864	0.767	0.591–0.864	0.003
T_O_I	2.411	0.689	0.682	0.767	0.552–0.827	0.013
T_O_2	2.158	0.678	0.682	0.744	0.537–0.818	0.020
T_O_3	2.656	0.682	0.727	0.767	0.543–0.821	0.017
T_O_4	2.306	0.700	0.682	0.721	0.568–0.831	0.009

**Notes:** P\_F\_I, ratio I in frontal regions during phasic REM sleep; P\_F\_4, ratio 4 in frontal regions during phasic REM sleep; P\_C\_4, ratio 4 in central regions during phasic REM sleep; P\_O\_I, ratio I in occipital regions during phasic REM sleep; P\_O\_2, ratio 2 in occipital regions during phasic REM sleep; P\_O\_4, ratio 4 in occipital regions during phasic REM sleep; T\_O\_I, ratio I in occipital regions during tonic REM sleep; T\_O\_2, ratio 2 in occipital regions during tonic REM sleep; T\_O\_3, ratio 3 in occipital regions during tonic REM sleep; T\_O\_4, ratio 4 in occipital regions during tonic REM sleep. Bold value denotes the largest value of the AUC among candidate markers.  
**Abbreviations:** ROC, receiver operating characteristic; AUC, area under the curve.

information processing during wakefulness.<sup>51</sup> Of note, occipital alpha power decreased during phasic periods was interpreted as visual-cortex activation associated with mental imagery processing.<sup>52,53</sup> Thus, iRBD patients with more pronounced visual-cortex activation are more susceptible to conversion into neurodegenerative diseases. Furthermore, the iRBD-C group showed an increment in delta power during phasic REM periods in this study. In fact, the low-frequency oscillations, including delta-power oscillations, represent EEG slowing. Notably, delta power increased in phasic states, denoted a deep sleep.<sup>20</sup> Additionally, our results demonstrated that iRBD phenoconverters displayed a decrease in sigma power during both the phasic and tonic states. In line with our results, a reduction of sleep-spindle activities was observed during NREM sleep state in AD, PD, iRBD, and PD patients who later developed dementia.<sup>54–56</sup> Researchers also proposed that decreased sleep-spindle activities in iRBD may involve impaired thalamocortical networks, reflecting early neurodegenerative changes.<sup>57</sup> However, to the best of our knowledge, few researchers have investigated the role of sleep-spindle activity during the REM state, especially during the phasic and tonic periods, respectively, in iRBD phenoconversion in a longitudinal context. Further studies with a larger sample size on this topic are warranted. Taken together, iRBD patients who were susceptible to converting to neurodegenerative diseases exhibited prominent motor- and visual-cortex activation and impaired thalamocortical networks at the baseline.

The specific pathogenesis of iRBD has not yet been fully understood. Briefly, converging evidence has shown that a complex but integrative neuronal system has been responsible for the pathophysiology of iRBD,<sup>58</sup> involving the sublaterodorsal tegmental nucleus,<sup>59</sup>  $\gamma$ -aminobutyric acid and glycine-containing neurons of the ventral medulla,<sup>60,61</sup> the cortical limbic system,<sup>62</sup> and the supplementary motor area bypassing the basal ganglia.<sup>63</sup> Our findings echo several studies, supporting the notion that cortical abnormalities are involved in iRBD. In particular, imaging studies demonstrated the motor pathway and generator responsible for dream-enacting behaviors.<sup>63,64</sup> Moreover, structural MRI measures showed that iRBD patients exhibited diffuse decreased cortical thickness in the frontal, parietal, and occipital cortex and lingual gyrus and fusiform gyrus.<sup>65–67</sup> Collectively, this study provided additional electrophysiological evidence for the involvement of cortical networks, including the motor- and visual-cortex and thalamocortical networks as mentioned above, in the pathophysiology of iRBD.

The results showed that iRBD phenoconverters tend to have less TST, stage 2 sleep, more PLMArI, and PLM-NREM than those who remained disease-free. In fact, previous longitudinal studies revealed a reduction in REM-sleep percentage in iRBD phenoconverters<sup>13</sup> and a decrease in stage 2 duration in PD patients who later developed dementia.<sup>42</sup> However, our findings concur with prior studies that found similar sleep macrostructure changes in PD patients compared to controls,<sup>68</sup> indicating early neurodegeneration in iRBD.

In addition, our study revealed that iRBD patients who have later developed neurodegenerative diseases exhibited significantly increased %tonic EMG activity and REMD in the third REM episode compared to those who remained disease-free. As for RWA, our results were consistent with previous findings, which indicated that increased tonic EMG activity could serve as a stable marker of neurodegeneration in iRBD.<sup>10–12</sup> The significant increase in REMD only during the third REM episode may indicate that this unique pattern becomes obvious during the late stage of REM sleep since the REM-sleep duration becomes longer as the night goes on.

We proposed that RBD severity, as assessed with RBD-HK, was not the predictor of the conversion to neurodegenerative diseases in iRBD patients, which has not been reported in previous literature. Notably, our study suggests that the optimal time for neuroprotective interventions would be when EEG slowing is observed instead of simply based on RBD severity. Therefore, performing PSG several times when RBD symptoms are noted is highly recommended.

The strengths of this study lie in the relatively comprehensive analyses of REM-sleep-related features derived from PSG data in iRBD patients. Moreover, the iRBD patients included in this study underwent a relatively lengthy follow-up duration, contributing to the accurate outcome prediction. Furthermore, our study provided evidence for the choice of timing of neuroprotective treatment.

There are several limitations of this present study. First, for a small proportion of the patients, their disease status was defined based on cognitive tests or a telephone interview with the physician. Nevertheless, an agreement between neurological specialists was obtained if necessary to minimize diagnostic errors. Second, diagnosis of the disease lacked the evidence from postmortem studies. Third, the sample size is relatively small, and thus subgroup analyses

were precluded. Also, selection bias should be considered since the patients were from one sleep center, and thus were not representative of all iRBD patients in the population. Moreover, the possibility of recall bias cannot be totally excluded. Finally, high-density EEG data are not available due to the shortage of the equipment at that time.

## Conclusion

In summation, this study indicated that the presence of EEG slowing, especially the more generalized EEG slowing during phasic REM sleep, could serve as the stable biomarker of neurodegeneration in iRBD. It is noteworthy that iRBD patients susceptible to converting to neurodegenerative diseases exhibited prominent motor- and visual-cortex activation and impaired thalamocortical networks at the baseline. Additionally, our results suggest that RBD severity was not the predictor of phenoconversion in iRBD. Therefore, we propose that undertaking PSG several times after the onset of RBD symptoms is essential for choosing the time point to conduct neuroprotective therapies. Nonetheless, further studies with a larger sample size exploring the probability of RBD severity as the biomarker in predicting neurodegeneration in iRBD are warranted.

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## Disclosure

The authors report no conflicts of interest for this work.

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