RESEARCH ARTICLE

Subthalamic γ Oscillation Underlying Rapid Eye Movement Sleep Abnormality in Parkinsonian Patients

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ABSTRACT: Background: Abnormal rapid eye movement (REM) sleep, including REM sleep behavior disorder (RBD) and reduced REM sleep, is common in Parkinson's disease (PD), highlighting the importance of further study on REM sleep. However, the biomarkers of REM disturbances remain unknown, leading to the lack of REM-specific neuromodulation interventions.

Objective: This study aims to investigate the neurophysiological biomarkers of REM disturbance in parkinsonian patients.

Methods: Ten PD patients implanted with bilateral subthalamic nucleus-deep brain stimulation (STN-DBS) were included in this study, of whom 4 were diagnosed with RBD. Sleep monitoring was conducted 1 month after surgery. Subthalamic local field potentials (LFP) were recorded through sensing-enabled DBS. The neurophysiological features of subthalamic LFP during phasic and tonic microstates of REM sleep and their correlation with REM sleep fragmentation and RBD were analyzed.

Results: Differences in subthalamic γ oscillation between phasic and tonic REM correlated positively with the severity of REM sleep fragmentation. Patients with RBD also exhibited stronger γ oscillations during REM sleep compared with non-RBD patients, and both increased β and γ were found before the onset of RBD episodes. Stimulation changes in simulated γ-triggered feedback modulation followed more closely with phasic REM density, whereas an opposite trend was found in simulated β-triggered feedback modulation.

Conclusion: Excess subthalamic γ oscillations may contribute to REM instability and RBD, suggesting that γ oscillation could serve as a feedback signal for adaptive DBS for REM sleep disorders. © 2024 The Author(s). *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: rapid eye movement (REM) sleep; deep brain stimulation (DBS); subthalamic nucleus (STN); local field potential (LFP)

The association between disorders in rapid eye movement sleep (REM sleep) and Parkinson's disease (PD) has long been established.[1,2] For instance, REM sleep behavior disorder (RBD) is one of the most consistent prodromal signs of PD, indicating a body-first trajectory that α-synuclein aggregation in pontine areas may precede depletion in the substantia nigra.[3] Several studies have also demonstrated REM sleep

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architecture disturbances such as decreased total REM duration and stability, and reduced REM density in PD patients,[4-7] highlighting the important role of REM sleep in pathogenesis and prognosis of PD.

REM sleep occupies 20% to 25% of nocturnal sleep in healthy adults and is crucial to various essential functions, including brain development, memory, and learning.[8,9] Previous studies considered REM as a homogeneous process,[10] neglecting the two distinct microstates, namely the phasic REM and tonic REM. In brief, phasic REM is characterized by bursts of eye movements, muscle atonia with transient twitches, and irregular vegetative activities, during which emotional and sensorimotor processes dominate. In comparison, tonic REM tends to be quiescent and long segments between phasic REM periods with muscle atonia and lack of eye movement, but showing elevated alertness to external environment.[11-16]

As an essential rhythm in REM, γ oscillations also vary between two microstates, being significantly higher in phasic periods and closely related to cognition and emotional regulation.[16,17] Interestingly, studies of epileptic patients show that phasic REM has an antiepileptic effect compared with NREM and tonic REM,[18,19] whereas elevated amygdaloid γ power has also been found following the rapid eye movements during REM sleep through intracranial electroencephalogram (EEG) recording.[20] As γ oscillation has essential roles in REM sleep, it is not clear whether it has a protective or harmful effect on REM sleep in parkinsonian patients.

On the contrary, subthalamic β oscillations have been proposed as a biomarker of bradykinesia and rigidity in parkinsonian patients.[21] Previous studies have found that β oscillations in both parkinsonian patients and 1-methyl-4-phenyl-1,-2,3,6-tetrahydropyridine (MPTP) nonhuman primate models play an essential role in NREM sleep fragmentation.[22-25] Elevated β oscillations have also been found in REM sleep and correlated with RBD episodes.[26,27] If pathologically elevated β oscillations also exist in REM sleep, it may indicate that NREM and REM sleep, to some extent, can share a common modulation strategy in parkinsonian patients.

To investigate these questions, here in this study we explored the neurophysiological patterns of REM microstates in a group of PD patients based on the concurrent polysomnography (PSG) monitoring and subthalamic (STN [subthalamic nucleus]) local field potential (LFP) recording data during a whole-night sleep. We established a statistical link between subthalamic γ oscillations during phasic REM states and REM sleep fragmentation as well as the occurrence of RBD. These results provide new insights into the mechanisms and referable biomarker of REM sleep disorders in PD.

Patients and Methods

Patient Cohort

Thirteen PD patients were initially included as previously described.[28] All participants underwent bilateral STN electrode implantation (mL301C; Beijing Pins Medical Co., Ltd., Beijing, China) and were connected to a deep brain stimulation (DBS) device that was capable of wireless LFP data acquisition (G106R, Beijing Pins Medical Co., Ltd.). One participant was excluded due to the abnormal high impedance of contacts (>100 kΩ).[28] Another 2 participants were also excluded from the analysis due to the insufficient REM sleep duration (<5 minutes) during the whole-night postsurgical sleep recording (described in detail in the PSG Monitoring and LFP Recording section). Thus, 10 participants were eventually included in this study analysis. The implantation sites were confirmed through presurgical structural magnetic resonance imaging and postsurgical computed tomography. Electrode reconstruction was performed using Lead DBS tool[29] (Fig. S1B).

This study was registered at ClinicalTrials.gov (NCT02937727) and was approved by the ethical committees of the surgical hospitals (Beijing Tiantan Hospital of Capital Medical University, Peking Union Medical College Hospital, and Qilu Hospital of Shandong University). Written informed consent was provided by all participants.

PSG Monitoring and LFP Recording

PSG and simultaneous LFP recordings were performed 1 month post DBS implantation and prior to the initial DBS programming. To minimize pharmacological influences, the patients were withdrawn from long-acting dopaminergic medication for at least 24 hours and from short-acting dopaminergic medication for at least 8 hours. Thus, the patients were in an *off* medication and OFF DBS state. LFP data were real time transmitted, displayed, and stored wirelessly via the sensing-enabled DBS (Pins Medical Co, G106R).[30] More details are listed in Supplementary Materials.

Sleep and REM Evaluation

The sleep stages were manually evaluated by two clinical experts independently according to the guidelines of the American Academy of Sleep Medicine.[10] Sleep stages were labeled as N1, N2, N3, REM, or wake in each 30-second epoch. Two microstates of REM sleep, phasic REM and tonic REM, were defined based on the presence or absence of REMs.[12] More details are listed in Supplementary Materials.

To assess the quality of REM sleep, we examined REM sleep fragmentation and RBD in each subject. Sleep fragmentation index (SFI) of REM sleep was defined as the number of transitions from REM to N1 or wake stage divided by the total REM sleep duration

in hours and can be used to measure the degree of fragmentation of REM sleep process.[31] The RBD diagnosis was made by three experienced physicians (Y.Z., X.Y., and G.Y.) using on video-based PSG monitoring and clinical histories according to the ICD-10-CM: G47.52 criteria.

Data Processing

We used mini-epoch to divide REM microstates and compare the neurophysiological features between microstates of REM sleep, allowing for more precise analysis.[17,32,33] Power spectral density for each LFP mini-epoch was calculated using Welch's method with a 0.5-second Hanning window and a 75% overlap. We defined frequency bands for δ (2–4 Hz), θ (4–9 Hz), α (9–13 Hz), low β (13–20 Hz), high β (20–30 Hz), low γ (30–50 Hz), and high γ (50–80 Hz) power band for further analysis.[34,35] More details of data processing are listed in Supplementary Materials.

Closed-Loop Modulation Simulation

We simulated β- or γ-triggered closed-loop DBS modulation strategies during REM sleep using overnight REM sleep data from a PD subject (subject 4). We calculated the signal features every 2 seconds using Welch's method and then normalized the β (13–30 Hz) and γ (30–80 Hz) power against the total energy across 2 to 80 Hz. Band power was preprocessed with a 30- or 2-second moving average window before the closed-loop algorithm. In our closed-loop algorithm design, stimulation output was controlled within a range of 1 to 2 mA, with an initial value of 1.5 mA. For the γ-triggered algorithm, we defined the upper and lower thresholds using the average γ energy during phasic and tonic REM periods. For the β-triggered control group, we established control thresholds at the 10th and 90th percentiles of normalized β power during REM sleep. A proportional control policy was used where variations in the feedback signal were mapped to stimulation parameters within these thresholds.

Statistical Analysis

We averaged the mini-epoch features from the same microstate of the whole night. Data from two hemispheres in each subject were averaged. Wilcoxon signed-rank test was used to investigate the differences in LFP characteristics between two REM microstates. For multiple comparison, Friedman test with Bonferroni corrections was conducted. A hierarchical mixed-effects model was used to explore the relationship between REM RBD and microstate features, with more details provided in Supplementary Materials. Correlation analyses in this study were conducted using Spearman's rank correlation coefficient. All data processing and statistical analysis were performed using custom-written scripts calling functions from the Signal Processing toolbox and Statistics and Machine Learning toolbox in MATLAB 2022a.

Results

Demographic Characteristics and Sleep Architectures of Recorded Patients

The average age of PD patients included in the study analysis was 56 ± 7.6 years (mean ± SD [standard deviation]), with a female-to-male ratio of 4:6 (details are provided in Tables S1 and S2). The average sleep duration was 283.3 ± 62.18 minutes, with REM sleep occupying 24.61% ± 8.11% (69.6 ± 27.3 minutes). The duration ratio of phasic REM to tonic REM was 6.8% ± 1.67%, which is comparable to the ratio in healthy participants in previous studies.[36] Based on the video-based PSG monitoring, complex motor or vocal behaviors with spontaneous atonia loss during REM stages were recognized in 4 patients. Together with video-PSG recording of RBD episodes and clinical history of repeated dream enactment with complex motor behaviors, the 4 patients were all diagnosed as RBD (Table S3).

Difference in STN LFPs between Phasic and Tonic REM

As shown in Figure 1A,B, phasic REM exhibited elevated power of δ ($P = 0.027$), low γ ($P = 0.002$), and high γ ($P = 0.002$) bands in STN LFPs compared with tonic REM. Functional connectivity of STN LFPs between the two hemispheres was quantified using phase locking value (PLV) and weighted phase lag index (WPLI), and compared between the two REM microstates. During the phasic REM segments, the PLV and WPLI in the high γ band were significantly higher than those in tonic REM segments (PLV: $P = 0.01$, WPLI: $P = 0.004$; Fig. 1C,D; Table S4).

We next compared the β and γ oscillations among the segments of phasic REM, tonic REM, wakefulness after sleep onset (WASO), and daily wakefulness (DW). For the low β oscillations during both phasic and tonic REM, microstates had lower power than the two wakefulness stages ($WASO_{low\ \beta}$ vs. tonic $REM_{low\ \beta}$: $P < 0.001$, $WASO_{low\ \beta}$ vs. phasic $REM_{low\ \beta}$: $P = 0.002$, $DW_{low\ \beta}$ vs. tonic $REM_{low\ \beta}$: $P = 0.006$, and $DW_{low\ \beta}$ vs. phasic $REM_{low\ \beta}$: $P = 0.057$). However, no statistical significance existed for high β oscillations (Fig. 2C,D). Interestingly, high γ oscillations demonstrated elevated power in phasic REM compared with WASO ($WASO_{high\ \gamma}$ vs. phasic $REM_{high\ \gamma}$: $P < 0.001$),

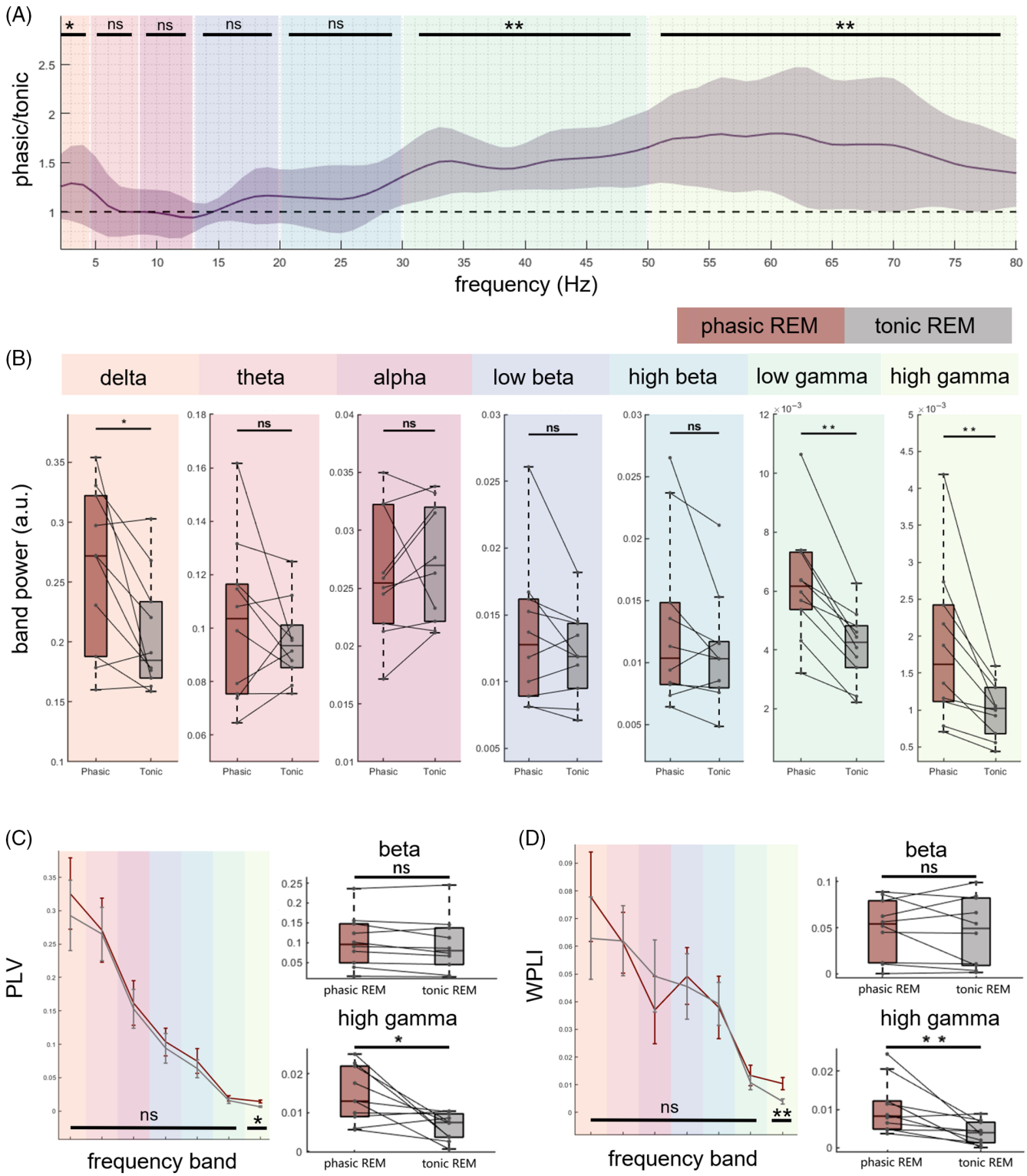


FIG. 1. Comparison of subthalamic local field potentials (LFP) under different rapid eye movement (REM) microstates. (**A**) Spectral power ratio of phasic REM versus tonic REM shows differences among frequency bands. The horizontal dashed line indicates a reference where the ratio is one. The purple shaded area represents the standard deviation (SD). (**B**) Spectral power comparison between two REM microstates. (**C**) Comparison of subthalamic nucleus (STN) LFP PLV between two hemispheres in each subject. (**D**) Comparison of STN LFP WPLI between two hemispheres in each subject. The bar represents the range of SD, and the box plots show the connectivity indices PLV and WPLI in the β (PLV: $P = 0.13$, WPLI: $P = 0.70$) and high γ (PLV: $P = 0.01$, WPLI: $P = 0.004$) frequency bands, respectively. ns, no statistical significance; PLV, phase locking value; WPLI, weighted phase lag index; *$P < 0.05$; **$P < 0.01$. [Color figure can be viewed at wileyonlinelibrary.com]

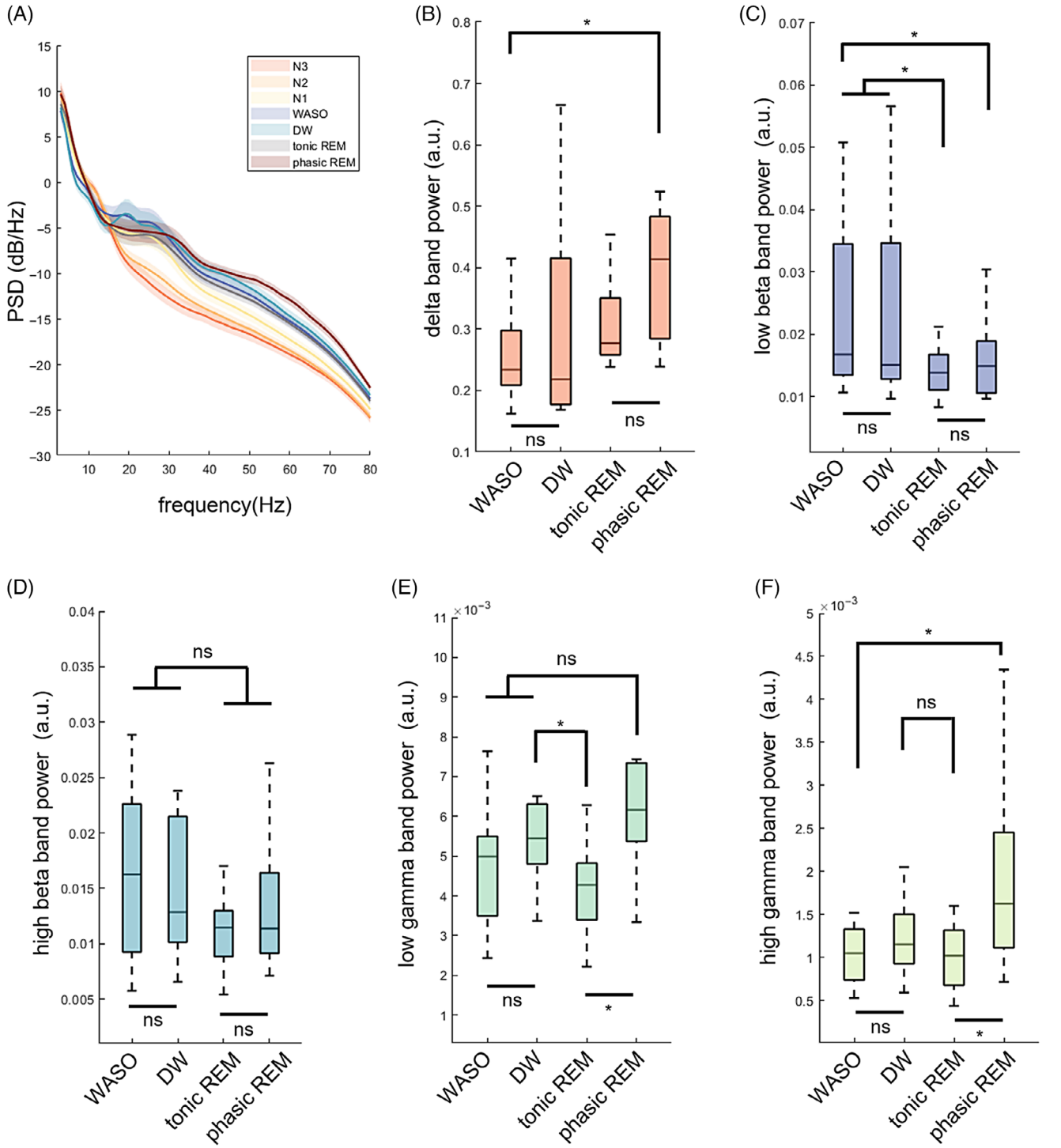


FIG. 2. The relationship between subthalamic nucleus (STN) local field potential (LFP) during rapid eye movement (REM) sleep microstates and wakefulness. (**A**) PSD of STN LFP across different sleep stages. The shaded areas represent the standard error of the mean. (**B**)–(**F**) Comparison among two REM microstates, WASO, and DW in δ, low β, high β, low γ, and high γ oscillations. DW, daily wakefulness; PSD, power spectral density; ns, no statistical significance; WASO, wakefulness after sleep onset; *$P < 0.0083$ (Bonferroni corrected). [Color figure can be viewed at wileyonlinelibrary.com]

whereas the γ oscillations in tonic REM exhibited the lowest compared to WASO or DW, especially in low γ oscillations ($DW_{low\ \gamma}$ vs. tonic $REM_{low\ \gamma}$: $P = 0.002$) (Fig. 2E,F). Taken together, these findings provide further evidence for the heterogeneities in subthalamic activities during REM sleep and support differentiating REM microstates when investigating REM disturbance in PD.

Differences in Subthalamic γ Oscillations between Phasic and Tonic REM Correlated with REM Sleep Fragmentation

As sleep fragmentation is one of the most common clinical manifestations in PD patients,[37] whether the neurophysiological activities of two REM microstates have distinct manifestations in this process remains unknown. To investigate this pathological issue, we first analyzed the relationship between REM microstates and sleep transitions. The phasic REM density was calculated, which is the ratio of phasic REM duration in each 30-second REM epoch. The density of phasic REM prior to N1/wake transitions was much higher than that prior to N2/N3 transitions ($P < 0.05$, Fig. 3A), indicating that the epochs preceding the transition to lighter sleep stages contain a higher proportion of phasic REM.

We next explored the relationship between the REM SFI (SFI_{REM}) and STN LFPs. Although only the correlation between REM SFI and difference in high γ oscillations between two REM microstates (Fig. 3D, Δhigh γ, $r = 0.867$, $P = 0.003$) survived multiple corrections ($P < 0.00625$, Bonferroni correction), positive trends also existed between REM SFI and high γ oscillation power in phasic REM,

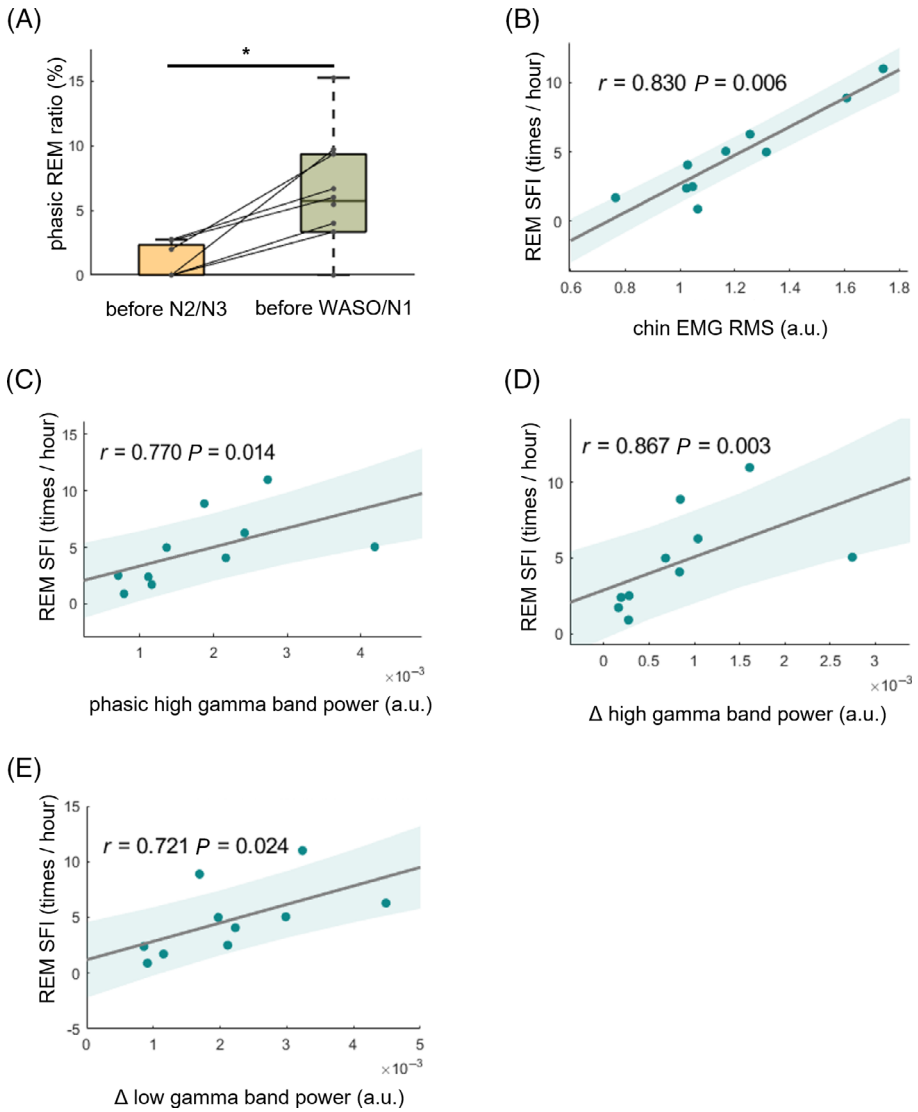
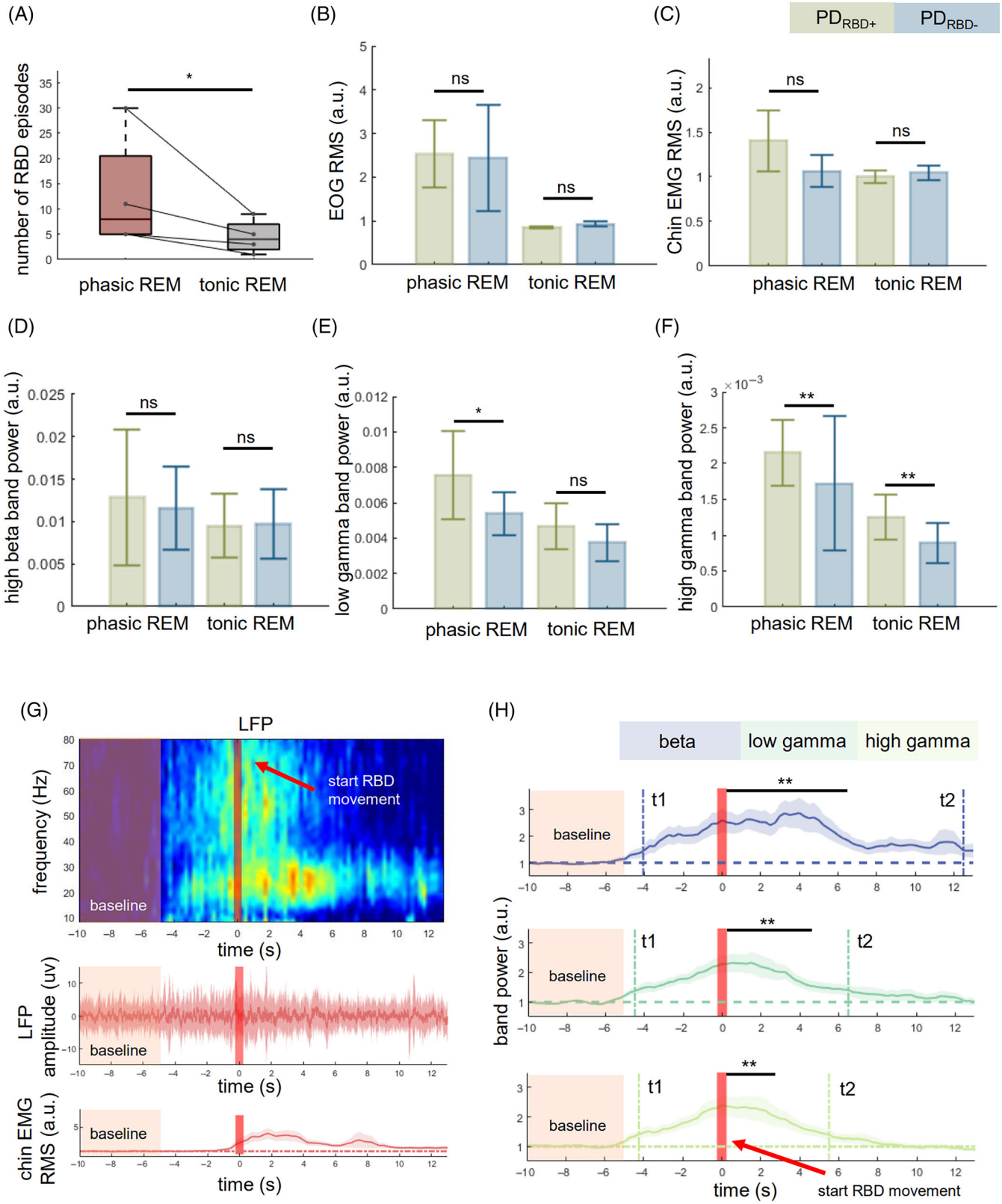


FIG. 3. Correlation of subthalamic γ oscillation in different rapid eye movement (REM) microstates with REM sleep fragmentation. (**A**) Comparison of phasic REM ratio (%) in the 30 seconds before transitioning toward deeper (N2/N3) sleep stages with that before transitioning to the lighter (wake/N1) sleep stages ($P = 0.031$). (**B**) The correlation between REM SFI and chin electromyogram (EMG) RMS. (**C**) The correlation between REM SFI and the power of phasic REM high γ oscillation. (**D**) The correlation between REM SFI and the difference in high γ oscillation power between phasic and tonic REM microstates. (**E**) The correlation between REM SFI and the difference in low γ oscillation power between phasic and tonic REM microstates. The shaded area represents 95% confidence interval of linear fitting. RMS, root mean square; SFI, sleep fragmentation index. [Color figure can be viewed at wileyonlinelibrary.com]

as well as the difference in low γ oscillations between the two REM microstates (Fig. 3C,E, high γ: $r = 0.770$, $P = 0.014$; Δlow γ: $r = 0.721$, $P = 0.024$). Notably, there was no significant trend between β oscillations and REM SFI (Table S5; Fig. S2).



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STN γ Oscillations Are Associated with REM Sleep Behavior Disorder

To explore the interactions among RBD, REM microstates, and STN LFPs, we marked the onset times of each RBD episode based on the video recording in the 4 RBD patients (Table S3). A total of 69 RBD episodes were identified. Consistent with prior research,[38] the majority of RBD episode onset occurred during phasic REM segments ($P < 0.05$, Fig. 4A).

Next, we used the linear mixed-effects model to explore the differences in STN LFPs between patients with (PD_{RBD+}) and without RBD (PD_{RBD-}). We found that PD_{RBD+} exhibited stronger γ oscillations during both phasic and tonic REM microstates throughout the night (Fig. 4E,F, PD_{RBD+} vs. PD_{RBD-}: low γ oscillations: $\beta_{\text{phasic REM}} = 1.52$, $P_{\text{phasic REM}} = 0.045$, $\beta_{\text{tonic REM}} = 1.32$, $P_{\text{tonic REM}} = 0.08$; high γ band oscillations: $\beta_{\text{phasic REM}} = 2.17$, $P_{\text{phasic REM}} = 0.005$, $\beta_{\text{tonic REM}} = 2.00$, $P_{\text{tonic REM}} = 0.009$), whereas no statistical difference was shown in β oscillations. To investigate whether these differences were contaminated by facial movement artifacts, we examined the differences in electrooculogram (EOG) and chin electromyogram (EMG) characteristics between the two microstates. No difference between the two groups of patients was shown in chin EMG RMS or EOG RMS (Fig. 4B,C). These results further validate the accuracy of the findings.

To obtain an in-depth understanding of the role of subthalamic γ oscillations in RBD, we analyzed the event-related changes in the STN LFPs associated with RBD episodes. We first took a 5-second window from −10 to −5 seconds prior to the video-identified start of RBD movement as baseline. The average spectral power of STN LFP (10–80 Hz) before and after RBD episodes was then normalized by the baseline spectrum power. The time points where the normalized β and γ band power exceeded the sum of baseline and twice the SD were figured out. We found that both β and γ oscillations began to synchronize ∼4 seconds before the onsets of RBD movements. However, whereas the synchronization level of β oscillations was maintained during the movement, γ synchronizations attenuated to baseline levels before the decrement of β or the end of the RBD movements (Fig. 4G, upper graph, and H, $t1_{\beta} = -4$ seconds, $t2_{\beta} = 12.5$ seconds; $t1_{\text{low }\gamma} = -4.5$ seconds, $t2_{\text{low }\gamma} = 6.5$ seconds; $t1_{\text{high }\gamma} = -4.25$ seconds, $t2_{\text{high }\gamma} = 5.5$ seconds). To avoid the interference of movement artifacts, we also plotted the changes in the chin EMG channels, of which the trend was not consistent with β and γ oscillations of STN LFPs (Fig. 4G, lower). Overall, these results suggest that the role of subthalamic γ oscillations may differ from that of β in RBD processes and may have more participations in REM sleep disorders.

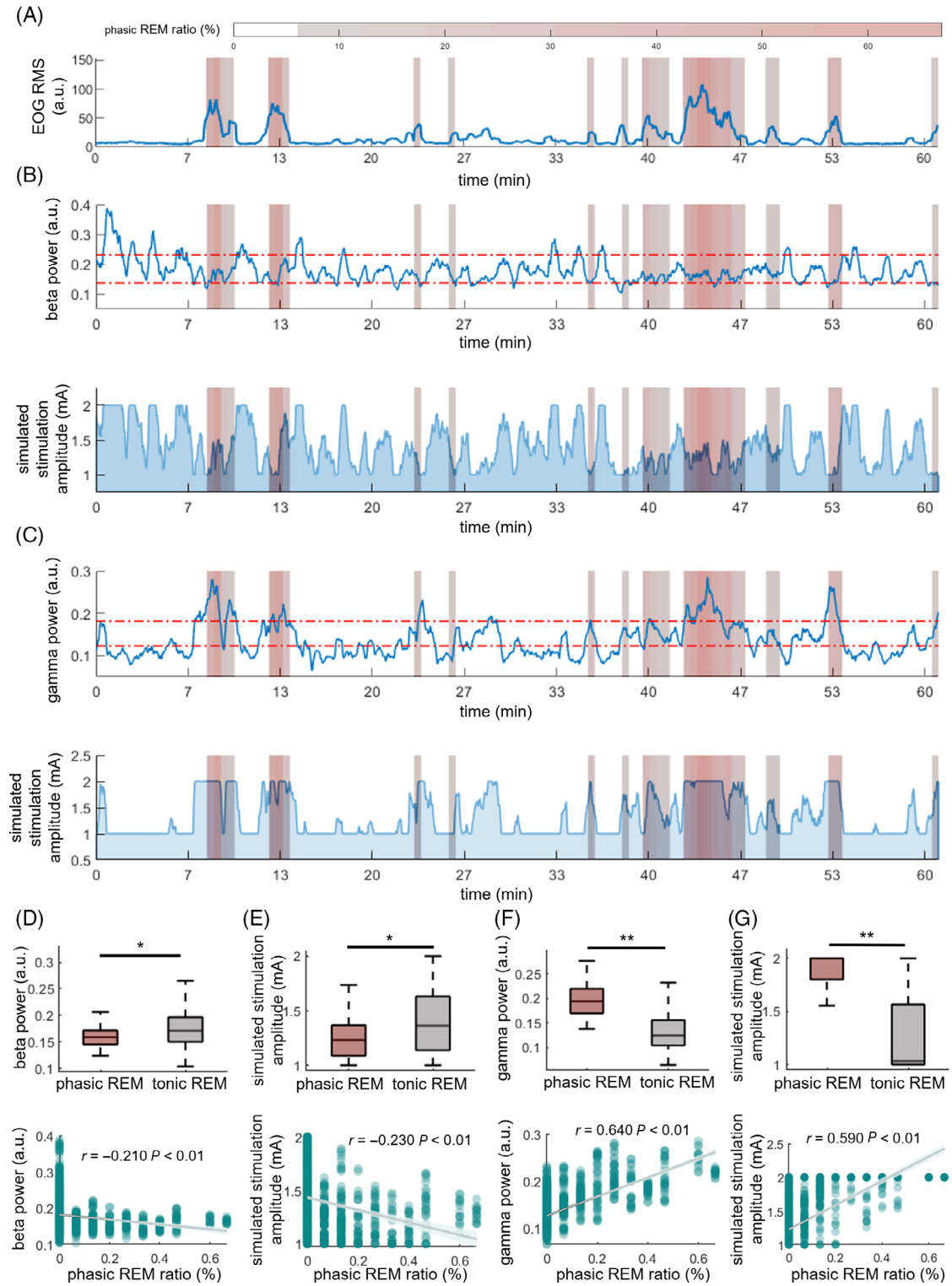
Subthalamic γ Oscillation Patterns Indicate Possible REM Sleep Closed-Loop Modulation Strategies

β-Triggered adaptive DBS has been shown to be promising in increasing efficacy and reducing side effects for PD. Here we showed that γ oscillation during REM sleep might be pathologically underlying REM sleep fragmentation and was also associated with RBD episode. Building on these findings, we assessed adaptive DBS strategies using β or γ oscillations as feedback signals in REM sleep through simulation in one subject (subject 4). The upper and lower thresholds were set based on the β and γ oscillations of REM sleep separately, and a proportional control policy was used to guide the stimulation adjustment. We have conducted the temporally precise simulation with a moving average of 30- and 2-second duration, respectively, corresponding to the commonly used 30-second epochs in sleep monitoring and 2-second epochs in REM microstates. Compared with the β-triggered strategy, the simulated stimulation changes followed more closely with RMS fluctuations of EOG (Fig. 5A–C; Fig. S4A–C) in γ-based modulation. According to the β-triggered feedback strategy, stimulation amplitudes in tonic REM were slightly higher than those in phasic REM ($P = 0.01$, Fig. 5E; $P = 0.01$, Fig. S4E), whereas an opposite trend was shown in γ-based feedback modulation ($P < 0.001$, Fig. 5G; $P < 0.001$, Fig. S4G).

FIG. 4. Microstate characteristics of subthalamic nucleus (STN) local field potential (LFP) in rapid eye movement sleep behavior disorder (RBD). (**A**) Comparison of the numbers of RBD episodes between two REM microstates. (**B**) Comparison of electrooculogram (EOG) root mean square (RMS) between PD_{RBD+} and PD_{RBD-} during two REM microstates. (**C**) Comparison of chin EMG RMS between PD_{RBD+} and PD_{RBD-} during two REM microstates. The shaded areas represent standard error of the mean. (**D**)–(**F**) Comparison of high β, low γ, and high γ band power between PD_{RBD+} and PD_{RBD-} during two REM microstates. (**G**) Average characterization of RBD episodes. The upper graph shows the normalized spectrogram plot of STN LFP (10–80 Hz) before and after the start of RBD episodes. The middle graph shows the average and standard deviation of STN LFP raw signal waveform. The lower graph shows the average RMS of chin EMG. The red line indicates the video scored start time of RBD movement. (**H**) Illustration of the β, low γ, and high γ band power changes before and after the start of RBD movements, with shaded areas representing the standard error of the mean. The time point "t1" and "t2" refer to the first and second time points, respectively, where the normalized band power exceeds the sum of the baseline and twice the SD ($t1_{\beta} = -4$ seconds, $t2_{\beta} = 12.5$ seconds; $t1_{\text{low }\gamma} = -4.5$ seconds, $t2_{\text{low }\gamma} = 6.5$ seconds; $t1_{\text{high }\gamma} = -4.25$ seconds, $t2_{\text{high }\gamma} = 5.5$ seconds). Pairwise comparisons of band power between each 1-second interval post-RBD onset and the baseline. Time ranges with statistical significance are illustrated: β (≤7 seconds), low γ (≤5 seconds), and high γ (≤3 seconds). $^{*}P < 0.05$; $^{**}P < 0.01$. [Color figure can be viewed at wileyonlinelibrary.com]

Discussion

Here in this study, we systematically investigated the subthalamic neurophysiological features during these two REM microstates underlying REM sleep fragmentation and RBD in PD and found that excess γ oscillations in the STN during REM may serve as a biomarker for adaptive DBS modulation in REM sleep disturbance.



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Excess Subthalamic γ Oscillations Associated with REM Sleep Instability

γ Oscillations have long been observed in multiple brain regions during human REM sleep. Previous research using EEG demonstrated elevated γ power in phasic REM compared to tonic REM in healthy individuals, with source localization mainly in fronto-limbic regions associated with emotional and perceptual processing.[39] Intracranial EEG studies also showed elevated γ power in amygdala after the rapid eye movements during REM sleep in epileptic patients.[20] In addition, when receiving auditory inputs, phasic REM with more increased γ oscillation exhibited less cortical activation and higher arousal threshold compared with tonic REM,[40] leading to an inference that γ oscillations in REM may prevent awakening.[35]

In this study, we observed a similar difference between phasic and tonic REM in STN LFPs, as previously reported in EEGs. Contrary to the formal conclusions, we observed that excessive γ oscillation during phasic REM may play additional roles in REM sleep instability in parkinsonian patients. Moreover, in the recorded PD patients, the quantitative relationship between subthalamic γ power during phasic REM and those observed in DW and WASO is also inconsistent with the previous findings that the γ power during wakefulness is the highest.[39] Further studies would be required to verify whether the elevation of subthalamic γ during the phasic period is a cause, an associative phenomenon, or a compensatory mechanism for REM sleep fragmentation, and if they play a role in cognitive functions such as memory consolidation and emotional processing.

On the contrary, not only in NREM sleep but in phasic REM as well exists increased low frequency power with wide synchronization.[41] Such brain rhythms facilitate a more detached state from the external environment and an elevated alertness threshold with auditory interference exposure.[40] Consistent with previous findings in the cortex, a higher subthalamic δ oscillation power was found during phasic REM periods than tonic REM periods, suggesting the function of δ oscillations partially retained in parkinsonian patients' REM sleep.

Notably, sleep differences across genders are still poorly understood. All patients diagnosed with RBD in our study were male even though there are 4 females of the 10 participants recorded in this study. Given the small sample size of this study, we cannot address the potential differences across genders. Previous studies on the gender effect on the prevalence and expression of RBD reported no difference in the prevalence of RBD in male and female patients.[42] However, they showed significant differences in clinical expression, with male patients demonstrating significantly more fights and aggressive behavior during dreams than female patients.[43]

Subthalamic β and γ Oscillations May Involve Differently in REM Sleep Disturbance and Implications in Closed-Loop REM Modulation

Subthalamic β oscillation has long been considered as a key biomarker for bradykinesia and rigidity in PD.[44,45] Recent studies on sleep disorders in PD have identified abnormal β oscillations during sleep. Compared with healthy nonhuman primates, MPTP-induced parkinsonian nonhuman primates exhibited elevated β oscillations in cortical-basal regions during NREM sleep[30] and correlated with the reduction in slow wave oscillations and spindles in parkinsonian states.[46] Similar findings were also shown in human studies,[23,30,47] where β bursts during NREM were also found to be negatively correlated with physiological sleep spindles.[30] Similarly, most existing studies on neuropathology of RBD have also focused on β oscillations. Increased β synchronizations have been reported during RBD episodes in both globus pallidus pars interna and STN of PD patients.[26,27]

In this study, we found that excess γ oscillations, rather than β activities, played a crucial role in REM sleep disturbance. As γ oscillations also have important physiological functions in normal phasic REM sleep, maintaining γ oscillation activities at a physiological level without affecting other frequency bands is crucial, rather than suppressing γ totally. Thus, the conceptual aim of adaptive stimulation during REM sleep is to suppress the overincreasing pathological oscillations while maintaining its normal function during the

FIG. 5. Comparison of simulated β- and γ-triggered closed-loop modulation in rapid eye movement (REM) sleep. (**A**) Root mean square (RMS) fluctuation of the electrooculography channel across the entire night of REM sleep in subject 4. The shaded area represents the percentage of phasic REM. (**B**) Simulated β-triggered closed-loop modulation of REM sleep. The upper graph shows the fluctuation of β power during the whole-night REM sleep. The two red dashed lines indicate the 10th and 90th percentiles of β power throughout the whole-night REM sleep separately. The lower graph shows the simulated output amplitudes over time with proportional control policy. (**C**) Simulated γ-triggered closed-loop modulation of REM sleep. The upper graph shows the fluctuation of γ power during the whole-night REM sleep. The two red dashed lines indicate the average γ power of tonic and phasic REM throughout the whole-night REM sleep separately. The lower graph shows the simulated output amplitudes over time with proportional control policy. (**D**) β (13–30 Hz) power distribution between two REM microstates in the upper figure and its correlation with the phasic REM ratio in the lower figure. (**E**) Simulated stimulation amplitude distribution between two REM microstates in β-triggered closed-loop modulation in the upper figure and its correlation with the phasic REM ratio in the lower figure. (**F**) γ (30–80 Hz) power distribution between two REM microstates in the upper figure and its correlation with the phasic REM ratio in the lower figure. (**G**) Simulated stimulation amplitude distribution between two REM microstates in γ-triggered closed-loop modulation in the upper figure and its correlation with the phasic REM ratio in the lower figure. RMS, root mean square; $^{*}P < 0.05$; $^{**}P < 0.01$. [Color figure can be viewed at wileyonlinelibrary.com]

dynamic process of sleep. A recent study from Shenghong He and colleagues demonstrated that β-triggered adaptive deep brain stimulation (aDBS) effectively suppressed β oscillations while preserving γ activity.[48] This study provides insights into selective oscillation rhythm modulation, and we will further explore whether γ-triggered aDBS may inversely modulate these rhythms by suppressing γ without interfering with other oscillations. The current threshold-based methods and Proportional-Integral (PI) controllers can help suppress pathological oscillations to the correct extent. Indeed, further research would be required to better understand the physiological functions of γ and the normal "range" of γ during REM.

Due to the limitation of the study design, here we demonstrated only a conceptual simulation of the γ-triggered adaptive modulation strategy and demonstrated different modulation effects on phasic and tonic REM microstates comparing with previously proposed β-triggered strategies,[23,46] suggesting that different control strategies may be required for REM sleep versus NREM sleep. In addition, the moving average time window has an impact on stimulation output, with the 2-second moving average leading to more fluctuations of simulated stimulations compared with the 30-second moving average. Therefore, there is a trade-off between capturing the fast changes in the biomarker and minimizing the potential discomfort caused by rapid adjustment of stimulation. Thus, the rationale and the effectiveness of this modulation pattern remain to be confirmed in further studies.

Limitations and Caveats

There are several limitations in our study. First, as a small-sized clinical study, only 10 patients in the *off* medication and OFF DBS status were included in the analysis. Considering the burden on patients, we conducted only one night of sleep recording, which may be influenced by first-night effect of PSG monitoring. The study did not assess individual ratings on sleep quality, thus lacking validation from the perspective of the patients' subjective feelings. Second, although peaks of artifacts observed in both the PSG and LFP recording systems were used for synchronization with manual verification, there still existed synchronization errors between the two systems. Thus, a more refined system synchronization method needs to be developed. Third, due to the lack of longitudinal follow-up, changes in REM sleep microstructures led by chronic DBS stimulation were not discussed in this study. Further study will include more subjects with different treatment states and longer sleep recording time to further study the pathophysiology of sleep disorders in PD and to develop better stimulation protocols to improve sleep in PD.

Conclusion

In conclusion, our data revealed that subthalamic γ oscillations, rather than β oscillations, may underlie REM sleep fragmentation and RBD in PD patients. These results may offer new insight into the pathophysiology of REM sleep disorders and the design of closed-loop modulation strategy. ■

Author Roles: (1) Research project: A. Conception, B. Study design, C. Organization, D. Data collection; (2) Clinical evaluation: A. Patient management and DBS surgical implantation, B Sleep Evaluation; (3) Data analysis: A. Data analysis, B. Verification; (4) Manuscript: A. Writing of the first draft, B. Edition and review of the manuscript.
L.G.: 3A, 3B, 4A, 4B
H.Y.: 1A, 3B, 4A, 4B
Y.C.: 1B, 1D
C.G.: 1D
H.H.: 1C
Y.G.: 2A
S.X.: 2A
Y.Z.: 2B
X.Y.: 2B
G.Y.: 2B
J.Z.: 2A
H.T.: 1A, 3B, 4B
L.L.: 1A, 1B, 1C

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Data

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