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Effects on resting-state EEG phase-amplitude coupling in insomnia disorder patients following 1 Hz left dorsolateral prefrontal cortex rTMS

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Abstract

Despite burgeoning evidence for cortical hyperarousal in insomnia disorder, the existing results on electroencephalography spectral features are highly heterogeneous. Phase-amplitude coupling, which refers to the modulation of the low-frequency phase to a high-frequency amplitude, is probably a more sensitive quantitative measure for characterizing abnormal neural oscillations and explaining the therapeutic effect of repetitive transcranial magnetic stimulation in the treatment of patients with insomnia disorder. Sixty insomnia disorder patients were randomly divided into the active and sham treatment groups to receive 4 weeks of repetitive transcranial magnetic stimulation treatment. Behavioral assessments, resting-state electroencephalography recordings, and sleep polysomnography recordings were performed before and after repetitive transcranial magnetic stimulation treatment. Forty good sleeper controls underwent the same assessment. We demonstrated that phase-amplitude coupling values in the frontal and temporal lobes were weaker in Insomnia disorder patients than in those with good sleeper controls at baseline and that phase-amplitude coupling values near the intervention area were significantly enhanced after active repetitive transcranial magnetic stimulation treatment. Furthermore, the enhancement of phase-amplitude coupling values was significantly correlated with

the improvement of sleep quality. This study revealed the potential of phase-amplitude coupling in assessing the severity of insomnia disorder and the efficacy of repetitive transcranial magnetic stimulation treatment, providing new insights on the abnormal physiological mechanisms and future treatments for insomnia disorder.

KEYWORDS
electroencephalography, insomnia disorder, phase-amplitude coupling, polysomnography, repetitive transcranial magnetic stimulation

1 | INTRODUCTION

According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), insomnia disorder (ID) is defined as difficulty initiating/maintaining sleep, waking too early, and/or nonrestorative sleep. The "hyperarousal" model suggests that ID patients are in neurobiological and psychological states of excessive alertness, as reflected by cortical hyperexcitability during both wakefulness and sleep (Lanza, DelRosso, & Ferri, 2022). Cortical hyperexcitability alters neuronal firing patterns and manifests as abnormal neural oscillations (Fernandez-Mendoza et al., 2016; Huang et al., 2012; Riemann et al., 2010; van der Werf et al., 2010). Previous electroencephalography (EEG) studies mostly used spectral analysis to characterize abnormal neural oscillations in ID patients, that is, higher beta and gamma powers and lower delta, theta, and alpha powers (Merica et al., 1998; Zhao et al., 2021). However, some EEG studies on ID have failed to observe significant differences in spectral power between ID patients and good sleeper controls (GSC) (Chen et al., 2014; Kang et al., 2018; Wu et al., 2013). Therefore, a more reliable and sensitive indicator is required to quantify the abnormal neural oscillations in ID.

One of the unique features of neural oscillations is that rhythms of distinct frequencies exhibit specific coupling properties (Canolty & Knight, 2010; Jensen & Colgin, 2007; Young & Eggermont, 2009). Cross-frequency coupling (CFC), which refers to the statistical relationship between the combination of amplitude and phase of two different frequency bands, is an electrophysiologically derived measure of oscillatory coupling in the brain. Phase-amplitude coupling (PAC), a type of CFC where the phase of a low-frequency rhythm modulates the amplitude of a high-frequency rhythm, is becoming an important indicator of information transmission in the brain (Muthuraman et al., 2020). It constitutes a flexible mechanism for combining information across different temporal scales within local cortical networks and plays a functional role in the execution of cognitive functions (Kikuchi et al., 2017; Malinowska & Boatman-Reich, 2016; Reinhart & Nguyen, 2019; Seymour et al., 2017; Spyropoulos et al., 2018). Concerning sleep disorders, patients with obstructive sleep apnea had significantly lower theta–gamma PAC in the sensorimotor cortex at all sleep stages (Gouveris et al., 2022). Moreover, one study used PAC and amplitude-amplitude coupling (AAC) to classify seven sleep disorders with 74% accuracy (Dimitriadis et al., 2021). Although PAC has not been extensively studied in ID, multiple converging lines of evidence support it as an important synchronization measurement that can be considered a promising marker of the neurophysiological mechanisms of ID.

Cognitive behavioral therapy for insomnia (CBT-I) and pharmacotherapy (benzodiazepines, hypnotics, etc.) are the most frequently recommended and effective interventions for patients with ID. However, CBT-I is limited by adherence issues and high costs, whereas benzodiazepines and hypnotics may cause tolerance, dependence, and addiction (Matthews et al., 2013; Morin et al., 2015). Therefore, new treatment options are needed to reduce ID symptoms or enhance other treatment modalities. Repetitive transcranial magnetic stimulation (rTMS) is a safe, non-invasive brain stimulation technique that shows potential for treating sleep disorders and sleep disorder-related cognitive impairment (Klomjai et al., 2015; Lanza, Fisicaro, Cantone, et al., 2022; Lanza, Fisicaro, Dubbioso, et al., 2022). Low-frequency rTMS over the left dorsolateral prefrontal cortex (DLPFC) showed a significant improvement in sleep quality in ID patients, although with inconsistent findings (Zhang et al., 2018). However, the neurophysiological mechanisms underlying the therapeutic effects of rTMS in ID remain poorly understood (Babiloni et al., 2021). Recently, rTMS has shown promising therapeutic potential in multiple neurological conditions, such as Parkinson's disease, stroke, and epilepsy (Assenza et al., 2017). Therefore, studies are needed to address the important gap and provide evidence for the use of rTMS to treat ID.

Based on the above-described body of evidence, we conducted a double-blind, sham-controlled trial to study the efficacy of DLPFC-rTMS in the treatment of ID and explore the associated neural mechanisms. We hypothesized that (1) significant differences in PAC values would be observed in ID patients and GSC at baseline, (2) active rTMS treatment would modulate abnormal PAC values in ID patients, and (3) the enhancement of PAC values was significantly correlated with improvements in sleep quality.

2 | MATERIALS AND METHODS

2.1 | Participants

Sixty patients were enrolled in this study at the Second Hospital of Hebei Medical University, Shijiazhuang, China. The inclusion criteria were as follows: (1) age 18–65 years, (2) right-handed, (3) meeting the diagnostic criteria for ID in the DSM-V, (4) a total score of ≥5 on the Pittsburgh Sleep Quality Index (PSQI) at screening, a total score of ≥8 on the insomnia severity index (ISI) at screening, and (5) signed

informed consent. The exclusion criteria were as follows: (1) other comorbid mental disorders, (2) serious neurological or medical diseases, (3) other sleep disorders, (4) frequent jet lag, (5) Epworth Sleepiness Scale (ESS) score > 11, (6) Beck Depression Index (BDI) score > 20 or Beck Anxiety Index (BAI) score > 45, (7) pregnancy, lactation, or plans to become pregnant during the study period, (8) structural brain abnormalities based on magnetic resonance imaging (MRI), and (9) use of psychiatric medication, hypnotics, or having been treated with CBT-I in the last 2 weeks.

Forty healthy subjects were also enrolled in the GSC group. The inclusion criteria were as follows: (1) Aged 18–65 years, (2) right-handed, (3) no symptoms or history of psychiatric disorders and sleep disorders, (4) a total score <5 on the PSQI at screening and a total score <8 on the ISI at screening, and (5) not taking any psychotropic medications or hypnotics during their lifetime.

Steps to exclude subjects of ID or GSC suffering from other sleep disorders are as follows. First, the doctor will ask the subject in person if he/she has obstructive sleep apnea syndrome, restless legs syndrome, and other diseases, while the subject will fill out scales such as BDI, BAI, ESS, Mini-Mental State Examination (MMSE), and Montreal Cognitive Assessment (MoCA). Subjects who score within the normal range on these scales will be allowed to join the group.

2.1.1 | Experimental design

Enrolled ID patients were randomized into the active treatment group ($n = 30$) and sham treatment group ($n = 30$). As shown in Figure 1a, 20 active or sham sessions of left DLPFC rTMS stimulation were delivered over four consecutive weeks (five times/week). Sixty ID patients underwent behavioral assessments, resting-state EEG recordings, and full-night sleep polysomnography (PSG) recordings before and after active or sham rTMS treatment. Forty GSC were subjected to the same assessment. Behavioral assessments included the PSQI, ISI, ESS, BDI, BAI, MMSE, and MoCA.

Two subjects in the active treatment group and one in the good sleeper control group withdrew from the experiment for personal reasons. The final numbers of participants in the experiment were 39 (good sleeper control group), 28 (active treatment group), and 30 (sham treatment group).

2.2 | rTMS procedure for ID patients

A pulsed magnetic stimulation device (M-100 Ultimate; Shenzhen Yingchi Technology Co. Ltd., Shenzhen, China) was used for rTMS therapy in ID patients. Stimulation was performed with a figure-of-eight stimulation coil at the left DLPFC (site: Cz to the left 3–5 cm, forward 5 cm). The following stimulation parameters were used (Zhang et al., 2018): stimulus frequency, 1 Hz; stimulus intensity, 80% of the motion threshold (motion threshold defined as the lowest stimulation power that can produce five finger movements out of 10 stimuli), stimulation number 10 pulses/string, string interval 2 s, a total of 150 strings, total stimulation pulses 1500, total stimulation time 30 min, one session per day, and 5 days per week for a 4-week treatment course (2 days off each weekend). Sham rTMS was also performed, as the coil was turned away from the skull at 90°. No side effects were reported during or after brain stimulation.

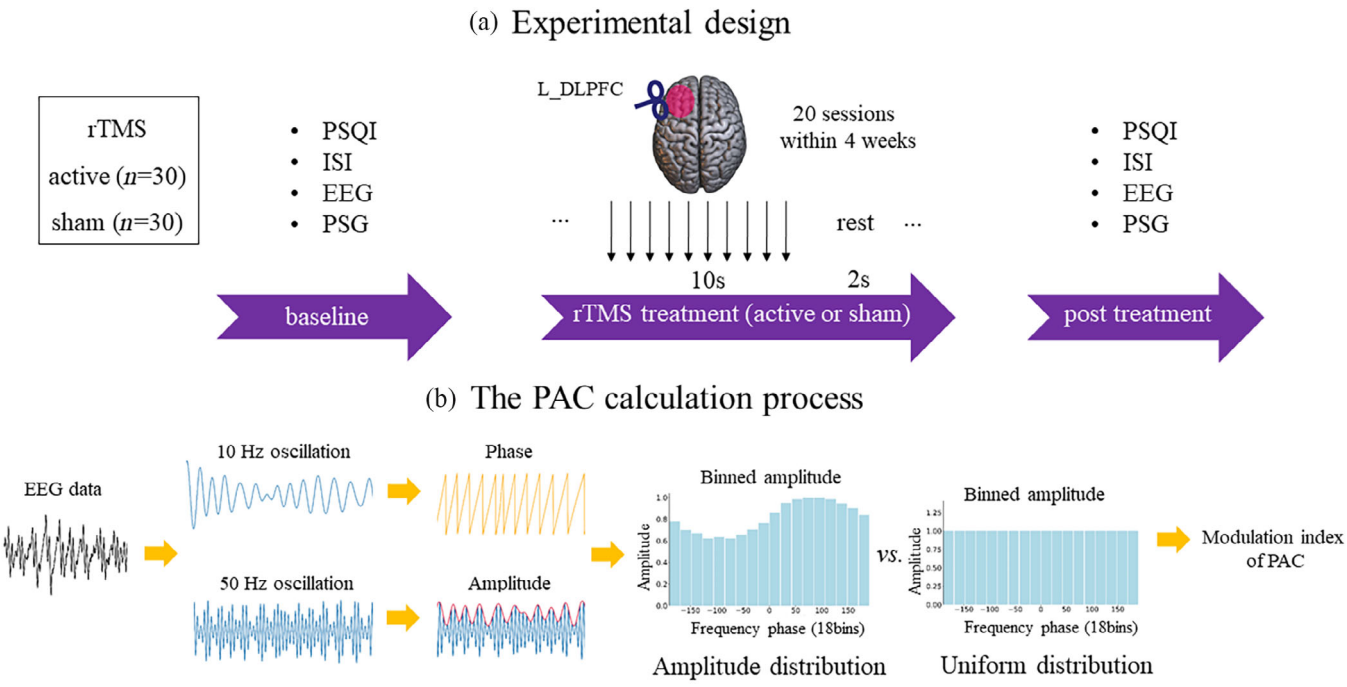

FIGURE 1 Experimental design and calculation process of PAC. (a) Experimental design. Sixty ID patients were randomly assigned to two groups to receive either active ($n = 30$) or sham ($n = 30$) rTMS treatment and received the same assessments before and after treatment. (b) The PAC calculation precess. The flow chart showed the evaluation process of PAC in detail.

2.3 | Resting-state EEG data acquisition

A 19-channel Nicolet system (Cephalon, Denmark) was used for the EEG recording. EEG data were collected at a sampling rate of 512 Hz, with analog bandpass filtering between 0.1 and 100 Hz. Nineteen Ag/AgCl electrodes were placed according to the international 10-20 system. Reference electrodes were placed on A1 and A2, and the ground electrode was attached to the forehead. The impedance of each electrode was maintained at below 10 kΩ. The eyes-closed resting-state EEG was recorded for 10 min in a shielded and sound-attenuated room in the morning. Participants were instructed to relax without thinking about anything during the EEG recording but without falling asleep.

2.4 | EEG data preprocessing

EEG data were processed offline using custom MATLAB scripts (MathWorks, MA, USA) and the EEGLAB toolbox (Delorme & Makeig, 2004). The steps are briefly described as follows: (1) The 50 Hz AC line noise artifact was removed using a notch filter; (2) non-physiological slow drifts in the EEG recordings were removed using a 0.1 Hz high-pass filter; (3) the filtered EEG data were re-referenced to the common average; (4) bad channels and bad epochs were manually rejected by experienced operators. The rejected bad channels were then interpolated from the EEG signals of adjacent channels via spherical spline interpolation; (5) eye movement and blink artifacts were removed using independent component analysis (ICA); and (6) the EEG data were re-referenced to a common average.

2.5 | PSG data acquisition and index analysis

PSG sleep monitoring was performed using a Grael 4 K system (Compumedics, Victoria, Australia). Including six-channel of EEG (C3, C4, F3, F4, O1, O2, standard 10-20 system, bilateral mastoid references), chin electromyography (EMG), and right and left outer canthi electrooculogram (EOG). The sampling rate was 512 Hz and the impedances were maintained below 10 kΩ. PSG indices included sleep onset latency (SOL), sleep efficiency (SE), and non-rapid eye movement sleep stage 3 (NREM 3) duration.

2.6 | Phase-amplitude coupling calculation

As shown in Figure 1b, the processed *EEG data* were filtered at the two frequency ranges of interest. Specifically, we used a range of phase (2–16 Hz) and amplitude–frequency (18–60 Hz) combinations to examine the extent to which specific low-frequency (delta, theta, and alpha) phase and high-frequency (beta, gamma) amplitude values were coupled within each electrode. Subsequently, the low-frequency phase and high-frequency amplitude were obtained using the Hilbert transform. Finally, the modulation index (MI) was calculated to characterize PAC (Tort et al., 2010), which measures the divergence of the amplitude distribution from a uniform distribution. The more the phase-amplitude distribution deviates from the uniform distribution, the higher the coupling (i.e., $0 \leq MI \leq 1$).

To improve measurement robustness and sensitivity and reduce spurious coupling (Aru et al., 2015), the PAC value was normalized by the z-score relative to the distribution of surrogate values, which was derived from random-point amplitude time block-swapping (200 iterations). We calculated the PAC value every 8 s, averaged the PAC values (approximately 40 epochs), and considered the average as the final PAC value. PAC was calculated using the TensorPac toolbox (Combrisson et al., 2020).

2.7 | Statistical analyses

All quantified data were statistically analyzed, and data normality was confirmed using the Shapiro–Wilk test ($p > .05$). Paired *t*-test, two-sample *t*-test, and two-way repeated-measures ANOVA, followed by a post hoc Tukey's test, were used for the analyses.

Cluster-based permutation test implemented in MNE-Python was used to correct for multiple comparisons and detect statistical differences in PAC (Gramfort et al., 2013; Maris & Oostenveld, 2007). Statistical significance was set at $p_{corrected} < .01$ were considered significant. Statistical differences in the preferred phase of PAC were calculated using the CircStat toolbox (Berens, 2009).

Linear relationships between PAC values and subjective and objective sleep measurements were determined by calculating Pearson's correlation coefficients. Data were analyzed using SPSS V.26.0 (SPSS Inc., Chicago, IL, USA). Graphs were plotted using GraphPad Prism 8.0.2 (GraphPad Software LLC, California, USA).

3 | RESULTS

3.1 | Demographic information and behavioral results

Demographic information and behavioral results of the ID patients and GSC are presented in Table 1. There were no significant differences in age, sex, ESS, MoCA, or MNSE between the ID patients and those with GSC ($p > .05$). There were significant differences in PSIQ, ISI, BDI, and BAI scores (all $ps < .0001$).

3.2 | Sleep quality impairment in ID patients and improvement after active rTMS treatment

PSG data from five active and six sham group patients were excluded from the analyses because of poor data quality. The final PSG data used for analysis were as follows: 39 (GSC group), 23 (active treatment group of ID patients), and 24 (sham treatment group of ID patients).

An independent sample *t*-test showed significant impairment in ID patients in both subjective sleep quality (PSQI: $t_{95} = 19.07$, $p < .0001$; ISI: $t_{95} = 18.29$, $p < .0001$) and objective sleep quality (SE: $t_{84} = 6.324$, $p < .0001$; NREM 3 duration: $t_{84} = 6.828$, $p < .0001$; SOL: $t_{84} = 4.774$, $p < .0001$) compared to GSC at baseline (Figure S1). Following the course of active rTMS treatment, subjective sleep quality improvement was indicated by reduced PSQI and ISI scores (Figure 2a). Similarly, objective sleep quality improvement was observed, as evidenced by increased SE, NREM 3 duration, and shorter SOL (Figure 2b). No significant changes in subjective or objective sleep quality were observed in the sham rTMS treatment group (Figure 2). No significant differences were observed in MMSE, MoCA, BDI, and BAI scores before and post-rTMS treatment.

TABLE 1 Demographic and behavioral measures (mean ± SD).

Variable	ID patients	GSC
N (male/female)	58 (30/28)	39 (18/21)
Age (years)	43.93 ± 10.93	40.62 ± 8.78
Edu (years)	13.36 ± 4.00	16.15 ± 5.414
Height (cm)	164.43 ± 7.73	168.38 ± 6.05
Weight (kg)	61.00 ± 10.96	65.69 ± 9.150
PSQI	12.98 ± 2.959	3.00 ± 1.686****
ISI	16.47 ± 4.971	1.61 ± 1.16****
ESS	7.96 ± 4.89	5.46 ± 3.55
BDI	12.00 ± 7.10	3.577 ± 4.012****
BAI	35.39 ± 8.511	26.61 ± 2.226****
MoCA	27.35 ± 2.31	28.23 ± 3.11
MMSE	28.32 ± 1.76	29.46 ± 1.12

Note: *$p < .05$; **$p < .01$; ***$p < .001$; ****$p < .0001$.
Abbreviations: BAI, Beck Anxiety Index; BDI, Beck Depression Index; ESS, Epworth Sleepiness Scale; GSC, good sleeper controls; ISI, insomnia severity index; ID, insomnia disorder; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; PSQI, Pittsburgh Sleep Quality Index.

3.3 | ID patients before rTMS treatment had weaker PAC values

Cluster-based permutation tests demonstrated that ID patients before rTMS treatment had weaker theta, alpha, and beta–gamma PAC values in the frontal and temporal regions (i.e., C4, delta-gamma; Cz, theta–gamma, alpha–gamma; T3, theta–gamma; Fz, theta–gamma; F3, alpha–beta and F7, alpha–gamma) than those with GSC (Figure 3).

PAC values at baseline showed significant negative correlations with the PSQI and ISI scores (Figure 4d). The GSC had a stronger PAC and lower PSQI and ISI scores, whereas the ID patients had weaker PAC and higher PSQI and ISI scores. Furthermore, we analyzed the preferred phase of the PAC, which is defined as the phase in which

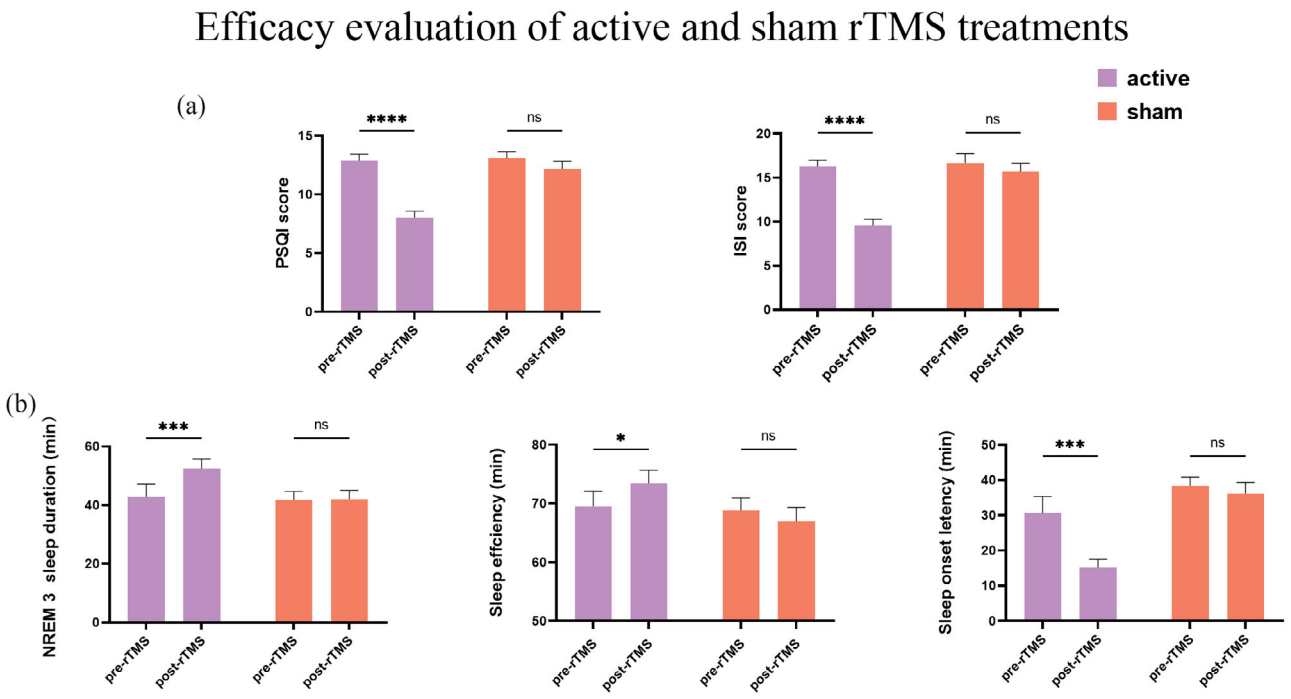

FIGURE 2 Improvement of subjective and objective sleep efficiency after active rTMS treatment. Two-way ANOVA revealed a significant "treatment × time" interaction effect in both subjective sleeping measurements (PSQI: $F_{56} = 24.14$, $p < .0001$; ISI: $F_{56} = 18.34$, $p < .0001$) and objective sleeping measurements (SE: $F_{45} = 7.265$, $p = .0099$; NREM 3 duration: $F_{45} = 7.149$, $p = .0104$; SOL: $F_{45} = 5.663$, $p = .0216$).
(a) Subjective sleep improvement was found by showing reduced PSQI ($t_{56} = 8.385$, $p < .0001$) and ISI ($t_{56} = 6.962$, $p < .0001$) in the active rTMS group. (b) Objective sleep improvement was found by showing increased sleep efficiency ($t_{45} = 2.539$, $p = .0291$), NREM 3 duration ($t_{45} = 3.852$, $p = .0007$), and shorter sleep onset latency ($t_{45} = 3.874$, $p = .0007$) in the active rTMS group (ns = not significant, *$p < .05$; **$p < .01$; ***$p < .001$; ****$p < .0001$).

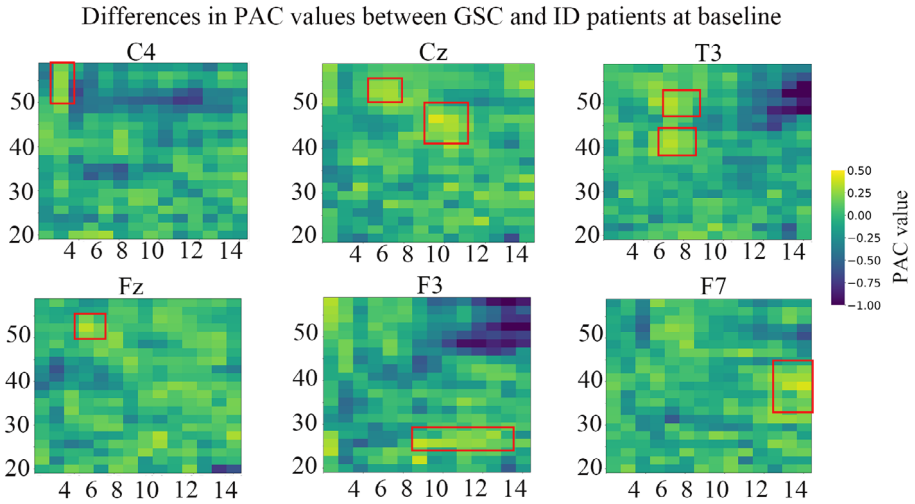

FIGURE 3 Differences in PAC values between GSC and ID patients at baseline (PAC values of GSC minus PAC values of ID patients), pink rectangles highlighted windows with significantly different PAC values using the cluster-based permutation test ($p_{corrected}$ <.01) (Figure S2). The horizontal axis represents the frequency for phase and the vertical axis represents the frequency for amplitude. The unit is Hz.

the amplitude distribution is at its maximum. This can be used to determine whether the amplitudes were aligned at a specific phase angle. However, no significant differences in the preferred phase were detected between ID patients and GSC, or before and after active treatment in ID patients (Figures 5c and S4).

3.4 | rTMS reinstated weaker PAC in ID patients

Of the 28 subjects with ID after active rTMS treatment, the EEG data of the two ID patients were excluded because of excessive artifacts. Active rTMS improved, rather than sham, theta–gamma, and alpha-beta PAC values at the F3, Fz, Cz, and T3 electrode sites. Phase-amplitude comodulograms (Figure 4a) demonstrated the difference in PAC values before and after active rTMS treatment (i.e., post–pre). The PCA values of clusters with significant differences within electrodes before and after active rTMS treatment were averaged and paired-sample *t*-tests were performed. The results showed that PAC levels significantly increased after active rTMS treatment (Figure 4b, paired t-test: F3: $t_{25} = 5.291$, $p < .0001$; Cz: $t_{25} = 7.240$, $p < .0001$; T3: $t_{25} = 5.456$, $p < .0001$; Fz: $t_{25} = 6.712$, $p < .0001$). It is worth mentioning that electrodes with significantly improved PAC values were distributed near the stimulation target (the left DLPFC) (Figure 4c).

3.5 | Correlation analysis between the change in PAC values and the improvement of sleep quality

Correlation analysis showed that there was a significant correlation ($r = -.661$, $p = .0002$, $n = 26$) between the increased PAC value at the Fz electrode and the improved PSQI score in the active treatment group (Figure 5a), and the increased PAC value at the F3 electrode was significantly correlated with the improved improvements in sleep onset latency ($r = -.5612$, $p = .0237$, $n = 23$) (Figure 5b). No significant correlation was found at other electrodes.

4 | DISCUSSION

Our major findings are (1) at baseline, the theta–gamma, alpha–beta, and beta–gamma PAC values of the frontal and temporal regions in the ID patients were lower than those in the GSC; (2) compared with sham rTMS, active rTMS improved theta–gamma and alpha-beta PAC values, of electrodes near the stimulation target (left DLPFC); (3) there were significant correlations between enhanced PAC values at the Fz and F3 electrodes and improved subjective (PSQI score) and objective sleep quality (SOL) in ID patients.

As an indicator of synchronization of distinct neural oscillations with different frequencies that might support dynamic communication within the brain, PAC has received much recent attention in the study of neurological disorders, for example, attention-deficit hyperactivity disorder, Alzheimer's dementia, autism spectrum disorder, bipolar disorder, depression, obsessive–compulsive disorder, social anxiety disorder, and schizophrenia (de Hemptinne et al., 2013; Devergnas et al., 2019; Schapira et al., 2009). In the present study, ID patients exhibited weaker PAC values for theta–gamma in the frontal region (Figure 3). The frontal cortex is a key node in arousal circuitry and is involved in multiple neuronal levels of metabolites such as corticosterone, adrenocorticotropic hormone, or thyrotropin. Our results are consistent with those of a previous study on sleep disorders, in which patients with obstructive sleep apnea had significantly lower theta-gamma PAC (Gouveris et al., 2022). Theta rhythm is a marker of sleepiness during wakefulness and early phases of spontaneous sleep. Gamma rhythms are related to learning, memory, and consciousness. Many studies have reported significantly increased gamma activity during wakefulness in ID patients (Zhao et al., 2021), this may reflect cortical hyperarousal. Meanwhile, ID patients exhibited weaker PAC values for alpha–beta and beta–gamma PAC. Beta–gamma PAC was found to be associated with sleep patterns and cognition in major depression disorder (Liu et al., 2022). Thus, we suggested that a possible complicated relationship existed among PAC, sleep, and cognition in ID patients. A comprehensive cognition assessment should be included in the

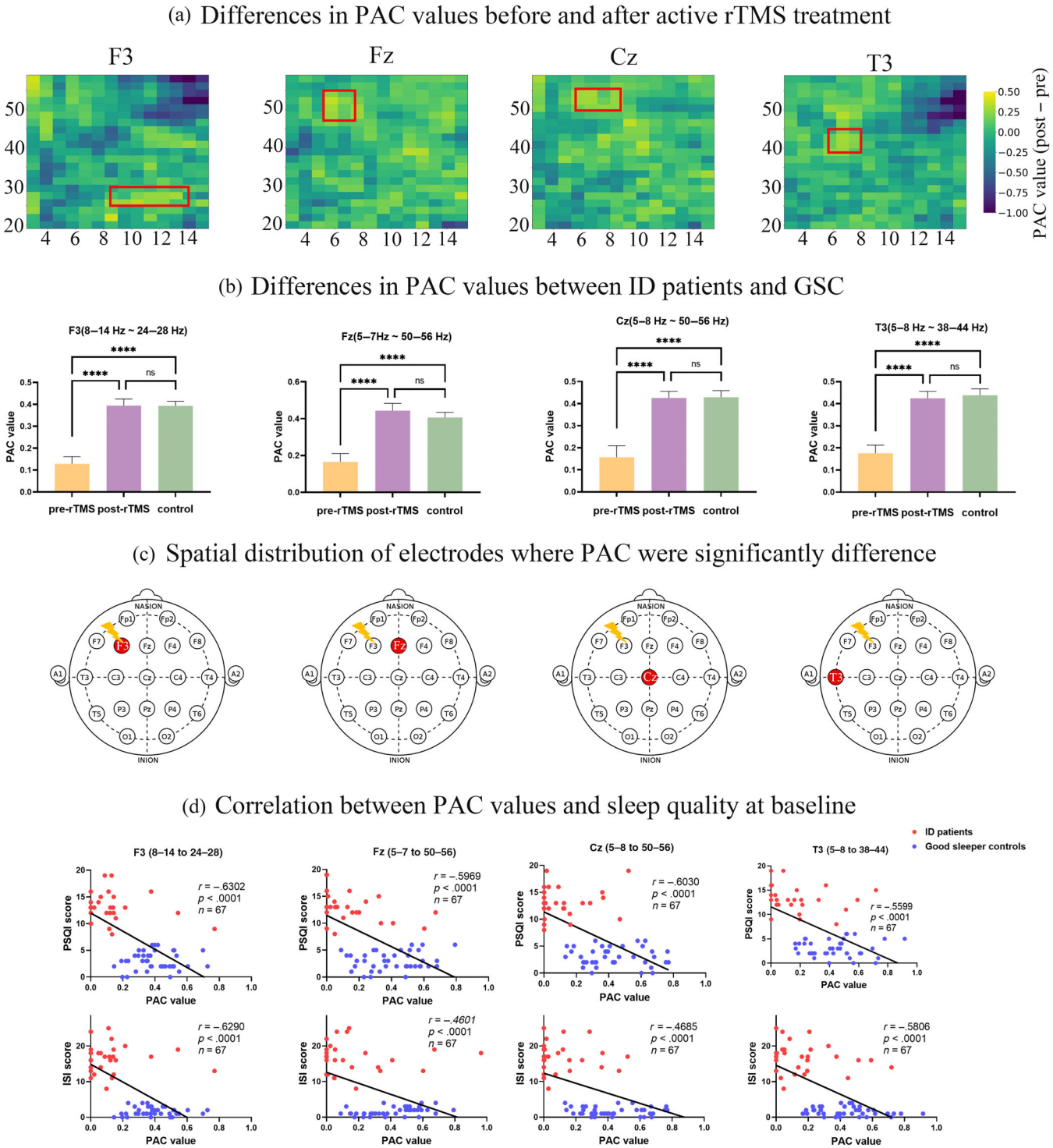

FIGURE 4 Improvement of impaired PAC in ID patients after active rTMS. (a) Differences in PAC before and after active rTMS treatment (post minus pre), pink rectangles highlighted windows with significantly different PAC values before and after treatment using the cluster-based permutation test ($p_{corrected}$ <.01) (Figure S3). (b) Differences in PAC values between ID patients and GSC. Histograms showed differences in PAC values of ID patients before and after active rTMS treatment. (c) Spatial distribution of electrodes where PAC were significantly difference. International standard 10-20 EEG electrode distribution map showing significant differences in PAC electrode distribution in the vicinity of rTMS stimulation (yellow lightning represented stimulation target: F3). (d) Correlation between PAC values and sleep quality at baseline. Pearson correlation demonstrated that PAC values of F3, Fz, Cz, and T3 electrodes exhibited significant negative correlations with PSQI and ISI scores at baseline (ns = not significant, $^{*}p < .05$; $^{**}p < 0.01$; $^{***}p < 0.001$; $^{****}p < 0.0001$).

future to support this hypothesis. Furthermore, we examined the relationship between PAC values and the PSQI and ISI scores. As depicted in Figure 4d, PAC values were significantly negatively correlated with PSQI and ISI scores at baseline; that is, ID patients with lower PAC values showed worse sleep quality, as demonstrated by higher PSQI and ISI scores. The abnormal decrease in PAC values

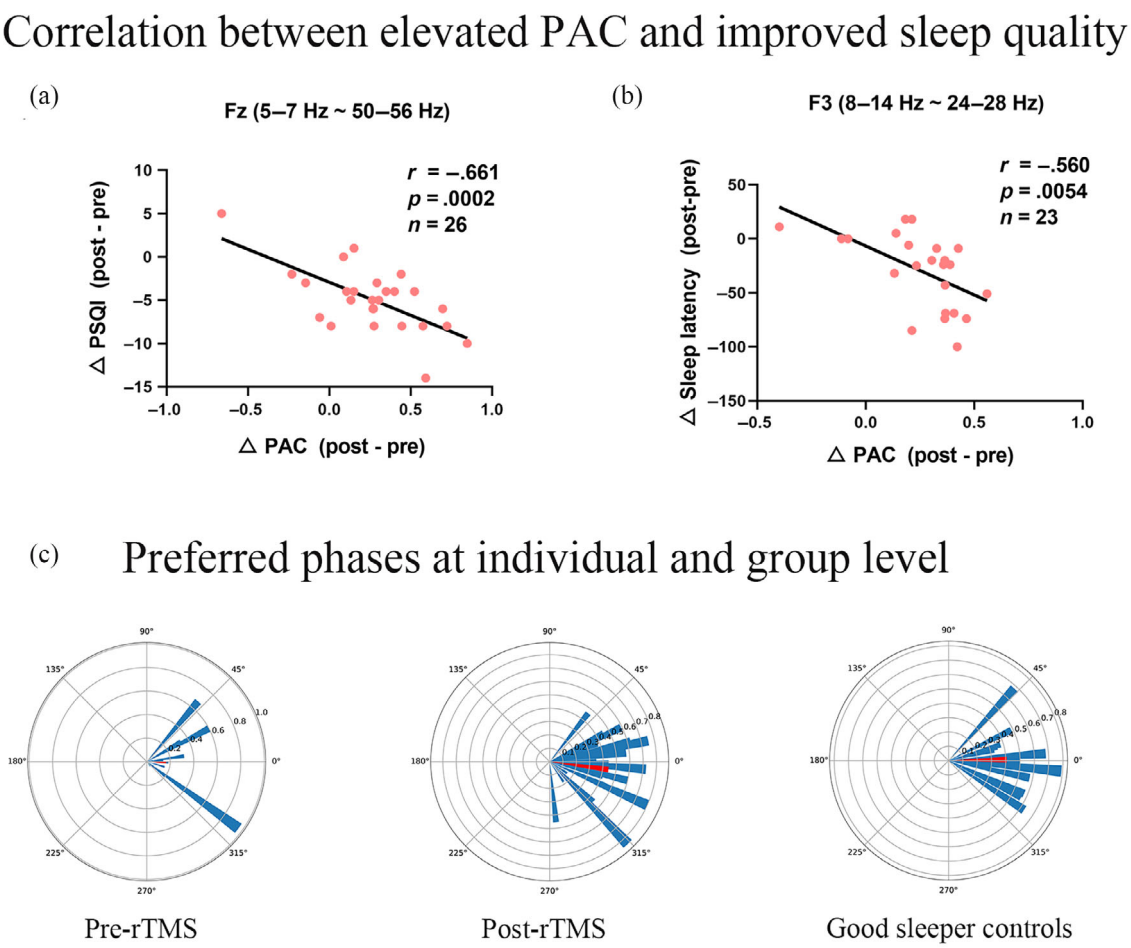

FIGURE 5 Correlation between elevated PAC and improved sleep quality and preferred phases at individual and group levels. (a) Correlation analysis showed that the change in PAC values (post–pre) on the Fz electrode was significantly negatively correlated with the change in sleep onset latency (post–pre). (b) Correlation analysis showed that the change in PAC on the F3 electrode (post–pre) was significantly negatively correlated with the change in SOL (post–pre). (c) Polar histograms show the individual- and group-level preferred phases; the dark blue line represents the individual preferred phase, the red line represents the group average preferred phase, and the length of the line represents the coupling strength. Circular statistics showed that the PAC-preferred phase of the Fz (5–7 Hz–50–56 Hz) electrode (pre-rTMS: −2.00° ± 35.20°, post-rTMS: −7.67° ± 29.70°, control: 4.59° ± 32.71°) was not significantly different between GSC and ID patients, and ID patients before and after active treatment ($p > .05$).

in ID patients may be associated with decreased control from theta rhythm to gamma activity.

The remarkable efficacy of rTMS in the treatment of ID has been widely reported (Feng et al., 2019; Jiang et al., 2013; Song et al., 2019; Zhang et al., 2018). Using subjective scales and PSG recordings, this study comprehensively evaluated the improvement in sleep quality of ID patients before and after active rTMS treatment, and found that rTMS had significant effects on ID patients (Figure 2). However evidence about the possible underlying mechanisms is still not sufficient. Our previous study reported that active rTMS may rewire disrupted cortico-hippocampal interactions in ID patients (Li et al., 2022). Meanwhile, left DLPFC rTMS improved impaired PAC in patients with depression (Noda et al., 2017). Whether rTMS can modulate PAC activity in ID patients has not been reported. Therefore, we investigated whether rTMS led to a change in PAC. According to our results, after active rTMS treatment, PAC values near the left DLPFC increased significantly (Figure 4b). Furthermore, we also explored the relationship between improved sleep quality and enhanced PAC in ID patients. Pearson correlation analysis showed that enhanced PAC at the Fz electrode was significantly associated with improvement in subjective sleep quality, as measured by the PSQI score, and there was a significant correlation between the increase in PAC at the F3 electrode and the decrease in sleep onset latency, although these two correlations were not found at the same electrode (Figure 5b,c). The correlation between PAC values and sleep quality suggests that improved sleep quality in ID patients is probably because low-frequency rTMS inhibited cortical hyperexcitability to some extent and reduced high-frequency activity. Low-frequency oscillations regained control over high-frequency oscillations, and this change in control capability was sensitively captured by PAC.

It is challenging to elucidate neural mechanisms underlying the therapeutic effect of rTMS in any neurological or psychiatric

disorders. By employing neuroimaging technologies including MRI and positron emission tomography (PET), studies suggest that rTMS intervention can induce both structural and functional neuroplastic changes in the human brain (Su et al., 2020). Considering the disrupted cortico-hippocampal interactions in ID patients, rTMS may rewire these impaired connections. Our current rTMS-EEG paradigm, together with previous rTMS-MRI studies (Li et al., 2022), would enhance our understanding of the neurobiological mechanism of the therapeutic effect of rTMS in ID patients. Meanwhile, the improvement of metaplasticity in ID patients by rTMS deserves further study (Cantone et al., 2021).

In summary, this study employed PAC to investigate abnormal neural oscillations in ID patients using resting-state EEG. Our results revealed for the first time that attenuated theta–gamma, alpha–beta, and beta–gamma PAC in ID patients and left DLPFC 1 Hz rTMS treatment ameliorated poor sleep quality and impaired theta–gamma and alpha–beta PAC in ID patients. Furthermore, enhanced PAC values are significantly associated with improved sleep quality. Therefore, PAC may be a novel sleep quality biomarker that improves our understanding of the neurobiological mechanisms of ID and provides new ideas for the treatment of ID.

This study had several limitations. First, the precise cortical locations of significantly improved PAC values have not been determined because source analysis was not possible due to the limited number of electrodes. Therefore, the. Second, the sample size was relatively small and our findings require a larger sample size for validation. Thus, our findings should be considered preliminary and should be replicated. Future studies could use high-density EEG to further improve spatial localization, including more subjects, and conduct more in-depth studies on the application of PAC in ID patients, such as using baseline PAC values to predict the efficacy of rTMS in ID patients.

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CONFLICT OF INTEREST STATEMENT

The authors report no biomedical financial interests or potential conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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