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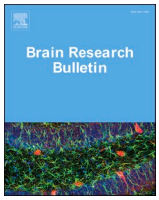

Research report

Predicting response to repetitive transcranial magnetic stimulation in patients with chronic insomnia disorder using electroencephalography: A pilot study

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ABSTRACT

Predicting responsvienss to repetitive transcranial magnetic stimulation (rTMS) can facilitate personalized treatments with improved efficacy; however, predictive features related to this response are still lacking. We explored whether resting-state electroencephalography (rsEEG) functional connectivity measured at baseline or during treatment could predict the response to 10-day rTMS targeted to the right dorsolateral prefrontal cortex (DLPFC) in 36 patients with chronic insomnia disorder (CID). Pre- and post-treatment rsEEG scans and the Pittsburgh Sleep Quality Index (PSQI) were evaluated, with an additional rsEEG scan conducted after four rTMS sessions. Machine-learning approaches were employed to assess the ability of each connectivity measure to distinguish between responders (PSQI improvement $>$ 25%) and non-responders (PSQI improvement $\leq$ 25%). Furthermore, we analyzed the connectivity trends of the two subgroups throughout the treatment. Our results revealed that the machine learning model based on baseline theta connectivity achieved the highest accuracy (AUC = 0.843) in predicting treatment response. Decreased baseline connectivity at the stimulated site was associated with higher responsiveness to TMS, emphasizing the significance of functional connectivity characteristics in rTMS treatment. These findings enhance the clinical application of EEG functional connectivity markers in predicting treatment outcomes.

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) is gaining popularity owing to its proven efficacy in treating neuropsychiatric disorders by modulating cortical excitability within a relatively short stimulation period (Pell et al., 2011). Recently, the use of rTMS therapy to alleviate insomnia symptoms has gained increased attention. Several studies have assessed the efficacy of rTMS in treating chronic insomnia disorder (CID) and reported significant improvements in insomnia symptoms in active rTMS groups (Jiang et al., 2013; Song et al., 2019; Jiang et al., 2019). However, different clinical studies revealed that rTMS has poor reliability, and currently, no biomarkers are available to predict its efficacy practically.

Large variability in the responsiveness to rTMS may result in the preservation of cortical excitability in group analysis. Few studies have reported the response rate of this treatment in patients with CID.

Abbreviations: rTMS, repetitive transcranial magnetic stimulation; CID, chronic insomnia disorder; PSQI, Pittsburgh Sleep Quality Index; EEG, electroencephalography; R, responder; NR, non-responder; DLPFC, dorsolateral prefrontal cortex; rsEEG, resting-state electroencephalography; HAMD, Hamilton depression rating scale; RMT, resting motor threshold; dwPLI, debiased weighted phase-lag index; ROI, regions of interest; RMFG, rostral middle frontal gyrus; CMFG, caudal middle frontal gyrus; IC, insular cortex; SMG, supramarginal gyrus.

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Generally, 30–50% of patients respond to rTMS (Lacroix et al., 2021; Miron et al., 2021), and some studies have indicated the presence of subgroups of rapid responders to rTMS (Kaster et al., 2019). This highlights the need for further research and development on rTMS as a treatment modality to enhance its effectiveness and predictability of its outcomes. Predicting rTMS treatment outcomes can greatly decrease the financial burden on patients and therapy duration.

By analyzing diverse elements, such as physical characteristics, neuroimaging data, genetic markers, and demographic information, researchers aim to develop predictive models that assess the probability of a patient responding to rTMS (Lacroix et al., 2021; Miron et al., 2021), (Kaster et al., 2019). Although previous work in this field has reported various clinical and biological markers capable of predicting rTMS treatment outcomes (Dh et al., 2008; Kito et al., 2008), these findings are inconsistent with those of other studies, suggesting that none of the physiological measures are clinically meaningful predictors of rTMS treatment (Krepel et al., 2020).

Recently, some studies focused on early biomarkers emerged in the treatment process that are primarily derived from self-rated clinical outcomes (Beck et al., 2020; Mondino et al., 2020). It is believed that observing changes in these biomarkers in the early stages of rTMS treatment could offer a superior prediction of treatment response. A retrospective study discovered that failure to exhibit clinical improvement at the midway point of the treatment process predicted no response to treatments with 88% accuracy (Feffer et al., 2018).

Neurophysiological and neuroimaging features may be more predictive of responsiveness than clinical variables as they provide objective and quantifiable measurements of brain activity. Previous studies have provided evidence that electroencephalography (EEG) changes precede clinical response to antidepressant medications, making them potential leading indicators of individual treatment response (Cook et al., 2002). Several studies have used baseline EEG features, such as band power, concordance, and alpha peak frequency, to forecast response to rTMS treatment (Bailey et al., 2018), (Arns et al., 2012; Watts et al., 2022). Accurate individual-level outcome prediction by certain biomarkers can reach 80% (Hasanzadeh et al., 2019; Bailey et al., 2019).

rTMS modulates brain activity through neural oscillations and entrainment, leading to the recruitment of neurons from local oscillatory networks, and affecting both local and long-range connections. Accordingly, the therapeutic benefits of rTMS may be partially explained by its functional connection with the brain networks. Some studies have linked neuronal network connectivity to rTMS responsiveness by demonstrating that responders have elevated baseline theta connectivity (Bailey et al., 2019); however, the results varied across relevant studies (Bailey et al., 2021). Additionally, associations between successful treatment and functional connectivity of the stimulated region have been confirmed both in patients with major depression and healthy individuals (Salomons et al., 2014; Ge et al., 2020; Nettekoven et al., 2015). Another study reported that responders with higher functional connectivity in a specific network at baseline could be classified as a subtype with a response rate that is twice that of other subtypes (Drysdale et al., 2017).

Insomnia is linked to functional brain dysfunction, including the dorsolateral prefrontal cortex (DLPFC) area (Cheng et al., 2022). In alignment with prior studies, we targeted the DLPFC for our intervention (Sun et al., 2021). The limited accessibility of functional magnetic resonance imaging hinders its use in clinical environments. Therefore, we used resting-state EEG (rsEEG) based functional connectivity as an electrophysiological marker to classify responders (R) and non-responders (NR) among patients with CID.

The overarching goal of this study is to explore whether and to what extent functional connectivity could predict rTMS responsiveness in patients with CID. The primary objective was to investigate how well functional connectivity could differentiate R from NR to rTMS at baseline and during treatment. Additionally, we aimed to identify specific neurophysiological signatures associated with the success of DLPFC-rTMS in patients with CID. By accomplishing these objectives, we sought to establish a foundation for evaluating and predicting responses to rTMS for insomnia treatment.

2. Material and methods

2.1. Participants

The research protocol was approved by the Ethics Committee of the Shenzhen People's Hospital. All participants provided written informed consent before participation.

All participants underwent a baseline interview, and data on demographic and behavioral assessments were collected, including the Pittsburgh Sleep Quality Index (PSQI) for sleep quality and the Hamilton Depression Rating Scale (HAMD) for mental state. Of the 44 patients who underwent eligibility screening, 36 participants (14 males; mean ± SD age: 49.4 ± 10.9 years) with a primary diagnosis of CID were included in the analysis (Table 1).

The inclusion criteria for patients with chronic insomnia disorder (CID) were in accordance with the diagnostic criteria of the International Classification of Sleep Disorders-Third Edition (ICSD-3). The key criteria were patients (1) aged 18–70 years old and right-handed; (2) with sleep disturbances lasting for $\geq$ 3 months; (3) having PSQI $\geqq$ 7; (4) score $<$ 25 on the 24-item HAMD; (5) without other sleep disorders, such as sleep apnea or restless legs syndrome. Participants were excluded from treatment only if they presented with clinical contraindications to rTMS, such as metallic implants, pregnancy, seizures, or a history of seizures. Moreover, no patients with a history of psychotic disorders or neurological illnesses were accepted for treatment in this study. All patients maintained stable doses of their current medications throughout the treatment period.

2.2. Study design

This single-arm open-label study was conducted to explore the efficacy of rTMS. The experimental design is illustrated in Fig. 1. Each patient participated in three EEG scans as follows: on day 1 (pre-treatment, Tp1), day 4 (after four rTMS sessions, Tp2), and day 10 (post-treatment, Tp3). To ensure data reliability, the EEG measurements were conducted in the same room by a single operator. The PSQI score, which reflects more severe symptoms with higher values, was collected at Tp1 and Tp3. The primary outcome was based on the percentage change in the

Table 1
Demographic characteristics and clinical information of responders and non-responders.

	CID patients (n = 36)		
	R (N = 13)	NR (N = 23)	*p* value
Sex (M/F)	5/8	9/14	0.97
Age	46.15 (11.90)	51.26 (10.12)	0.21
Pre-rTMS PSQI	16.23 (2.98)	14.39 (3.56)	0.11
Post-rTMS PSQI	8.15 (2.82)	13.87 (3.05)	$<$ 0.001
Pre-rTMS HAMD	14.00 (5.74)	12.34 (3.87)	0.37
Post-rTMS HAMD	7.08 (5.26)	10.2 (4.07)	0.09
RMT	40.54 (11.30)	37.22 (12.75)	0.43
Medication (SD/AD/AP)	N 11/8/0	N 16/14/2	

Note: Data are presented as means (standard deviations). Statistical significance using the Chi-square test for sex and two-sided *t*-test for continuous data was set at $p < 0.05$). R: responder; NR: non-responder; RMT: resting motor threshold; PSQI: Pittsburgh Sleep Quality Index; HAMD: Hamilton Depression Rating Scale. Medications were categorized into three groups: sleep aid (SD), including benzodiazepines and non-benzodiazepines; antidepressant (AD); and antipsychotic (AP).

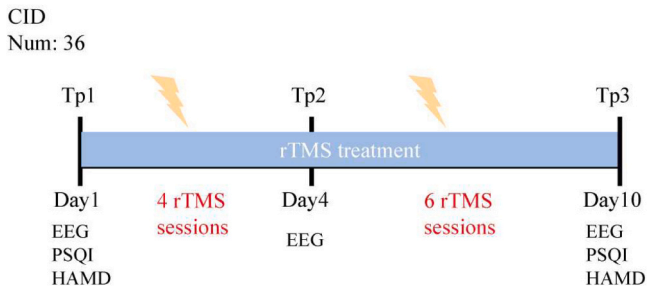

Fig. 1. Trial design schematic. Each participant with CID received active rTMS treatment targeting the right DLPFC at a frequency of 1 Hz for 10 consecutive days within two weeks. The EEG data were acquired at three time points: pre-treatment (Tp1), after the four rTMS sessions (Tp2), and post-treatment (Tp3). Eight minutes of eyes closed rsEEG data were recorded during the collection.

PSQI score between pre- and post-treatment. Patients with CID were categorized as R to rTMS treatment with PSQI reductions over 25% using a threshold criterion obtained from previous rTMS studies (Rm et al., 2002). In this sample size of patients with chronic conditions, this criterion was clinically meaningful, and ensured that the responders had a clear stimulation reaction.

2.3. rTMS treatments

rTMS stimulation was performed using a figure eight-shaped focal coil attached to a MagPro 100 magnetic stimulator device (MagVenture, Denmark). The resting motor threshold (RMT) was evaluated as described previously in the guidelines for noninvasive stimulation (Rossini et al., 2015). The target site of the right DLPFC was determined to be the F4 electrode site according to the International 10–20 EEG system (Mir-Moghtadaei et al., 2015). rTMS was delivered at 1 Hz (10 s trains, 1 s intertrain interval, and 1360 pulses per session), with a 100% RMT stimulus strength. The patients received one rTMS treatment session daily for 5 days a week over a two-week course. In each session, adverse events associated with rTMS were documented and reported.

2.4. EEG acquisition and preprocessing

EEG data were collected from 64 channels using a BrainAmp DC amplifier (Brain Products GmbH, Germany) in an eyes-closed condition for 8 min within a metallic-shielded room. FCz was used as the online reference, and AFz was used as the ground. Data were initially sampled at 5000 Hz with impedances kept below 5 KΩ for all channels. All participants were asked not to consume caffeine or energy-related drinks for approximately 24 h prior to EEG collection. The offline preprocessing steps were briefly described as follows. (1) down-sampled the raw data to 250 Hz; (2) omitted the bad segments contaminated by artifacts manually; (3) applied a bandpass filter of 0.5–70 Hz and notch filter of 50 Hz on signals; (4) rejected the bad channels and then interpolated them using neighboring channels via spherical spline interpolation; (5) removed remaining artifacts like eye movement, persistent muscle artifact, heart noise and channel noise using independent component analysis; (6) re-referenced to the common average.

2.5. Estimating functional connectivity

All connectivity analyses were performed in source space. The time series for each voxel was reconstructed using the Brainstorm toolbox (Tadel et al., 2011). First, the head model was computed using OpenMEEG with a FreeSurfer average brain template using the symmetric boundary element method (Gramfort et al., 2010). A total of 3003 rotating dipoles with unconstrained orientations were created on the cortical surface. For each voxel, the current density time series was reduced to a single direction by principal component analysis. Additionally, the lead-field matrix was obtained after co-registration of the electrode locations and anatomical magnetic resonance imaging. The inverse operator that mapped the current density from the sensor space to the source space was estimated using the minimum norm estimation method with depth weight and regularization (Toll et al., 2020). Finally, the initial 3 min of EEG data were binned into 10 s time epochs for connectivity analysis.

We computed the functional connectivity of two classical EEG bands, theta (4–8 Hz) and alpha (8–13 Hz), for each voxel, as previous studies have often focused on these bands in the resting state (Bailey et al., 2018; Corlier et al., 2019). The connectivity analyses were computed at the vertex level by quantifying the phase relationship between the time-series oscillations. Here, we used the debiased weighted phase lag index (dwPLI) to illustrate the non-zero phase lag statistical interdependencies between each vertex. It is a conservative approach to estimate connectivity minimizing spurious field spread and the impact of volume conduction (Vinck et al., 2011). Then, the average dwPLI values across all possible vertex pairs were mapped onto the Desikan-Killiany template, representing the connectivity between each pair of regions of interest (ROI) (Desikan et al., 2006). This template identified 68 cortical regions. The rostral middle frontal gyrus (RMFG), which is the anterior division of the DLPFC, served as a stimulation site in this context. As a result, individuals were depicted through 67-dimensional global functional connectivity matrix based on right RMFG at each frequency band.

2.6. Classification analysis

We built a machine learning model to assess the effectiveness of discriminating R from NR. Our analysis included the following three situations: pre-treatment (Tp1), during rTMS treatment (Tp2), and treatment-induced connectivity changes between these two time points (Tp2-Tp1). That is, the baseline functional connectivity maps were subtracted from the corresponding maps at Tp2 for each participant to quantify the treatment-induced connectivity changes resulting from rTMS. In addition, each situation includes two frequency bands, alpha and theta. A total of 6 sets of feature matrices are used to build machine learning models, each containing 67 connectivity features.

In this work, the most relevant features were selected using the sequential floating forward selection algorithm. This technique operates by first selecting the best individual feature (referred to as the first feature in this context) and then evaluating the remaining features to determine the second feature that optimizes the classification rate when combined with the first one. This iterative process continues until no further improvement in classification rates is observed when a new feature is added. Notably, the SFFS method introduces a backward elimination step into the sequential search process. At each step, an evaluation is performed to determine if the removal of a feature improves the classification rates. If this is the case, the reduced feature set is adopted as the new feature set and the forward search proceeds accordingly. The connectivity matrices were used to train a random forest classifier, and the classification performance was evaluated using the leave-one-out cross-validation procedure. Finally, the group with the best classification performance was selected from the 6 feature matrices, and the connectivity with the largest contribution to accuracy was selected.

The response prediction criteria included accuracy, specificity, sensitivity, and area under the curve (AUC), with higher values signifying better discrimination ranging from 0 to 1.

2.7. Statistical analysis

For continuous data, the Friedman test was used to check for differences without a normal distribution, whereas a two-sided *t*-test was used when a normal distribution was observed ($p < 0.05$). To determine if PSQI and functional connectivity changes differed between the R and

NR groups before and after treatment, a two-way repeated-measures analysis of variance (ANOVA) was performed with group (R and NR) and time (pre- and post-treatment) as fixed variables. The Greenhouse-Geisser correction was applied to ANOVA comparisons to account for sphericity violations, and the Benjamini and Hochberg method was used to correct for multiple comparisons and control the false discovery rate.

3. Results

3.1. Clinical response

At the post-treatment assessment, 13 of the 36 participants (36%) in the CID group met the criteria for responder status (Table 2). At baseline, no significant differences were found regarding age, sex, PSQI score, HAMD score, or RMT between the responder and non-responder groups. Two-way repeated-measure ANOVA assessing PSQI revealed a significant main effect of time (F (Pell et al., 2011; Vinck et al., 2011) $= 92.11$, $p < 0.0001$), as well as an interaction between group and time (F (Pell et al., 2011; Vinck et al., 2011) $= 71.11$, $p < 0.0001$). *Post-hoc* tests showed that the final PSQI score after rTMS treatment was significantly lower among the responders compared to non-responders (post hoc t-test $= 5.186$, $p < 0.0001$, FDR corrected) (Fig. 2A).

3.2. Classification analysis

Next, machine learning techniques were employed in different situations to explore the predictive potential of individual-level measures. Among the three conditions analyzed, the baseline right RMFG-based connectivity matrix outperformed the other two conditions in the overall classification, regardless of the theta or alpha band (Table 2). Specifically, the theta-band baseline connectivity features exhibited the highest predictive capability for treatment response, achieving an accuracy of 84.3% (See supplementary for ROC curves). In contrast to the baseline alpha classifier, the theta connectivity classifier showed higher accuracy and sensitivity, albeit with relatively lower specificity in testing performance. Within the baseline theta band scenario, three cortical connectomes stood out in the model: connections from the right RMFG to the left caudal middle frontal gyrus (CMFG), the left insular cortex (IC), and the right supramarginal gyrus (SMG) played the most significant role in distinguishing R from NR (Fig. 2B).

3.3. Changes in the RMFG-based functional connectivity after rTMS

To gain deeper insights into the dynamic changes induced by rTMS at the group level, we proceeded to evaluate the global brain connectivity seeded from the RMFG during the treatment period (see Fig. 3). The results of two-way repeated-measure ANOVA indicated no significant interaction between group and time. Nevertheless, it is noteworthy that the global theta band connectivity based on RMFG in the R group was significantly lower at baseline than that in the NR group. We observed a clear convergence in the distribution of rTMS-induced connectivity changes between R and NR. On average, patients in the R group

Table 2
Summary of classification performance of the different connectivity features.

	Theta			Alpha		
	Tp1	Tp2	Tp2-Tp1	Tp1	Tp2	Tp2-Tp1
ACC	**88.89**	86.11	83.33	**88.89**	77.78	80.56
SEN	**92.30**	84.62	69.23	76.92	84.62	76.92
SPE	86.96	86.96	91.30	**95.65**	73.91	82.61
AUC	**0.843**	0.762	0.793	0.759	0.759	0.763

Note: Accuracy (ACC): the percentage of correct response predictions made by the classifier; Specificity (SPE): the percentage of non-responders who were predicted to be non-responders; Sensitivity (SEN): the percentage of responders who were identified as responders; AUC: area under receiver operating characteristic curve

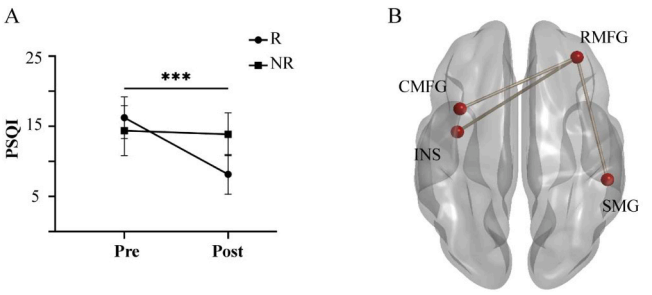

Fig. 2. A) Changes in the PSQI of R and NR before and after rTMS treatment; B) The corresponding selected three features classifying R and NR: RMFG-LCMFG, RMFG-LINS, and RMFG-RSMG; Note: * **indicate significant differences at $p < 0.001$.

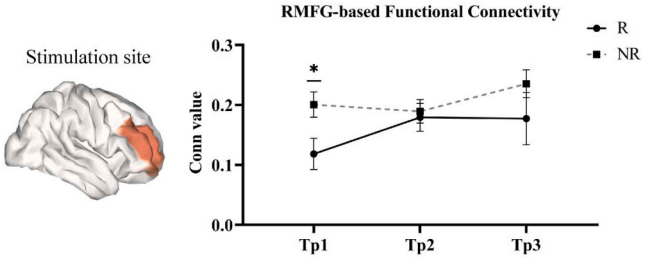

Fig. 3. Changes in theta band RMFG-based functional connectivity over time. Two-way repeated-measure ANOVA (group x time) showed no significant interaction effect of time and group (F (2.68) $= 1.152$, $p = 0.322$) as well as a main effect of time (F (1,34) $= 4.125$, $p = 0.0501$) in RMFG-based global connectivity anbetween. Multiple comparisons revealed that the R and NR groups at baseline reached significant differences (mean diff $= -0.08239$, $p = 0.0207$, FDR corrected). Error bars represents SEM; R: responders, NR: non-responders; Note: * $p < 0.05$.

demonstrated an immediate increase in RMFG-based global connectivity following rTMS at Tp2, whereas the NR group did not show such an increase (See supplementary for more details).

4. Discussion

The effectiveness of rTMS treatment in individuals with chronic insomnia varies, and it remains challenging to identify objective biomarkers that can predict treatment outcomes either prior to, or early in the treatment process. According to our findings, the baseline functional connectivity features (Tp1) in the theta band had superior discriminatory ability between the R and NR groups than those observed during treatment (Tp2) or those induced by treatment (Tp2-Tp1). Additionally, DLPFC-rTMS responders had lower baseline RMFG-seeded global connectivity than non-responders. In conclusion, our study provides empirical evidence supporting the strong relationship between treatment responsiveness and the functional connectivity of the stimulation site. We discovered that functional connection plays a critical role in determining the efficacy of rTMS treatment, and it holds potential as a valuable tool for evaluating and predicting response to rTMS in clinical practice.

Insomnia refers to persistent difficulties with sleep initiation, duration, or quality, which lead to daytime dysfunction (Morin et al., 2015). In this study, we focused on patients with CID, given that it represents a significant risk factor for neuropsychiatric disorders and maladaptive cognition, with neither medicine nor cognitive behavioral therapy providing sustained remission (Olaithe et al., 2021). Clinical evidence regarding the effectiveness of rTMS therapy in patients with insomnia is limited, and as mentioned above, responses to DLPFC-rTMS vary considerably among individuals. Our results revealed an overall rTMS

effectiveness rate of 36%. This underscores the importance of considering large inter-individual variability when conducting rTMS studies, and helps explain the inconsistent results observed across studies.

EEG is a valuable tool for investigating brain activity and directly reflecting neural processes. The analysis of EEG-based functional connectivity allows the examination of synchronized neural activity across different brain regions, gaining insights into the functional organization of the brain. Our findings suggest that patients with lower DLPFC-seeded functional connectivity in the theta band before treatment may benefit more from low-frequency DLPFC-rTMS treatment, reinforcing its role as a predictive factor for patients with CID. The clinical implication is that by excluding patients with higher baseline DLPFC connectivity from the right DLPFC low-frequency paradigm, we can reduce the proportion of patients who would not respond, resulting in higher efficacy.

Currently, the direct association between the strength of connectivity and successful treatment outcomes has not been established. Previous studies have reported mixed findings, with some showing positive correlations between higher connectivity and responsiveness and others showing negative correlations (Salomons et al., 2014; Nettekoven et al., 2015; Ge et al.,). These findings emphasize that the rTMS treatment effectiveness did not necessarily hinge on higher connectivity. Further research is required to better understand the intricate relationship between connectivity profiles and treatment responses, as well as the underlying mechanisms involved.

Fig. 3 seems to indicate an increase in functional connectivity originating from the stimulation site after rTMS treatment. This observation is consistent with the summary by Beynel et al. that active rTMS induces significant changes in functional connectivity (Beynel et al., 2020). Both low-frequency and high-frequency stimulation lead to increased functional connectivity, although these two frequencies of rTMS have previously been associated with opposite effects. Typically, low frequency ($<$1 Hz) is thought to inhibit, and high frequency ($\geqq$5 Hz) to facilitate cortical excitability. This implies that rTMS may potentially treat the disorder by rewiring the disrupted cortical connections (Li et al., 2022).

Feffer et al. demonstrated that patients who did not respond to rTMS treatment midway through the process could be reliably identified as non-responders with high accuracy (Feffer et al., 2018). Based on their findings, we explored whether similar functional connectivity markers could be observed earlier after four treatment sessions. As anticipated, our results indicated that only individuals who responded to treatment displayed increased connectivity profiles. This observation suggests that early changes in functional connectivity could serve as predictive indicators of response to rTMS treatment. However, it is essential to acknowledge that both respondents and non-respondents were not homogeneous. Even among the respondents, response rates to treatment varied significantly. This substantial variability poses a considerable challenge and limits the generalizability of these findings. Herein, further research involving more homogenous patient cohorts would be needed to validate and refine these phenomena.

Theta and alpha frequency bands are associated with specific brain states and cognitive functions, making them particularly interested in studying the brain's functional connectivity and information processing during the resting state (Klimesch, 1999). Integrating EEG measures into machine learning models has shown potential in predicting treatment responses as data-driven techniques are capable of classifying two groups intuitively (Bailey et al., 2018; Hasanzadeh et al., 2019; Corlier et al., 2019). Our focus was to analyze the association between functional connectivity and rTMS treatment efficacy, rather than constructing the most discriminative model for predicting treatment response status. Therefore, we did not incorporate other types of features or combine features from various frequency bands. Certainly, combining all possible features may improve classification accuracy.

In addition, we made no presumptions about the linear relationship between neurophysiological characteristics and clinical outcomes. In fact, we plotted the changing curve of functional connectivity of the stimulation site over time, the functional connectivity did not follow a straightforward linear trend with each subsequent stimulation session. Our results confirmed that neurophysiological changes are more dynamic during stimulation (Ji et al., 2020).

We hypothesized that cortico-cortical connectivity influences the therapeutic effects of rTMS (Salomons et al., 2014; Eshel et al., 2020). Specific connectivity patterns may indicate individuals who are more likely to benefit from DLPFC-rTMS. During our investigation, we identified three cortical regions that were particularly influential in the classification process. One of these regions is the CMFG, situated in the frontal lobe, and primarily associated with executive function and working memory (McCarthy et al., 1996). The IC, another significant region, acts as a central hub in the salience network. Previous studies have linked insular network abnormalities to the neural circuitry underlying insomnia (Chen et al., 2014). Additionally, the SMG also plays an important role in this process. This region is part of the somatosensory association cortex and participates in complex cognitive functions (Deschamps et al., 2014). This finding demonstrated that the connectivity of the stimulation site to specific downstream regions was responsible for the clinical effects of rTMS, providing insights into the potential neurophysiological mechanisms underlying the responsiveness of patients with CID to DLPFC-rTMS treatment.

This study had some limitations. First, the sample size was small, with only 13 respondents included in the analysis owing to the low response rate. This limited sample size may reduce the generalizability of the findings and the statistical power of the analysis. Second, the effect size of PSQI was higher for treatment durations of 20 days than for 10 days (Jiang et al., 2019); therefore, the PSQI assessment conducted after 10 treatment sessions may exclude delayed responders in the non-response group. Finally, while we emphasize that only patients with chronic insomnia were considered in this study, the patients reported various insomnia complaints, such as initial, intermediate, and terminal insomnia. Given the high heterogeneity of insomnia itself and the small sample size, it is not surprising that no conclusive picture has emerged. Further studies with larger sample sizes are required to validate and strengthen our findings.

5. Conclusions

Despite advancements in the diagnosis and management of insomnia, it remains largely unrecognized and untreated. In this study, we examined the functional signatures of low-frequency DLPFC-rTMS treatment in patients with CID to introduce an additional approach for evaluating and predicting rTMS responsiveness. Our findings suggest that baseline connectivity characteristics in the theta band offer a more effective differentiation between responders and non-responders than relying solely on connectivity in the early stages of treatment or treatment-induced connectivity changes. This discovery has significant potential to facilitate the optimization of manipulation protocols for personalized treatment, thereby increasing the rTMS use in clinical practice; however, future studies with a larger sample size will enhance the robustness and reliability of our results.

Author statement

Lin Zhu: Formal Analysis and Writing; Zian Pei: Software; Ge Dang: Validation; Xue Shi, Xiaolin Su, Xiaoyong Lan and Chongyuan Lian: Investigation; Nan Yan: Conceptualization and Supervision; Yi Guo: Conceptualization and Funding acquisition.

CRediT authorship contribution statement

Shi Xue: Investigation. **Dang Ge:** Validation. **Pei Zian:** Software. **Zhu Lin:** Formal analysis, Writing – original draft, Writing – review & editing. **Guo Yi:** Conceptualization, Funding acquisition. **Yan Nan:** Conceptualization, Supervision. **Lian Chongyuan:** Investigation. **Lan Xiaoyong:** Investigation. **Su Xiaolin:** Investigation.

Declaration of Competing Interest

The authors declare no conflict of interest related to the submitted manuscript.

Data availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.brainresbull.2023.110851.

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