



Original Article

Repetitive transcranial magnetic stimulation (rTMS) modulates time-varying electroencephalography (EEG) network in primary insomnia patients: a TMS-EEG study

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ABSTRACT

Introduction: Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive method, and its application in the treatment of primary insomnia (PI) is poorly researched. PI is considered to be a functional disorder with abnormal brain network connections. TMS combined electroencephalography (EEG) is a valuable method for directly probing excitability and dynamic connectivity of different regions in the brain. We aimed to investigate the therapeutic efficacy of rTMS and its impact on brain network connections in PI patients.

Methods: Twenty patients with PI were recruited in this study and received 1 Hz rTMS treatment for 14 consecutive days. The severity of symptoms was evaluated using the Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index (ISI) and the Epworth Sleepiness Scale (ESS). Twenty minutes TMS-EEG were performed before and immediately after treatment. EEG data was collected by 10-20 EEG system with the sample rate of 1024 Hz. Time-varying EEG network was analyzed using the adaptive directed transfer function. The EEG network results of patients were compared with those of 20 healthy subjects.

Results: In the present study, we found that PSQI, ISI, and ESS ratings of the patients decreased significantly ($P < 0.05$) after rTMS treatment, and the improvement in ratings lasted one month. Compared with healthy subjects, single-pulse TMS targeting right posterior parietal cortex of PI patients before therapy showed excessive information outflow from the left occipital region, the frontal mid-line region and the right posterior temporal region, in succession. Meanwhile, inadequate information outflow was seen in the right central region, right parietal region, as well as in the right temporal region. Compared with prior treatment, PI patients showed increased information outflow in the left temporal region and decreased information outflow in the frontal mid-line region.

Conclusion: Low frequency rTMS targeting the right posterior parietal cortex has significant positive effects on the treatment of PI that can last for at least one month and can reverse abnormal changes of time-varying EEG networks.

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1. Introduction

Insomnia is a common disorder that has significant long-term health consequences. Primary insomnia (PI) is one of the most prevalent chronic sleep disorders [1] and is not attributable to a medical, psychiatric, or environmental cause [2]. It is refers to the difficulty of falling asleep or maintaining sleep for at least one

month [3]. Epidemiologically, 10% of the adult population experiences chronic insomnia. Moreover, in the future PI is predicted to rises to 25% globally [4]. Previous studies have shown that patients with PI may present with a variety of psychiatric disorders [5]. In addition, PI is known to be associated with impaired neuropsychological performance [6]. This has been recognized as an important public health issue, which has increased the burden on social and health expense [7]. Yet, despite its large socio-economic and physical impacts, its efficacy and safety issues may largely limit the clinical application of currently available treatment strategies.

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At present, pharmacological and cognitive behavioral treatments (CBT) for PI are used [8]. Medications that are used have developed over time, but the optimal treatment program of the most commonly used strategies produce undesired side effects. However, in the past three years, the potential relationship between the use of sedative hypnotics for insomnia and increased mortality has become a topic of major controversy. Several retrospective cohort researches have already looked at the daily intake of 10 mg zolpidem, and have associated it to an overall increased risk of cancer and falls [9,10].

CBT is a multimodal treatment that combines many behavioral and cognitive interventions including sleep hygiene, stimulus control, sleep restriction, relaxation training, and cognitive restructuring [11]. Currently, a hierarchy comprising five levels of CBT stepped care is suggested; furthermore, for professional and pragmatic reasons, it is always applied by nurses and therapists [12]. However, because of the shortage of local therapist that have the necessary training, CBT is not widely available. Moreover, in many countries, CBT can be expensive for PI patients to afford and can be seen as financially unsustainable for clinicians because of restrictions due to medical insurance [13].

Repetitive transcranial magnetic stimulation (rTMS) is a type of non-medication treatment. Although rTMS has been shown to be effective in many neuropsychiatric disorders, for example, depression [14] and selected anxiety disorders, such as post-traumatic stress disorder [15] and obsessive compulsive disorder [16], the effectiveness of rTMS in treating PI has not been adequately addressed. Lanza et al., found that rTMS may be effective in neuromodulation in restless legs syndrome (RLS) [17,18]. To date, there have only been a few published researches relating to rTMS for the treatment of PI. Our research group, led by Huang et al., demonstrated that 1 Hz rTMS to the right posterior parietal cortex is effective for both anxiety and insomnia symptoms in patients with comorbid GAD and insomnia [19]. However, neural substrates remain poorly understood.

At the time of this writing, the most useful method of studying brain network connections are functional magnetic resonance imaging (fMRI) and electroencephalography (EEG). fMRI is based on the blood-oxygen-level dependent effect and has high spatial resolution but with low time resolution [20]. EEG signal mainly use directed transfer function [21] to observe brain connections, which has high time spatial. Currently, adapted directed transfer function (ADTF) [22] can reveal connections between different brain regions at different frequencies with time [23,24], which is called a time-varying EEG network. Excitatory changes induced by various stimuli can also be expressed through brain network connections. Moreover, a single-pulse TMS (sTMS) does not only change the neural activity in the stimulated areas but modulates the excitability of interconnected distant sites [25]. Furthermore, a TMS pulse can induce a synchronization of distant cortical areas. Thus, it modulates the information, which processes and changes the functional connectivity patterns in specialized interconnected cortical modules [26]. TMS-EEG have been applied to study and quantify brain network connectivity [27].

Previous studies demonstrated the effectiveness of rTMS treatment and found that rTMS may be a potential tool for modifying neural activity in stimulated areas, as well as in functionally connected cortical regions [28,29], more research should be focused on the mechanisms of neural network connectivity. Given the previous evidence of abnormal brain connections in PI patients, together with the findings of rTMS treatment of insomnia, we hypothesized that PI may be a brain functional disease with abnormal brain network connections, and that rTMS therapy may correct this network anomaly, and thus achieves a therapeutic effect. In the present study, we tested our hypothesis by stimulating the right

posterior parietal cortex with a low frequency rTMS as well as by using ADTF analyses of TMS-EEG signals to investigate the changes of the time-varying EEG network before and after treatment, compared with the healthy control (HC) group.

2. Subjects and methods

2.1. Subjects

This study was approved by the Ethics Committee of Capital Medical University Xuanwu Hospital. All PI patients were outpatients from the Department of Neurology, Xuanwu Hospital, Capital Medical University. All HC were recruited by advertising. All participants provided written informed consent to participate in this study.

PI patients were recruited consecutively and required to meet the Diagnostic and Statistical Manual (DSM-V) of Mental Disorders by American Psychiatric Association. DSM-V insomnia disorder was given if all the following criteria's were met: (1) dissatisfaction with sleep quality or quantity; (2) complaint of one or more of the following sleep difficulties: difficulty initiating sleep, difficulty maintaining sleep, early morning awakening, or a nonrestorative sleep; (3) significant distress or interference with personal functioning in daily living as a result of sleep difficulty; (4) sleep difficulty occurs at least three times a week; (5) sleep difficulty is present for at least three months; and (6) sleep difficulty occurs despite adequate opportunity and circumstances for sleep. All participants underwent a complete physical and neurological examination, standard laboratory tests, as well as some psychological assessments. These psychological assessments included Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Insomnia Severity Index (ISI), Hamilton Depression Scale (HAMD), and the Hamilton Anxiety Scale (HAMA). The inclusion criteria for PI patients were as follows: age 18–65 years; PSQI score >6; no neurological or psychiatric disorders, such as depression (HAMD ≤ 17), and anxiety (HAMA ≤ 14); no other sleep disorders (such as sleep-related movement disorders, hypersomnia, or parasomnia); right-hand dominance (determined by Chinese Handedness Inventory that suits Chinese people, including 10 test items) and native Chinese speakers; the insomnia drugs did not change in the four weeks prior to treatment. HC were required to meet the following criteria: no history of sleep disorders; age 18–65 years; PSQI ≤ 5; good sleep quality and no history of work time at day and night alternation; no neurological or psychiatric disorders, such as depression (HAMD ≤ 6), and anxiety (HAMA ≤ 6); no other sleep disorders; and right-hand dominance. The exclusion criteria included: patients with metal implants in their body; epileptic patients; pregnant women, and lactating women. Finally, a total of 40 subjects were recruited, which included 20 PI patients [A total of six patients took insomnia related medication, including four with benzodiazepine drugs (2 mg, Qn), one with melatonin (1 mg, Qn), one with non-benzodiazepine hypnotics dexzopiclone Tablets (2 mg, Qn)] and 20 HC participants, matched according to sex, age and education (Table 1).

Table 1
Demographics and clinical characteristics of subjects.

Variables	PI (n = 20)	HC (n = 20)	P value
Age (years)	49.2 ± 9.4	40.3 ± 9.5	0.152
Gender (male/female)	12/8	12/8	0.116
Education (years)	13.2 ± 3.1	12.9 ± 3.5	0.258

Data are presented as mean ± SD. P values were obtained by two-tailed two independent sample t-test. Abbreviation: PI, primary insomnia; HC, healthy control.

2.2. Data acquisition

All PI patients had their resting motor threshold (RMT) measured, which was defined as the lowest stimulation power that could trigger at least five motor evoked potentials, with a wave amplitude of $>50 \mu\text{V}$ among 10 trials [30]. Patients had their 20 min TMS-EEG data reported before and after rTMS therapy with magnetic resonance (MR)-compatible EEG amplifier (Yunshen, Beijing, China) and a cap (Greentek, Wuhan, China) providing 32 TMS-compatible coated-electrodes. This was positioned according to a 10–20 EEG system, and was digitized with the sample rate of 1024 Hz. Electrodes CPz and nasal tip served as the reference and ground, respectively. Healthy control group participants only had one TMS-EEG data set. During the entire experimental task, electrode impedances were consistently maintained below 5 k Ω .

Subjects were sat on a semi-reclined chair with their forearms rested on armrests. Care was taken so that subjects could remain relaxed. To limit the subjects from hearing ambient noise and the sound made by the coil discharge, they were given ear plugs. Single-pulse TMS was applied with a figure-of-eight coil (70 mm diameter) connected to a monophasic Magstim stimulator (Magstim Co. Ltd., UK). sTMS was stimulated in the right posterior parietal cortex, 80% RMT. The interval of each sTMS was set at 4 s to avoid a TMS effect and synchronous recordings of EEG was performed.

2.3. Neuropsychological assessment

Each participant underwent a series of neuropsychological assessments to evaluate their sleep situation and mental status. This included, the PSQI, the ESS, the ISI, the HAMD and the HAMA. For PI patients we completed neuropsychological assessments at three time points: before treatment, after treatment and one month after treatment. We conducted assessments for the healthy control group once only.

2.4. Treatments

We used the Rapid 2 rTMS stimulator (Magstim, Co. Ltd, UK) for PI patients with rTMS therapy. All patients were treated with rTMS between 2 pm and 4 pm. Stimulations were delivered to the right posterior parietal cortex (P4 electrode site in the 10–20 EEG system). The following stimulation parameters were used: stimulus frequency 1 Hz; stimulus intensity 80% RMT; stimulation number 3 pulses/string; string interval 1 s; total of 500 strings; total stimulation pulses 1500; total stimulation time 34 min. The treatment was applied once a day continuously for two weeks. Bedside rescue medication and facilities were available during treatment. Meanwhile, the healthy control group did not receive any therapy.

2.5. Data preprocessing

2.5.1. Time-varying network analysis

EEG data analysis was divided into data pre-processing and time-varying network analysis. The time-varying network analysis usually requires several segmentations to enable the construction of a reliable network to capture brain architectures and networks. Compared to the time-varying network analysis for the evoked EEG, which usually has definite stimulus labels, our study utilized the TMS stimulate as stimulus labels. For each labeled disturb event, the time point corresponded to the peak of the label set as time “0”, then to 0.5s data before “0” and 1s data after “0” were extracted, which lead to a total of 1.5s for each segment. Next, to reduce the

calculation load in the following time-varying network analysis, these segments were further 8-rate down-sampled [31], resulting in 32 Hz. To uncover dynamic information processing during TMS disruption, ADTF was used to construct time-varying network [22].

2.5.2. Time-varying multivariate adaptive autoregressive (tv-MVAAR) model

For each artifact-free segment, the tv-MVAAR model was defined as

$$X(t) = \sum_{i=1}^p A(i, t)X(t-1) + E(t) \quad (1)$$

where $X(t)$ represents the data vector of the EEG signal, $E(t)$ represents the multivariate independent white noise, and $X(i, t)$ represents the matrix of tv-MVAAR model coefficients that are estimated by the Kalman filter algorithm [32,33]. Represents the order of the model that is automatically determined by the Akaike Information Criterion (AIC) within the range of 2–20 as,

$$AIC(p) = \ln[\det(\chi)] + 2M^2p/N \quad (2)$$

where M represents the number of the electrodes, p represents the optimal order of the model, N represents the number of the time points of each time series and χ represents the corresponding covariance matrix.

2.5.3. Adaptive directed transfer function

Parameters $A(f, t)$ and $H(f, t)$ in the frequency domain are defined as follows;

$$A(f, t) = \sum_{k=0}^p A_k(t) e^{-j2\pi f \Delta tk} \quad (3)$$

$$A(f, t)X(f, t) = E(f, t) \quad (4)$$

$$X(f, t) = A^{-1}(f, t)E(f, t) = H(f, t)E(f, t) \quad (5)$$

where A_k denotes the matrix of the tv-MVAAR model coefficients, $X(f, t)$ and $E(f, t)$ are the Fourier transformations of $X(t)$ and $E(t)$ represents the frequency domain, respectively.

Moreover, the normalized ADTF describing the directed flow from the j th to the i th node is defined by Equation (6), and the final integrated ADTF is defined in Equation (7) within the frequency band of interest as follows;

$$\gamma_{ij}^2(f, t) = \frac{|H_{ij}(f, t)|^2}{\sum_{m=1}^n |H_{im}(f, t)|^2} \quad (6)$$

$$Q_{ij}^2(t) = \frac{\sum_{k=f_1}^{f_2} \gamma_{ij}^2(k, t)}{f_2 - f_1} \quad (7)$$

The normalized total information outflow of the j th node is further estimated in Equation (8) as;

$$Q_j^2(t) = \frac{\sum_{k=1}^n Q_{kj}^2(t)}{n-1}, \text{ for } k \neq j \quad (8)$$

where n is the total number of nodes.

2.6. Statistical analysis

For demographic and clinical variables, between-group differences, as well as before and after treatment in the same group were examined using two-sample, two-tailed t-tests. These variables included age, education, and neuropsychological measurement scores (PSQI, ESS, ISI, HAMD, and HAMA). In addition, we used a two-tailed Chi-square test to determine between-group data differences related to gender. Time-varying EEG networks were analyzed using two-tailed t-test.

3. Results

3.1. Neuropsychological characteristics

Neuropsychological data are shown in Table 2. As expected, patients with PI had higher PSQI, ESS and ISI scores than the HCs ($P < 0.05$), and significant decline after rTMS treatment and one month after treatment (Table 2).

3.2. Time-varying EEG network patterns

Based on the above time-varying network analysis, Fig. 1 and Fig. 2 show the corresponding time-varying EEG network patterns of PI patients before and after treatment as well as HCs.

In HCs, sTMS targeting the right posterior parietal cortex can induce a continuous increase of information outflow in the right occipital region, left temporal region and frontal mid-line. We found decreased information outflow in the right and left central regions, and right temporal regions. Compared with healthy subjects, sTMS targeting the right parietal region of PI patients before therapy showed excessive information outflow in the left occipital, the frontal mid-line and right posterior temporal regions, in succession. Meanwhile, it showed inadequate information outflow in the right central, right parietal and the right temporal regions. Compared with results before treatment, sTMS targeting the patients' right parietal region after treatment increased information outflow in the left temporal region and decreased information outflow in the frontal mid-line region.

4. Discussion

To the best of our knowledge, this study was the first to use low frequency rTMS to treat PI via stimulating the right posterior parietal region. The ADTF analysis of time-varying EEG network was performed to better understand the underlying neural connection mechanisms of PI patients. In the present study we found that low frequency rTMS stimulating the right posterior parietal cortex was effective to improve the symptoms of insomnia in PI patients, and that PI abnormal time-varying EEG networks showed a trend

toward normalized status after rTMS therapy. Some potential explanations for this are mentioned below.

Many studies have used fMRI to show that chronic insomnia disorder involves abnormal connectivity of brain networks involving the anterior cingulate cortex and the thalamus [34–38]. Chen et al., studied the correlation between the salience network and emotional regions in insomnia patients and found that the patients had increased functional connectivity between the insula and salience network [39]. Moreover, elevated functional connectivity between the insula and the emotional circuit was demonstrated in PI patients [40]. We consider that PI is a disease of abnormal brain function, where different cortex areas have abnormal connections. For such disease, it is difficult to quickly reverse the abnormal brain network connections using oral drugs and CBT. Non-invasive brain stimulation techniques, such as TMS and transcranial direct current stimulation enable stimulation of the human cortex in vivo, and offer useful insights into the functional integrity of intracortical circuits using electrophysiology and neuromodulation [41].

Previous rTMS studies have revealed that cortical hyperexcitability is a characteristic feature in some disorders, including chronic insomnia and RLS [42–44]. Jiang et al., applied rTMS stimulations to the right dorsolateral prefrontal cortex (DLPFC); stimulus frequency of 1 Hz; a stimulus intensity of 80% RMT; total stimulation pulses of 1800. This was performed once a day, continuously for two weeks. Related serum indicators (serum corticosterone and adrenocorticotrophic hormone) and the PSQI were used to evaluate the effect of rTMS treatment. It was shown to have advantage over medication or psychotherapy treatments [45]. Zhang et al., found the benefits of acupuncture cooperated with TMS on the treatment of chronic insomnia [46]. sTMS can be used to identify and monitor changes in cortical reactivation as well as the integrity of inhibitory and excitatory intracortical circuits [47]; rTMS is always used to modulate brain excitability and cortical function [48]. Li et al., suggested that PI patients are characterized by an abnormal organization of the right frontoparietal network [49]. Furthermore, Zhou et al., demonstrated that PI patients display abnormal amplitude of low-frequency fluctuation in the right parietal lobe [50]. Thus, the right parietal cortex is an important abnormal site in PI patients. For this reason, our study uses 1 Hz rTMS to directly hyperpolarize neural cells of the right posterior parietal cortex by pulsed magnetic field and by inhibiting the hyper-excited state of the brain cortex, which improves the patient's insomnia symptoms; the curative effect can last for one month.

We used ADTF to analyze TMS-EEG signals, as well as to prove the existence of network abnormality in patients with primary insomnia. Compared with HCs, PI patients showed more enhanced connections in the frontal mid-line and left posterior temporal regions, and decreased connections in the right central and right temporal region after using 1 Hz rTMS treatment. Related fMRI

Table 2
Neuropsychological characteristics of the subjects.

Variables	PI			HC
	Before treatment	After treatment	1 month after treatment	
PSQI	15.60 ± 2.25	10.85 ± 2.93*	10.90 ± 3.11*	2.53 ± 1.59 [#]
ESS	3.80 ± 1.26	1.62 ± 1.03*	1.15 ± 0.98*	0.82 ± 0.75 [#]
ISI	18.30 ± 5.24	10.65 ± 4.93*	9.92 ± 6.30*	1.63 ± 1.08 [#]
HAMD	8.12 ± 3.32	7.01 ± 3.46	7.51 ± 3.28	3.27 ± 1.65
HAMA	7.44 ± 4.13	6.90 ± 4.35	7.28 ± 4.92	2.86 ± 2.39

Data are presented as mean ± SD. * $P < 0.05$ versus before treatment in the same group, [#] $P < 0.05$ HC versus PI before treatment. Abbreviation: PI, primary insomnia; HC, healthy control; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale; ISI, Insomnia Severity Index; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale.

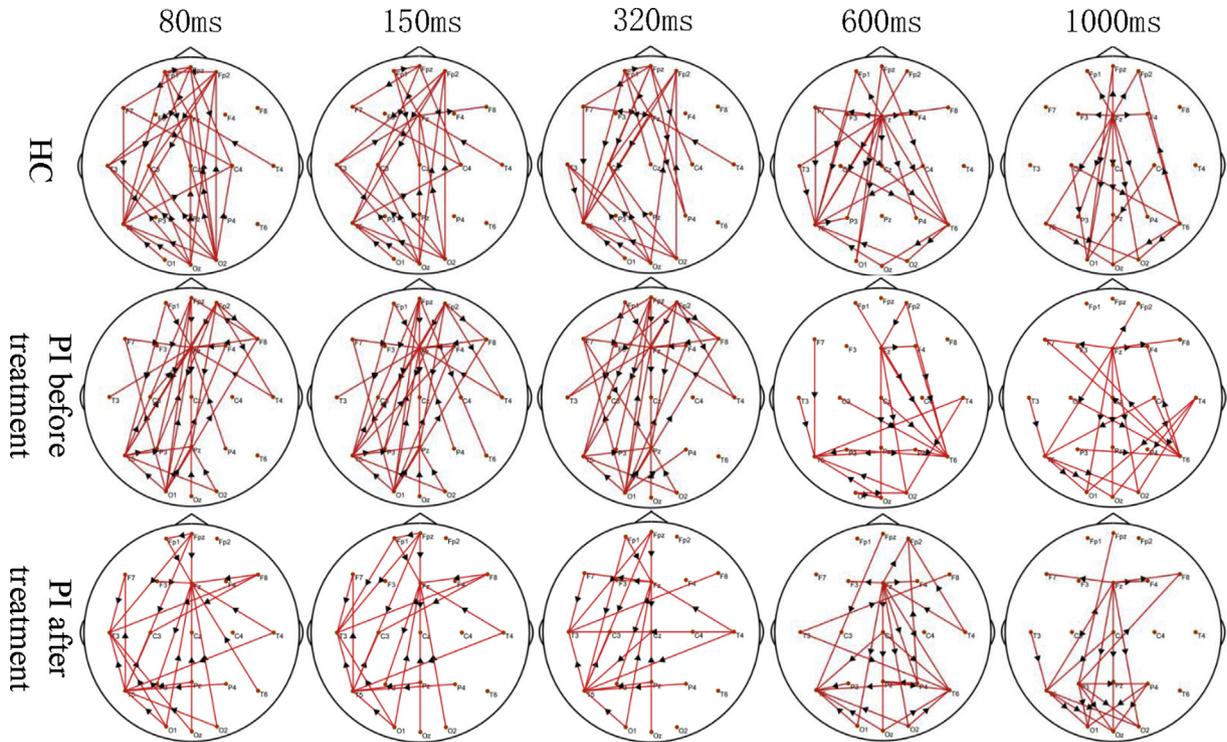


Fig. 1. Enhanced time-varying EEG network connections after sTMS stimulation compared to before stimulation. Abbreviation: PI, primary insomnia; HC, healthy control.

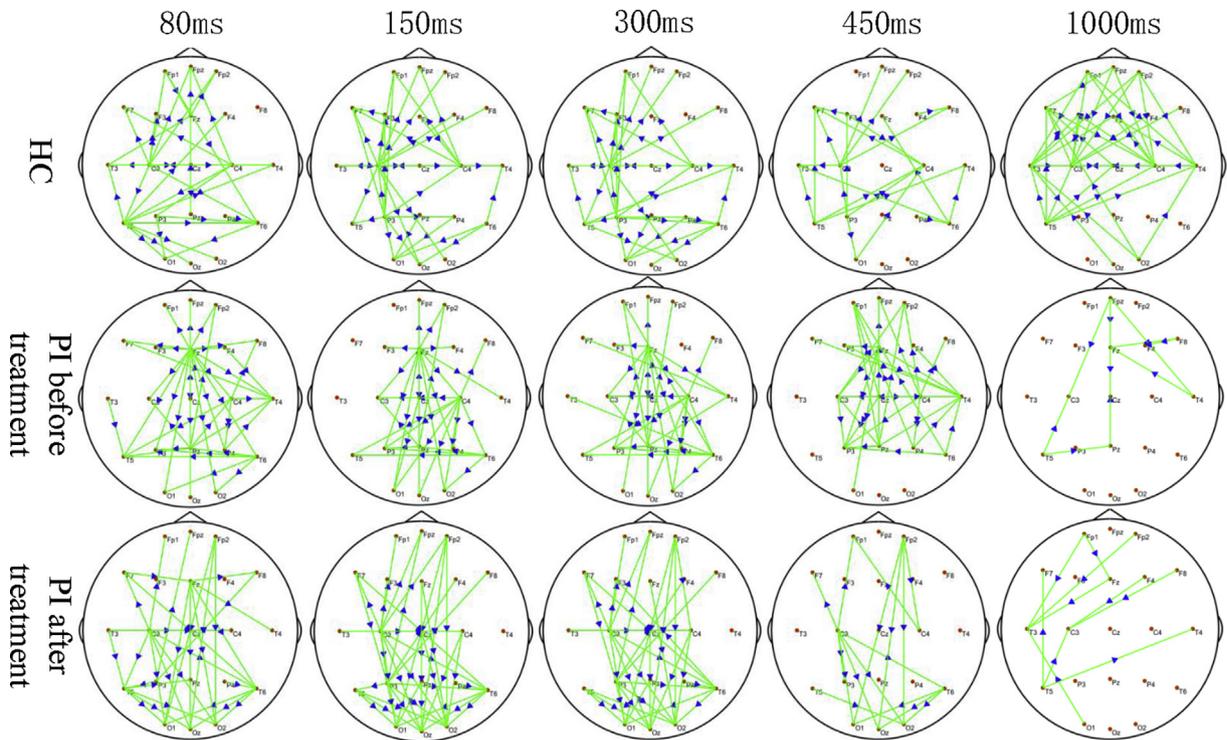


Fig. 2. Decreased time-varying EEG network connections after sTMS stimulation compared to before stimulation. Abbreviation: PI, primary insomnia; HC, healthy control.

research found that in PI functional connectivity within the default mode network (DMN) subregions were disrupted. Compared with good sleepers, PI patients showed significantly decreased region-to-region functional connectivity between the medial prefrontal cortex and the right medial temporal lobe [51]. PI appeared to have altered the functional connectivity between the parietal and frontal lobes [52]. In addition, PI patients had lower fractional anisotropy values mainly in the right anterior limb of the internal capsule, right posterior limb of the internal capsule, right anterior corona radiata, right superior corona radiata, and right superior longitudinal fasciculus [53]. We stimulated the right posterior parietal cortex and reduced connections between frontal and temporal lobes coincided with the DMN main region, thus we also verified the existence of DMN abnormalities in patients with PI [54–56].

In contrast to earlier findings, time-varying EEG network was detected in the study. The most obvious finding that emerged from the analysis was that the TMS-EEG network obtained similar results from the fMRI. This observation may support the hypothesis that PI may be a disorder of brain functional connectivity, in which case neuromodulation treatment could reverse this abnormality.

There are several factors that may limit this study, and some of them may merit further investigation. First, we did not organize a false stimulation group. Second, the cut-offs selected to define depression and anxiety in the two groups of participants were as follows: scores of ≤ 17 for HAMD and ≤ 14 for HAMA in patients, whereas scores of ≤ 6 for HAMD and ≤ 6 for HAMA in controls. This might enroll patients with secondary insomnia due to mild depressive syndromes. Third, six patients were taking insomnia drugs during the course of treatment, which may impact cortex excitability. Fourth, we did not use the neuro-navigated system to locate therapeutic targets, and the accuracy of stimulation may be lower than expected. Finally, a standard overnight polysomnography was not given to patients. Future studies with a more rigorous design should be conducted to address these aforementioned issues.

5. Conclusion

The present study was designed to determine the effectiveness of low frequency rTMS therapy for PI. We found that the curative effect lasted at least one month. PI patients showed abnormal changes of time-varying EEG networks. Our study revealed that excessive information outflow in the left posterior temporal region and frontal mid-line region; and inadequate information outflow in the right central, right parietal and right temporal regions. Low frequency rTMS treatment targeting the right parietal region may reverse these changes and improve clinical symptoms.

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Conflict of interest

The authors declare no competing financial interests.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: <https://doi.org/10.1016/j.sleep.2019.01.007>.

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