mPFC-rTMS for patients with insomnia disorder using resting-state functional magnetic resonance imaging: a protocol for a randomized controlled trial

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Abstract

Background

Insomnia is the most common sleep disorder. Repetitive transcranial magnetic stimulation (rTMS) is safe and effective for insomnia disorder (ID). Convergent evidence show that medial prefrontal cortex (mPFC) may be involved in the regulation of sleep and awakening at the cortical level, and may serve as a potential target of rTMS in the treatment of ID. The purpose of this clinical trial is to study the efficacy of mPFC-rTMS in the treatment ID and explore the neural mechanism using resting-state functional magnetic resonance imaging (fMRI).

Methods and design:

this will be a parallel group randomized, patient- and assessor-blinded trial. The study will recruit 60 ID patients assigned to a real mPFC-rTMS group or a sham mPFC-rTMS group. The allocation ratio is 1:1, with 30 subjects in each group. Interventions will be administered five times per week over a 4-week period, with an 8-week follow-up period. All participants will undergo neuropsychological and fMRI evaluations. The primary outcome measures of this study is the change scores of Pittsburgh Sleep Quality Index (PSQI). The secondary outcome measures include the fMRI measurements, the Hamilton depression scale (HAMD), the Hamilton anxiety scale (HAMA), a sleep diary, and a polysomnography. Assessment of all parameters will be performed at baseline, post-treatment, and during follow-up.

Discussion

it is expected that the study results will provide strong evidence of the effectiveness and the neural mechanism by which mPFC-rTMS improves sleep quality in ID patients.

Trial registration:

Chinese Clinical Trials Register, ChiCTR2100054154. Registered on 10 December 2021.

Introduction

Insomnia is the most common sleep disorder[1]. Due to the increase of social pressure and aging population, the prevalence of insomnia will continue to increase [2]. A recent meta-analysis of the prevalence of insomnia disorder (ID) in the general population in China showed that the prevalence rate of ID is 15.0%[3]. The long-term existence of insomnia may be the cause of the huge social and economic burden of this disease, and can lead to cognitive dysfunction, psychological abnormalities and increased suicide tendency[4]. Therefore, early identification and early effective therapies of ID patients are especially important.

At present, the first line therapies for insomnia recommended by sleep guidelines is cognitive behavioral therapy and hypnotic medication. However, many insomniac have poor compliance with cognitive behavioral therapy in clinical practice and long-term use of hypnotic medication also have side effects and increase suicide risks. In recent years, there has been an increasing number of novel physical methods to treat insomnia, such as repetitive transcranial magnetic stimulation (rTMS), which has emerged as a new option due to its low side effects.

As a neuromodulation technique, the common therapeutic target of rTMS is the dorsolateral prefrontal cortex (DLPFC). Many studies [5–7] applied rTMS (on right DLPFC, 1Hz) for insomniacs and the results indicated that rTMS can improve the sleep quality of insomniacs and the effect is better than hypnotic medication without side effects. These results suggest that rTMS is safe and effective for primary insomnia.

Huang[8] et al choose the posterior parietal lobe as stimulated position for insomnia patients with generalized anxiety. They showed that the anxiety and insomnia symptoms were improved significantly. However, some studies suggest that rTMS does not significantly improve insomnia symptoms in Parkinson's disease[9]. A recent meta-analysis suggested that rTMS was effective in ID patients, while placebo effect of sham stimulation was significant[10].

Aforementioned studies are focus on the right DLPFC or posterior parietal cortex with low frequency rTMS. Although rTMS display a certain effect, but there are still some patients cannot benefit from it. The current studies have not take involved abnormal brain network of insomnia patients as stimulation target, then in this study, we will explore the therapeutic effects and neural basis of another new stimulated target.

Insomnia is an abnormal sleep pattern. Two important neurotransmitter receptors (dopamine receptors and adenosine receptors) involved in sleep arousal are expressed in the nucleus accumbens(NAc)[11, 12]. In addition, the glutamate neurons of thalamus paraventricular nucleus and the ventral tegmental area can control awakening by regulating the NAc[13, 14]. Therefore, the NAc may play an important role in regulating sleep and awakening. Lazarus et al[15] proposed a network model of sleep-wake regulation, suggesting that adenosine and dopamine receptors in NAc regulate sleep-wake behavior through cortical activation, mainly involving the excitatory neural projection from the medial prefrontal cortex (mPFC) to NAc. In addition, mPFC can directly project excitatory neurons downward to the sleep-wake regulatory system such as tuberopapillary nucleus of hypothalamus, lateral hypothalamus and locus blueleus).These results suggest that mPFC may be involved in the regulation of sleep and awakening at the cortical level, and may serve as a potential target of rTMS in the treatment of chronic insomnia.

Two recent neuroimaging studies used functional Magnetic Resonance Imaging (fMRI) to analyse resting state functional connection (RSFC) of NAc in ID patients and revealed abnormal RSFC between NAc and mPFC which suggest the brain related to the severity of insomnia[16, 17]. Shao et al[16] proposed abnormal NAC- mPFC circuit in ID. In addition, the hypothalamus, a central role in sleep-wake regulation was recently used as the seed for functional connection by fMRI and the results showed that the bilateral

hypothalamus and bilateral mPFC resting state functional connection were enhanced in ID patients, and were positively correlated with sleep quality[18]. Moreover, neuroimaging revealed reduced gray matter density[19, 20], abnormal regional homogeneity (ReHo)[21], amplitude of low frequency fluctuations (ALFF)[22] and reduced activation of mpfc[23, 24]. These studies suggest that mPFC may play an important role in the pathophysiological mechanism of insomnia.

Therefore, we hypothesized that 1Hz rTMS stimulation over mPFC would improve insomnia symptoms of ID patients by altering mPFC -seed functional connectivity in the group receiving real mPFC -rTMS group compared with the sham mPFC -rTMS group.

Methods/design

Objective

The study objectives are: 1) to determine the efficacy of mPFC -rTMS for ID; and 2) to elucidate the neural mechanisms for the effects of mPFC -rTMS on ID.

Trial design

This study is designed as a prospective parallel group, patient and assessor blinded, randomized controlled single center clinical trial with two parallel groups. Digital randomization table will be performed as block randomization with a 1:1 allocation assigned to either a real mPFC -rTMS group or a sham mPFC -rTMS group. The neuropsychological measurements, a 1-week sleep diary, a 1-day polysomnography (PSG) and fMRI scans will be performed at baseline, post-treatment (immediately after completion of the 20-day treatment) and eight weeks follow-up (eight weeks after the last session). The detailed flowchart is shown in Fig. 1.The trial will be conducted in accordance with the SPIRIT reporting guidelines[25]. Ethical approval has been granted from ethics committee of Zhenjiang mental health center (202007) and the trial is registered at ChiCTR (CHiCTR2100054154).

Sample size

This study aims to determine the efficacy and brain mechanism of **mPFC** -rTMS in ID patients. Based on preliminary experiments, the PSQI score significantly decreased by 4.43 ± 3.60 in the group treated with mPFC -rTMS compared to 1.30 ± 2.58 in the control group. Based on a power analysis, 26 patients per group were required to detect a significant difference (power = 0.9, α = 0.05, two-sided). Thus, considering for a 15% drop out rate, we plan to recruit 30 patients per group to compensate. As to fMRI research, there is no known sample size calculation. However, for the exploratory study, 15 to 30 patients are adequate to test the null hypothesis[26].

Participants and recruitment

We will post recruitment information in the hospital to recruit participants who report clinically-significant insomnia. Prior to recruitment, investigator will inform participants the benefits, as well as possible risks

(poor therapeutic effects and adverse events associated with rTMS) in the study. All participants will sign informed consent forms before collecting data and randomization.

Investigators will decide whether the participants meet the inclusion criteria based on the scores of PSQI, HAMD and HAMA. The eligible participants will complete a baseline rs-fMRI, a 1-week sleep diary and a 1-day polysomnography (PSG). All participants who satisfy the inclusion criteria will be randomly divided into either a real mPFC -rTMS group or a sham mPFC -rTMS group in a ratio of 1:1.

Inclusion criteria

Participants who compliance with all the following criteria will enrolled in the clinical trial:

1. Aged 18–65

2. Meeting the diagnostic criteria for insomnia disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
3. PSQI score > 11 points; HAMD-14 score < 7; HAMA score < 14; and HAS score > 32
4. Sign informed consent forms for this study

5. Have not received medications for anxiety, depression, or insomnia within 4-week prior to enrollment in the study

6. No history of staying up late and shift in the past 4-week

Exclusion criteria

Participants who compliance with one or more the following criteria will be excluded in the clinical trial:

1. Having a family history of mental illness or other mental illness

2. A history of alcohol and drug abuse

3. Insomnia caused by other sleep disorders such as sleep apnea syndrome and restless legs syndrome

4. Serious medical diseases including cardiovascular system, nervous system, urinary system, respiratory system, digestive system and other serious physical diseases

5. Pregnant or breastfeeding women

6. Received physical therapy such as rTMS, transcranial direct current stimulation or electroshock in the last months

7. Contraindication for MRI including claustrophobia; abnormal signal or obvious asymmetrical head structure by MRI

Randomization, allocation concealment and blinding

The eligibility participants will be randomly assigned to either a real or a sham mPFC -rTMS group with a 1:1 allocation. This study will use Statistical Analysis Software (version 9.3, SAS Institute Inc., Cary, NC, USA) to generate the random allocation sequence. The list of randomization will be closed in computer-generated opaque envelopes with sequence numbers printed on the outside of the envelopes. After researchers screened the eligible patient, the envelopes will be opened by the researchers. The trained operators who operate rTMS will not be blinded to allocation and therefore will be excluded from assessments and data processing. Participants, statistical analysts and assessors will be blinded. Unblinding should only be performed in case of an emergency, such as any serious adverse events.

Intervention

The subjects will be prohibited from receiving any other relevant treatment include drug that can improve sleep during the trial period. All relevant treatments and compliance will be recorded in the case report form.

Real mPFC -rTMS group (shown in Fig. 2)

All operators who operate mPFC -rTMS will receive training to ensure consistent rTMS technique on all participants. Deep transcranial magnetic stimulation (dTMS) was administered using a Magstim Rapid2 TMS stimulator (Magstim, Whitland, U.K.) with H7 coil (Brainsway, Jerusalem, Israel). The front rim of helmet was fixed at one cm above the nasion, then treatment location of H7-coil stimulates is mPFC bilaterally. Before the first treatment session, single pulse TMS was delivered to measure the resting motor threshold (RMT) of extensor halusis brevis muscle of the participant's toes. RMT was defined as the minimum intensity, which elicited 3 motor evoked potential (MEP) responses in 6 attempts. Treatment parameters were 1 Hz, 5 second stimulation, 1 second stimulation intervals with a stimulation intensity of 80% of RMT. The number of repetitions was 200, the total number of pulses was 1000 and the total stimulation time was 20 min. The real mPFC -rTMS therapy will be performed 1 times per day at 5 days per week for 4 weeks.

Sham mPFC -rTMS group (shown in Fig. 2)

The sham mPFC -rTMS group will be delivered by a single helmet with sham coils. The sham coil is designed to induce similar noise and scalp sensations with same parameters as the active stimulation group.

Functional MRI scanning procedure

The resting-state fMRI data will be obtained at Zhenjiang Mental Health Center with a Philips 3.0 Tesla MRI scanner. All fMRI images will be acquired from a Gradient echo - echo plane imaging under the following parameters: 30 slices, repetition time(TR) = 2000 ms, echo time(TE) = 30 ms, thickness = 5 mm, field of view(FOV) = 240 ×240 mm, flip angle = 90°, and matrix size 64mm × 64mm and total 185 volumes. Participants will required to stay awake, keep eyes closing, do not move, close eyes, and do not try to think about anything. The real and sham mPFC -rTMS groups will be examined three times (baseline, post-treatment and follow-up).

Follow-up procedure

Eight weeks after the end of treatment, the PSQI, fMRI, HAMD, HAMA, PSG, and sleep diary records will be collected.

Outcome

Primary outcome

Our primary outcome will be the mean change scores of insomnia severity assessed using PSQI between the baseline, post-treatment assessment, and 8-weeks follow-up. The PSQI is a 19 item insomnia assessment tool consisting of seven component scores, including sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disorders, hypnotic medication and daytime dysfunction. The higher score reflect the worse of the sleep quality.

Secondary outcomes

Secondary outcome in this study will be mean change scores of HAMD and HAMA, the weekly average of the components in the sleep diaries during the 1-week period, and changes of the Sleep Latency(SL), Sleep efficiency(SE), Total Sleep Time(TST), and so on which are collected through PSG between the baseline, post-treatment assessment, and 8-weeks follow-up.

Sleep diary

The sleep diary will be kept by the ID patients to record their sleeping and waking times as well as additional sleep-related factors. It is a useful tool to assess sleep quality and monitor whether treatment is working.

HAMD and HAMA

The HAMD and HAMA will be used to assess depression and anxiety of ID patients. In this study, we will adopt the 17-item scale of HAMD and 14-item scale of HAMA. The HAMD and HAMA score more than 7 point are considered as may be present depressive and anxiety symptoms.

Psg

We will use PSG to collected sleep parameters (TST, sleep latency, actual total sleep time, sleep efficiency) and sleep stage (N1, N2, N3, REM sleep, percentage of total sleep time in each phase).

Safety monitoring

Potential adverse events of mPFC-rTMS include mild headache, memory impairments and seizures. Participants will be asked to report any adverse events at each patient visit. There is no anticipated harm and no compensation for participants.

Quality control and guarantee

At the begaining of study, the whole research process, criteria for inclusion and exclusion, rTMS operation, curative effect observation, data collection and management, and adverse event reporting and recording will be trained for the researchers.

The trial will be withdrawal under the following conditions:

1. Patients with deterioration condition

2. Patients with serious adverse events who need to stop rTMS treatment

3. Other serious physical diseases during the test

4. From the medical and ethical perspective, the researcher considered that it is necessary to terminate the research

5. Participants are reluctant to continue the study and withdrawal of informed consent for non-medical reasons

6. Withdrawal of informed consent
The research data will be recorded and **stored** correctly, completely, and consistent with the original data **in the form of double data entry** under the study management team which is set up to take charge of the quality control and supervise the research process. The scale evaluation is completed by designated persons. PSG is conducted by professionals in the Sleep rehabilitation center of Zhenjiang mental health center. fMRI is conducted by professionals in the Imaging department of Zhenjiang mental health center. When the subjects drop out, The researchers will interview by face to face, phone or mail and so forth to ask for reasons, record the time of the last treatment, and complete the evaluation items as far as possible. Patients with deterioration condition, adverse events, other serious physical diseases will be taken corresponding treatment measures. Patients who have been ranked with random numbers will be included in the statistical analysis if they receivied more than half of the treatment course. All dropouts will be analyzd according to intention-to-treat principle after the trial.

Statistical analysis

For clinical data, statistical analyses will be analyzed using Statistical Package for the Social Sciences (version 19.0). Two-sided tests will be considered statistically significant if $P \leq 0.05$. Cases of any missing data should be listed and the reasons should be indicated. The main efficacy analyses will be conducted based on the intention-to-treat principle. Sociodemographic information and outcome indicator will be presented with the mean ± standard deviation or the frequency (%) for the real mPFC-rTMS group and the sham mPFC-rTMS group. Independent t tests will be used to compare of outcome indicators between the two groups before and after mPFC-rTMS. Paired t tests will be used to compare the pre-rTMS and post- rTMS outcome indicators within each group. A repeated measures analysis of

variance with adjustments for non-sphericity will be applied to analyze group differences and time-dependent effects of rTMS on outcome indicators.

For fMRI data, statistical analyses will use SPM12 (http://www.fil.ion.ucl.ac.uk/spm), Data Processing & Analysis of Brain Imaging toolbox (http://rfmri.org/dpabi) and VBM8 toolbox (http://dbm.neuro.unijena.de/vbm) plugged into MATLAB_R2018a (Mathworks, Inc., Natick, MA, USA). Original data will be preprocessed: slice timing, affine head motion, and nonbrain extraction, spatial smoothing and temporal filtering will be applied. The regional resting-state fMRI time series will extract for the bilateral mPFC by using the average functional time series of all voxels within each region. Significance was set at a p value < 0.05 after correcting for multiple comparisons using false discovery rate(FDR) correction. Pearson correlation will be used to investigate the RSFC between bilateral mPFC and the whole-brain regions, and then a Fisher' s r-to-z transform is employed. mPFC-based functional connectivity pre-rTMS and post-rtms between the real and sham mPFC-rTMS group will be compared using independent t tests. Paired t tests will be used to compare pre-rTMS and post-rtms mPFC-seed functional connectivity within each group.

Discussion

Previous studies have shown that rTMS is effective in treatment insomnia, but no study select targets based on neural network connectivity. We review literature and find that mpfc may be one of the potential targets. Therefore, it is necessary to carry out further clinical trials to clarify the efficacy and possible neural mechanisms of mPFC-rTMS for ID patients. It is expected that this clinical trial will provide important data of the effect of rTMS and its possible neural mechanisms for ID.

We speculate that this effect may have relevance to the modulation mpfc-based functional connectivity. If our hypothesis is correct, functional connectivity maps of the sleep-related regions will be more modulated in the group receiving real mPFC-rTMS than in the sham mPFC-rTMS group. These results will provide insight into the potential mechanism of rTMS for ID.

Trial status

The protocol version number is 1.1 and the date is 11 January 2020.The ethics committee of Zhenjiang mental health center approved the study protocol on 3 January 2022 (permission 202007). This trial was registered in 10 December 2021 (ChiCTR2100054154). The trial started in 1 March 2022. The trial is currently recruiting participants. We predict that recruitment will be completed by 28 February 2023.

Declarations

Acknowledgments

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Authors' contributions

SJJ,LGH and WZB participated in the clinical trial design and ZDW wrote the drafting manuscript and plans for the analysis of the data. ZJ and DKM participate in data collection and are in charge of the recruitment. LS and XWY conduct the rTMS operation. WZB is the corresponding author of this article. All authors read and approved the publication of this protocol.

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Availability of data and materials

All study-related data will be stored securely at the Zhenjiang mental health center. The datasets analyzed during the current study are available from the corresponding author for a future secondary analysis.

Ethics approval and consent to participate

The ethics committee of Zhenjiang mental health center approved the study protocol on 3 January 2022 (permission 202007). This trial was registered in December 2021 (ChiCTR2100054154). Informed consent will be required for study participation.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

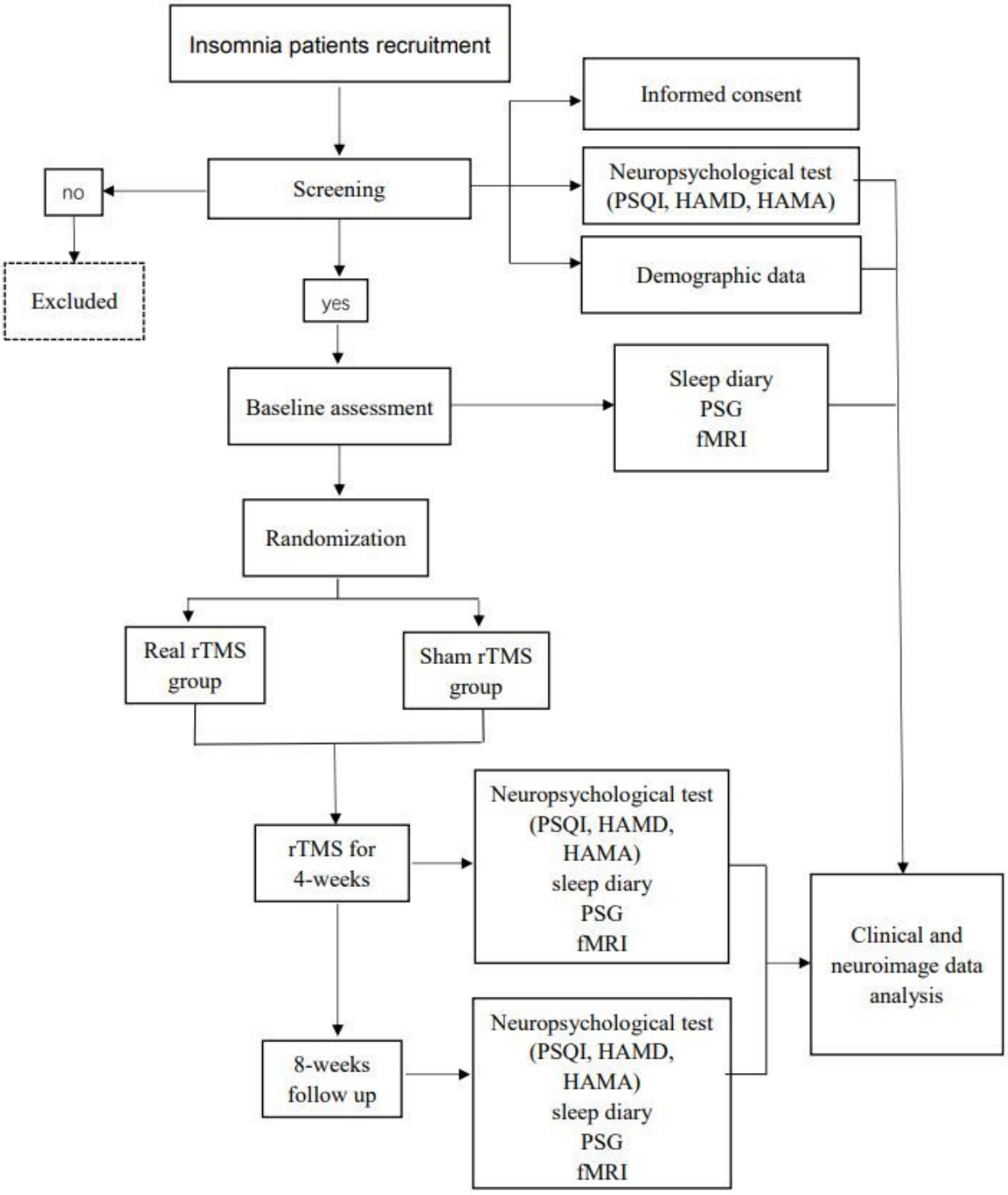

Figure 1

Flow chart of study. PSQI Pittsburgh Sleep Quality Index, HAMD Hamilton Depression scale, HAMA Hamilton Anxiety scale, PSG polysomnography, fMRI functional magnetic resonance imaging

	STUDY PERIOD						
	Enrolment	Allocation	Treatment period				Follow-up period
TIMEPOINT**	*-1 week*	0	*1 week*	*2 week*	*3 week*	*4 week*	*12 week*
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Baseline assessment	X						
Allocation		X					
INTERVENTIONS:							
Real rTMS group			X	X	X	X	
Sham rTMS group			X	X	X	X	
ASSESSMENTS:							
PSQI	X					X	X
HAMD]	X					X	X
HAMA	X					X	X
Sleep diary	X					X	X
PSG	X					X	X
fMRI	X					X	X
Adverse events			X	X	X	X	

Figure 2

Enrollment schedule, treatment, and outcome measures. PSQI Pittsburgh Sleep Quality Index, HAMD Hamilton Depression scale, HAMA Hamilton Anxiety scale, PSG polysomnography, fMRI functional magnetic resonance imaging

Supplementary Files

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