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Comparisons of transcranial alternating current stimulation and repetitive transcranial magnetic stimulation treatment therapy for insomnia: a pilot study

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To the editor:

Insomnia disorder has a serious and widespread detrimental effect on humans with comorbidity with other mental or physical health problems.[1 2] In recent years, non-invasive brain stimulation (NIBS) techniques, especially transcranial magnetic stimulation (TMS) and transcranial electrical stimulation, have been increasingly used for the treatment of brain diseases, including insomnia disorder.

Low-frequency repetitive transcranial magnetic stimulation (rTMS) has been proven to reduce neuronal excitability to modulate the abnormal hyperarousal of patients with insomnia. The efficacy of rTMS for insomnia has been observed, and rTMS may be a safe and effective option for insomnia treatment.[3] However, the stimulation effects of rTMS have varied substantially across studies and individuals. rTMS was found to produce region-specific effects that critically depend on the connectivity profile of target regions, and an extended, trans-scale model has been developed.[4] Unfortunately, it could not simply generalise across different protocols, which hindered the development of more precise and effective regulation for brain abnormalities. A previous review indicated that dorsolateral prefrontal cortex (DLPFC) stimulation by rTMS could modulate the release of key neurotransmitters in the sleep–awake cycle. Even though the proposed mechanisms were still speculative, the review indicated that the stimulation of DLPFC (right, left and bilaterally) with low frequencies (1 Hz) could improve sleep architecture and quality.[5] Continued research into better rTMS protocols for treating insomnia disorder and further study of the mechanisms of efficacy were still warranted.

It is also worth noting that transcranial alternating current stimulation (tACS) has received much attention in recent years. tACS was able to modulate neural oscillations of specific frequencies through entrainment.[6] Such frequency specificity facilitated the precise modulation of the brain, leading to a better therapeutic effect. Currently, tACS has been showing results for initial sleep regulation and insomnia treatment.[7 8] Since the role of the theta rhythm as a marker of sleepiness during wakefulness and early phases of spontaneous sleep onset is well known,[9] the theta band could potentially serve as a target for modulation. Moreover, abnormalities in neural oscillatory activity in the theta band of the brain in patients with insomnia have been observed.[10 11] More importantly, previous studies found that 5 Hz tACS of the DLPFC before bed in healthy subjects induced an accelerated effect on the sleep onset process,[12] and theta-tACS during wakefulness resulted in increased sleep pressure and greater slow-wave activity in sleep after the stimulation.[13] Therefore, frequency-specific modulation of theta activity might have a therapeutic effect on patients with insomnia disorder. Additionally, a preliminary study suggested that a personalised frequency of tACS increased sleep quantity and reduced sleep onset better than a fixed frequency, even though the subjects recruited in the study were not patients with diagnosed insomnia disorder.[8]

However, the strategy of rTMS for insomnia disorder remained unexplored, and whether theta-tACS could treat insomnia disorder had yet to be validated. In addition, few studies

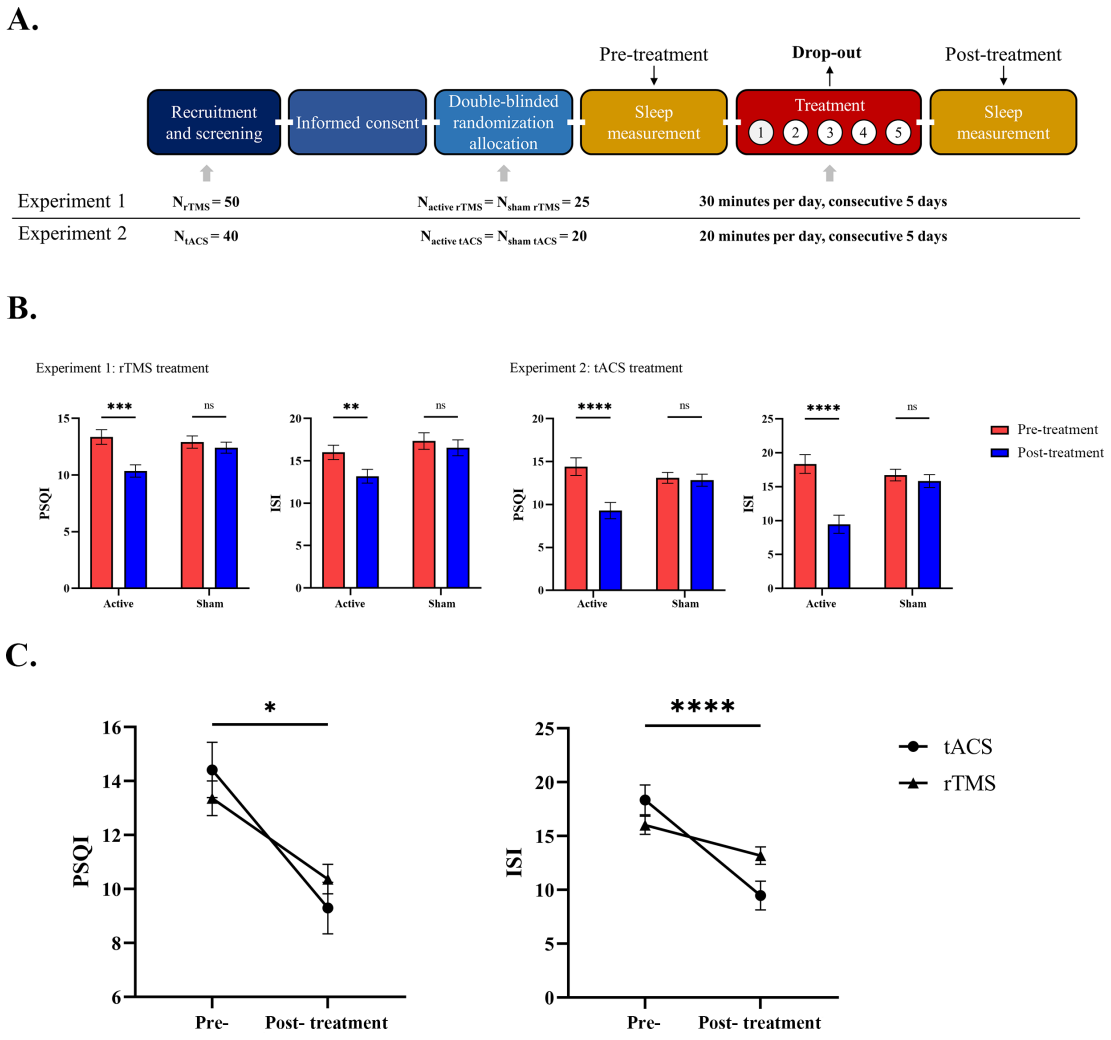

Figure 1 (A) Flowchart of the two independent experiments. (B) In experiment 1, the PSQI (p=0.001) and ISI (p=0.002) scores were significantly reduced in patients with insomnia after the active 1 Hz rTMS treatment. In experiment 2, the PSQI (p<0.0001) and ISI (p<0.0001) scores were significantly reduced after the active 5 Hz tACS treatment. In contrast, no significant difference was found in the sham groups in either of the two experiments (Wilcoxon matched-pairs signed-rank tests). (C) The two-way repeated measures ANOVA (treatment×time) revealed significant interaction effects (treatment×time) for subjective sleep measurements (tACS: $N_{pretreatment}$=$N_{post\text{-}treatment}$=17; rTMS: $N_{pretreatment}$=$N_{post\text{-}treatment}$=22; PSQI: *F*=5.942, p=0.020; ISI: *F*=22.77, p<0.0001). Error bars indicate SE. *p≤0.05, **p≤0.01, ***p≤0.001, ****p≤0.0001, ns, not significant. ANOVA, analysis of variance; ISI, Insomnia Severity Index; PSQI, Pittsburgh Sleep Quality Index; rTMS, repetitive transcranial magnetic stimulation; SE, standard error; tACS, transcranial alternating current stimulation.

have compared the efficacy of the two NIBS techniques for insomnia disorder. Therefore, the current study investigated the efficacy of low-frequency rTMS and theta-tACS for insomnia disorder, and a further comparison was performed. Moreover, another experiment was conducted to investigate whether a personalised frequency of theta-tACS could obtain better efficacy for patients with insomnia disorder.

An overview of the first two experiments is illustrated in figure 1A. The two separate experiments were identical except for the different treatment protocols. A double-blind, sham-controlled experimental design was employed (see online supplemental information). In addition, the patients in experiment 3 were randomised into two groups and received treatments with the same process, differing only in the stimulation frequency (figure 2A). Subjective sleep data (Pittsburgh Sleep Quality Index (PSQI) and Insomnia Severity Index (ISI)) were collected before and after the treatment. We used the diagnostic criteria for insomnia disorder outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), to enroll 50 patients (29 female, mean (standard deviation (SD)) age: 44.92 (11.79) years) in experiment 1, 40 patients (22 female, 46.93 (10.52) years) in experiment 2 and 30 patients in experiment 3 (17 female, 47.1 (7.88) years). The study was conducted at the Second Hospital of Hebei Medical University from August 2019 to June 2023. All the participants were outpatients (details in online supplemental table 1). It should be noted that the patients did not have comorbidities with depression or anxiety. In addition, all patients participating in the experiments were asked not to use hypnotic

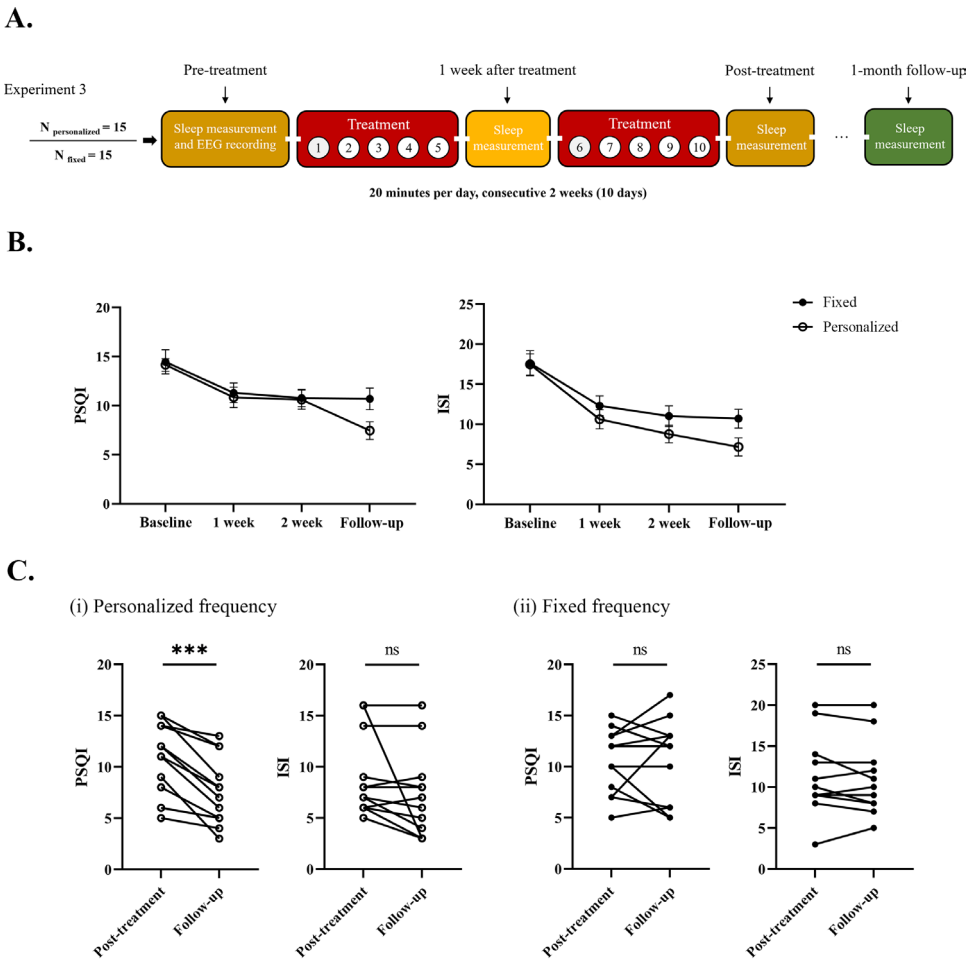

Figure 2 (A) Flow chart of experiment 3. The process of recruiting patients was the same as in the previous two experiments and has been omitted here. Patients were randomised into personalised frequency and fixed frequency groups with the same process except for the difference in stimulation frequency. (B) The variation tendency of PSQI and ISI scores at four time points (before treatment, 1 week after treatment, 2 weeks after treatment and at 1-month follow-up) for patients receiving fixed frequency tACS treatment and personalised frequency tACS treatment. (C) Patients with insomnia disorder treated with a personalised frequency had a significant decrease in PSQI scores at the 1-month follow-up period compared with post-treatment scores (Wilcoxon matched-pairs signed-rank test, p=0.001), with no significant change in ISI scores. For patients in the fixed frequency group, there was no significant change in either PSQI or ISI scores at the follow-up period compared to post-treatment. Error bars indicate SE. ***p≤0.001, ns, not significant. EEG, electroencephalogram; ISI, Insomnia Severity Index; PSQI, Pittsburgh Sleep Quality Index; SE, standard error; tACS, transcranial alternating current stimulation.

drugs or receive other treatments related to insomnia 2 weeks prior to and throughout their participation in the study. All stimulation treatments were performed during the daytime while the participants were awake. Written and informed consent was obtained from all participants.

In experiment 1, the patients were randomly separated into active (n=25) or sham (n=25) groups. Then, five sessions of rTMS on the left DLPFC were delivered over 5 consecutive days (30 min per session). Due to personal reasons, the number of patients who completed the entire experimental process was 22 in the active group and 24 in the sham group. Low-frequency rTMS was administered using a MagPro R30 TMS stimulator with an '8'-shaped coil (MagVenture, Denmark). The location of the left DLPFC was determined according to the '5 cm rule' (5 cm anterior to the motor hot spot for producing the maximal motor response in the left abductor pollicis brevis muscle). The rTMS stimulation was delivered at 1 Hz, and the stimulus intensity was set at 80% of the resting motor threshold. Sham rTMS was carried out by rotating the coil by 90°.

In experiment 2, the patients were randomly separated into active (n=20) or sham (n=20) groups. Then, five sessions of tACS on the left DLPFC were delivered over 5 consecutive days (20 min per session). Due to personal reasons, the number of patients who completed the entire experimental process was 17 in the active group and 18 in the sham group. Theta-frequency stimulation was administered with a ±2 mA sinusoidal current oscillating at 5 Hz, using high-definition transcranial alternating current stimulation (HD-tACS) (Soterix Medical, New York, New York). Stimulation electrodes were placed in a 4×1 montage, including four surrounding (AF3, F1, F5 and FC3) and one central (F3) electrodes, according

to the international 10–10 electroencephalogram (EEG) system. The sham group received theta-tACS for 10 s at the beginning and end of the phase.

In experiment 3, the patients were randomly separated into fixed frequency (n=15) or personalised frequency (n=15) groups. Then, 10 sessions of tACS on the left DLPFC were delivered over 2 consecutive weeks (20 min per session). Due to personal reasons, the number of patients who completed the entire experimental process was 13 in the fixed frequency group and 13 in the personalised frequency group. For the fixed frequency group, the same stimulus parameters were used as in experiment 2. Resting-state EEG data were collected for the personalised frequency group to calculate the personalised frequency before the treatment (see online supplemental information).

No adverse effects were reported in the study. In the first two experiments, there were no significant differences in pretreatment PSQI and ISI scores between the patients participating in the two different treatment protocols (two-sample t-test, PSQI: t=0.906, p=0.371; ISI: t=1.528, p=0.135). In addition, Shapiro-Wilk tests indicated that the data followed a normal distribution. Then, two-way repeated measures analysis of variance (ANOVA) were conducted to examine the interaction effects between time (before or after treatment) and treatment protocols (rTMS or tACS) on PSQI and ISI, and a significant interaction effect on both subjective sleep measurements was found (PSQI: F=5.942, p=0.020; ISI: F=22.77, p<0.0001; Bonferroni correction: p<0.025) (figure 1C), and the Levene's test demonstrated homogeneity of variances.

Considering the small sample size, Wilcoxon matched-pairs signed-rank tests were performed, and the results revealed that patients in the active stimulation group of both rTMS and tACS treatment protocols had significantly improved sleep quality (PSQI: rTMS, Z=−3.454, p=0.001; tACS, Z=−3.643, p<0.0001) and reduced insomnia severity (ISI: rTMS, Z=−3.084, p=0.002; tACS, Z=−3.632, p<0.0001). In contrast, no significant change was found in the sham group (PSQI: rTMS, Z=−1.210, p=0.226; tACS, Z=−1.068, p=0.285; ISI: rTMS, Z=−1.242, p=0.214; tACS, Z=−1.651, p=0.099) (figure 1B). In detail, patients with insomnia disorder showed a 22.45% and 17.61% decrease in their PSQI and ISI scores, respectively, after 5 consecutive days of 1 Hz rTMS treatment. In contrast, the PSQI and ISI scores of patients treated with 5 Hz HD-tACS for 5 consecutive days decreased by 35.51% and 48.40%, respectively.

In experiment 3, subjective sleep assessments were carried out at four distinct time points, as depicted in figure 2B, illustrating the trend of changes. Interestingly, Wilcoxon matched-pairs signed-rank tests indicated that the PSQI scores of the patients treated with personalised frequency tACS had a significant reduction from the end of the 2-week treatment to the 1-month follow-up (Z=−3.195, p=0.001), whereas this did not occur in the fixed frequency tACS treatment group (Z=−0.313, p=0.754) (figure 2C).

In the first two experiments, the current study validated the efficacy of 5 consecutive days of 1 Hz rTMS and 5 Hz HD-tACS modulation over the left DLPFC for insomnia disorder by demonstrating subjective sleep quality improvement and reduction of insomnia severity. Although the mechanisms by which rTMS and tACS modulated the brain were distinct, both treatment protocols showed significant efficacy. Interestingly, we compared the efficacy between the two treatment protocols through a repeated measure ANOVA and a significant 'treatment×time' interaction effect was observed, implying that tACS might have greater improvement for insomnia disorder compared with rTMS under the protocols used in the current study.

Additionally, although the previous study obtained some initial findings suggesting that, compared with using fixed stimulation frequency, personalised frequency of tACS improved sleep better, it was not specific to the population of patients with insomnia disorder, and it used a within-subject design that was not conducive to follow-up testing of the long-term effects of different treatment protocols. In contrast, we employed a between-subject design in experiment 3, and we extended the duration of tACS treatment to 10 days, according to previous studies[7 8] and with the consideration of observing the lasting effects in the follow-up period. The results of the Wilcoxon matched-pairs signed-rank tests revealed that personalised frequency of tACS could bring greater long-term efficacy for patients with insomnia disorder than using a fixed frequency, as evidenced in particular by sustained reductions in PSQI scores of the patients.

The neurological mechanisms of insomnia disorder were complex and were associated with abnormal brain function and neural oscillations.[10 14] With the existing understanding of the principles of the two NIBS techniques mentioned above,[4 6] tACS benefited from the ability to modulate neural oscillations specifically by targeting frequencies directly, which might make it easier to achieve more precise modulation of the brain in patients with insomnia disorder and achieve better or more rapid results. Moreover, the use of a personalised frequency could, to some extent, deal with the problem of individual differences in the frequency of neural oscillations among patients and could further improve the efficacy.

In conclusion, our study suggested that both the 1 Hz rTMS and the 5 Hz HD-tACS on the left DLPFC have demonstrated efficacy for insomnia disorder. Additionally, we found greater improvement with tACS than with rTMS after 5 consecutive days of treatment. Moreover, we also found that treatment with a personalised theta frequency brought longer durationality compared with using a fixed 5 Hz frequency. Currently, tACS as a NIBS technique has not yet become a routine treatment for insomnia disorder in clinical practice, and our findings have provided evidence of its efficacy and a specific treatment protocol for its wide application in future clinical treatment of insomnia disorder. Moreover,

using personalised frequency tACS could bring about more sustained improvements in patients' sleep quality. However, when making clinical treatment decisions, given the differences between individual patients, it should be noted that the predictive outcome of the treatment effect of these NIBS therapies is well worth considering. Researchers are already working on these predictions, although they are not widely used in clinical practice.

The current study still has some limitations. The sleep quality should be monitored by polysomnography, and the different underlying mechanisms of rTMS and tACS should also be investigated by neuroimaging technologies such as EEG and magnetic resonance imaging. Finally, the experiments had only a small number of subjects, especially experiment 3.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by the Ethics Committee of Medical Research at The Second Hospital of Hebei Medical University, Shijiazhuang, China (approval letter no: 2022-R758). The experimental procedure was fully explained and informed written content was obtained from all participants. Participants gave informed consent to participate in the study before taking part.

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