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Medial parietal alpha-frequency transcranial alternating current stimulation for chronic insomnia: a randomized sham-controlled trial

Li Wang[1], Yanlin Chen[1], Zhixin Piao[1], Xuecun Gu[2], Hongzhi Liu[2], Di Wang[2], Zilong Yan[1], Yanru Liu[3], Guang Shi[2], Qing Cui[2], Tiantian Liu[1], Yang Li[2], Zhulin Xiao[4], Wei Meng[5], Tianyi Yan[1] and Kun Wang[2]

[1]School of Medical Technology, Beijing Institute of Technology, Beijing, China; [2]Department of Neurology, Beijing Puren Hospital, Beijing, China; [3]Department of Clinical Psychology, Beijing Huilongguan Hospital, Beijing, China; [4]Beijing Lianying Yinghe Medical Imaging Diagnosis Center, Beijing, China and [5]Department of Radiology, Harbin Medical University, Harbin Medical University Cancer Hospital, Harbin, China

Original Article

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Corresponding authors:
Wei Meng, Tianyi Yan and Kun Wang;
Emails: articlemengwei@163.com; yantianyi@bit.edu.cn; 1962774045@qq.com

Abstract

Background. Patients with chronic insomnia are characterized by alterations in default mode network and alpha oscillations, for which the medial parietal cortex (MPC) is a key node and thus a potential target for interventions.

Methods. Fifty-six adults with chronic insomnia were randomly assigned to 2 mA, alpha-frequency (10 Hz), 30 min active or sham transcranial alternating current stimulation (tACS) applied over the MPC for 10 sessions completed within two weeks, followed by 4- and 6-week visits. The connectivity of the dorsal and ventral posterior cingulate cortex (vPCC) was calculated based on resting functional MRI.

Results. For the primary outcome, the active group showed a higher response rate (≥ 50% reduction in Pittsburgh Sleep Quality Index (PSQI)) at week 6 than that of the sham group (71.4% versus 3.6%) (risk ratio 20.0, 95% confidence interval 2.9 to 139.0, p = 0.0025). For the secondary outcomes, the active therapy induced greater and sustained improvements (versus sham) in the PSQI, depression (17-item Hamilton Depression Rating Scale), anxiety (Hamilton Anxiety Rating Scale), and cognitive deficits (Perceived Deficits Questionnaire-Depression) scores. The response rates in the active group decreased at weeks 8–14 (42.9%–57.1%). Improvement in sleep was associated with connectivity between the vPCC and the superior frontal gyrus and the inferior parietal lobe, whereas vPCC-to-middle frontal gyrus connectivity was associated with cognitive benefits and vPCC-to-ventromedial prefrontal cortex connectivity was associated with alleviation in rumination.

Conclusions. Targeting the MPC with alpha-tACS appears to be an effective treatment for chronic insomnia, and vPCC connectivity represents a prognostic marker of treatment outcome.

Introduction

Insomnia is one of the most prevalent health problems worldwide (Riemann et al., 2022). Chronic insomnia is associated with a constellation of negative physical and mental consequences (Roach et al., 2021). As the main treatment for insomnia, pharmacotherapy has concerns regarding side effects and potential dependency, and cognitive behavioral therapy for insomnia (CBT-I) is time-consuming and rarely used although recommended as first-line treatment (Riemann et al., 2022; Roach et al., 2021). This dilemma calls for the development of new treatments.

Non-invasive brain stimulation (NIBS) has shown great promise in treating insomnia, owing to its ability to non-invasively modulate brain function. Major NIBS techniques include repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). rTMS uses pulsed magnetic fields to non-invasively penetrate the skull and act on the specific cortex, affecting neural electrical activity in the brain. Published research applied low-frequency rTMS to unilateral or bilateral dorsolateral prefrontal cortex (DLPFC) or right posterior parietal cortex (Huang et al., 2018; Qi et al., 2022). tDCS works in a polarity-dependent fashion, with anodal stimulation increasing and cathodal stimulation decreasing cortical excitability. Systematic reviews and meta-analyses suggest that while the efficacy concerning objective sleep is conflicting, subjective assessments show clear improvements after applying tDCS over the PFC (Donde et al., 2021; Herrero Babiloni et al., 2021; Krone, Feher, Rivero, & Omlin, 2023; Ma et al., 2021). However, most of the evidence is derived from healthy individuals or patients with neuropsychiatric diseases; only a few were conducted on primary insomnia. The methodological issues such as insufficient blinding, a lack of sham condition, small sample sizes, or lack of follow-up may also limit the generalizability of treatment. Transcranial alternating current stimulation (tACS) entertains endogenous neural rhythms by delivering periodic microcurrents

to cortical sites. Compared with tDCS or rTMS which work with a unitary principle of excitation or inhibition, tACS affords the advantage of modulating not only the amplitudes and frequency but also the phases of oscillations. Two studies conducted in patients with chronic insomnia have shown the potential of tACS in modulating sleep (Motamedi et al., 2023; HX Wang et al., 2020). Nevertheless, these studies targeted the PFC, and the stimulation was delivered in a non-focal manner. Attempts at new targets and stimulation modes may provide more optimized options for the treatment of insomnia.

Plenty of neuroimaging evidence has advanced our understanding of activation and connectivity in the intrinsic human brain. The central networks and connectional 'hubs' suggested by these neuroimaging evidence provide potential targets for interventions (van den Heuvel & Sporns, 2013). The default mode network (DMN), with the medial parietal cortex (MPC) and PFC as core components, is highly active during the resting state and represents a hybrid hub for local and distant connections (Buckner & DiNicola, 2019; Margulies et al., 2016). The precuneus is an important node within the MPC and is involved in consciousness processing and sleep-wake regulation (Buckner & DiNicola, 2019; Kalauzi, Vuckovic, & Bojic, 2012). DMN is modulated by alpha oscillations (8–12 Hz) (Clancy et al., 2022), a primary rhythm of intrinsic neural activity originating from the parietooccipital cortex. It was shown that sleep deprivation (SD) led to reduced alpha-band activity and network connectivity with the precuneus as the key nodes (YJ Wang et al., 2020; Wu et al., 2021). Dysconnectivity in the precuneus might be an indicator of chronic insomnia and associated cognitive deficits (Dong et al., 2018; Fasiello et al., 2022; Pang et al., 2017). Further, alpha-frequency tACS applied over the parietooccipital midline cortex elevated endogenous alpha power and medial parietal-to-frontal connectivity in healthy volunteers (De Koninck, Guay, Blais, & De Beaumont, 2021; Zaehle, Rach, & Herrmann, 2010), accompanied by a relief of anxiety arousal (Clancy et al., 2018; Clancy et al., 2022). The evidence inspired us that the MPC may be a potential target for for insomnia interventions, with alpha frequency is an alternative candidate for such interventions.

Based on the above considerations, we conducted this randomized controlled trial (RCT) to investigate the efficacy and safety of medial parietal alpha-frequency tACS for treating insomnia. Fifty-six patients with chronic primary insomnia were assigned to an active or sham intervention delivered by a 4×1 high-definition (HD)-tACS (i.e. an optimized form of tACS that provides a more precise targeting of the cortical sites). In addition to sleep symptoms, the effects of tACS on mood symptoms and cognitive deficits were also evaluated based on their implications for the recovery of the patients. PCC connectivity was also analyzed based on pretreatment resting functional MRI to investigate neural correlates of treatment response.

Methods

Design

This is a randomized sham-controlled clinical trial to investigate the efficacy and safety of alpha-frequency tACS applied over MPC for the treatment of chronic primary insomnia (Figure 1). The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The protocol was approved

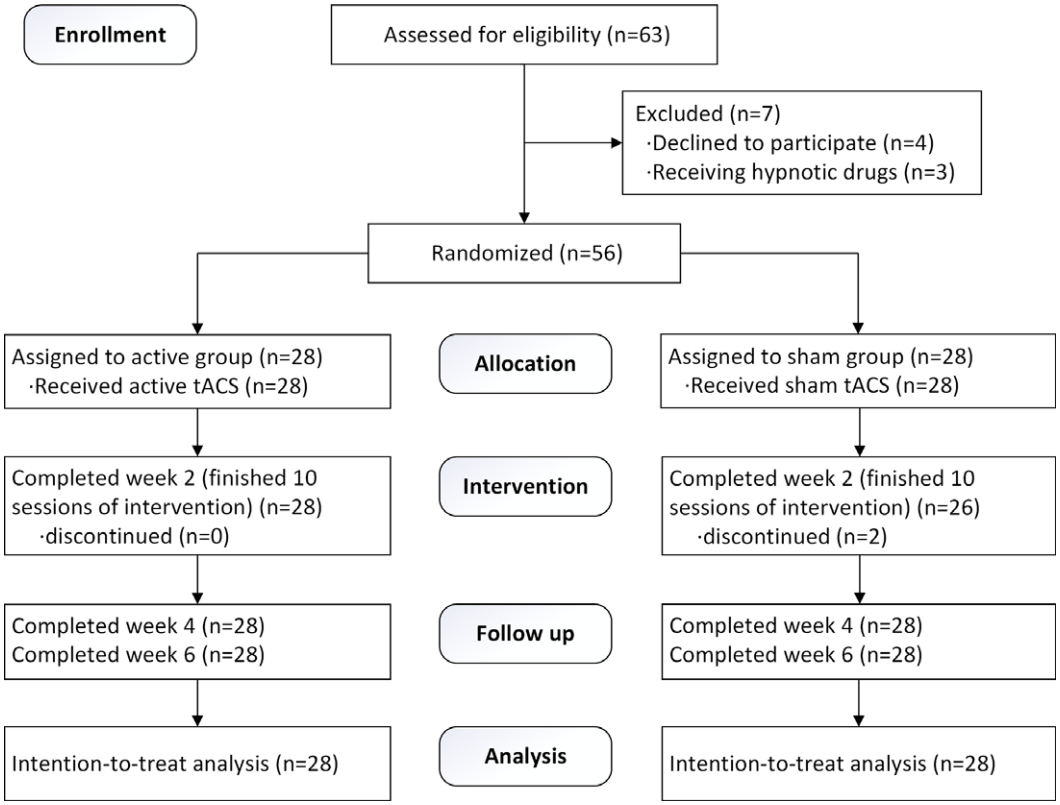

Figure 1. CONSORT flow diagram. *Note*: tACS, 'transcranial alternating current stimulation'.

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by the Ethics Committee of Beijing Puren Hospital (approval number: pr11-2021-1) and was pre-registered at the Chinese Clinical Trial Registration Center (ChiCTR2200057847) (See Supplementary Material S1 for Protocol). The protocol was reported in this paper according to the guidelines of the Consolidated Standards of Reporting Trials (CONSORT) (See Supplementary Material S2 for Checklist). Written informed consent was obtained for each subject prior to the experiment.

Participants

Fifty-six patients with chronic primary insomnia were recruited at the Department of Neurology, Beijing Puren Hospital, Beijing, China from March 2022 to December 2022.

Key eligibility included the diagnosis of chronic primary insomnia determined by DSM-5; the total score of the Pittsburgh Sleep Quality Index (PSQI)) > 8 (HX Wang et al., 2020); impairments in daytime function (i.e. ≥ 2 on daily disturbance scores of the PSQI) (HX Wang et al., 2020); having at least three nights per week of difficulties in falling asleep/maintaining sleep, or early awakening for more than three months.

Exclusion criteria included unstable medical conditions, active suicidality defined by a score of 3 or 4 on the suicide item of the 17-item Hamilton Depression Rating Scale ($HDRS_{17}$), substance dependence/abuse within the last 6 months, history of neuropsychiatric disorders, exposure to neuromodulation treatments within the last 6 months, psychoactive medications within the last 2 weeks, current psychotherapy including cognitive behavioral therapy, mindfulness therapy, etc., pregnancy or lactation, and contraindications to tACS.

We used the response rate at week 6 as the primary outcome, defined as at least a 50% reduction in the total PSQI scores relative to baseline. In our pilot study, the response rates in the active and sham groups were 50% and 10% respectively. With a 1:1 ratio, two-tailed $\alpha = 0.05$, and a degree of confidence of 80%, 21 subjects were required for each group. Considering a dropout rate of 20% and a block size of 4, the sample size was inflated to 28 per group.

tACS administration

tACS interventions were performed using a 4×1 configuration HD-tACS system (Volcan Medical, Nanjing, China). During the treatment, the subjects sat on a chair and were instructed to relax. Stimulation was delivered with a ±2 mA sinusoidal current oscillating at 10 Hz for 30 min (5 sessions a week for two consecutive weeks in the daytime), with impedance maintained below 15 kΩ during the treatment. The sham group received tACS for one minute ramped up and down at the beginning and end of each session. Five Ag/AgCl ring electrodes with a 12 mm radius were placed with one central electrode at Pz and 4 surrounding electrodes at CPz, P1, P2, and POz according to the International 10–20 EEG system (Figure 2a); such electrode arrangement was set to maximize targeted stimulation of the MPC. The electric field simulation by SimNIBS 4 (Thielscher, Antunes, & Saturnino, 2015) (0.20 V/m; with a ±2 mA bipolar sinusoidal current) showed a maximal electrical intensity at the precuneus (Montreal Neurological Institute (MNI) coordinates: x=−13, y=−75, z=57), relative to minimal electric fields (<0.02 V/m) in the frontal regions (Figure 2b). Communication with the technician is minimal.

The study was terminated for those participants who failed to complete assessments, had serious adverse reactions, or withdrew upon their own requests.

Randomization and blinding

A randomization sequence was generated based on a 1:1 ratio and fixed-block design. Randomization was assigned by an external researcher who had not participated in data collection. Patients, clinical assessors, and other study staff were kept blinded to the assignment until completion of the study. During recruitment, those with prior exposure to tES were excluded to reduce the risk of un-blinding. All patients were instructed to refrain from communicating any sensations with clinical staff or other participants. The integrity of blindness was evaluated at the end of RCT by asking the patients and assessors to guess assignments, with available options of 'Yes', 'Not sure', or 'No'. An external statistician who has not been involved in data collection completed the statistical analysis of treatment outcomes.

Assessments and outcomes

Treatment effects were assessed at the end of 2-week interventions (W2), week 4 (W4) and week 6 (W6) observation periods. Sleep symptoms were assessed using the PSQI, a standardized

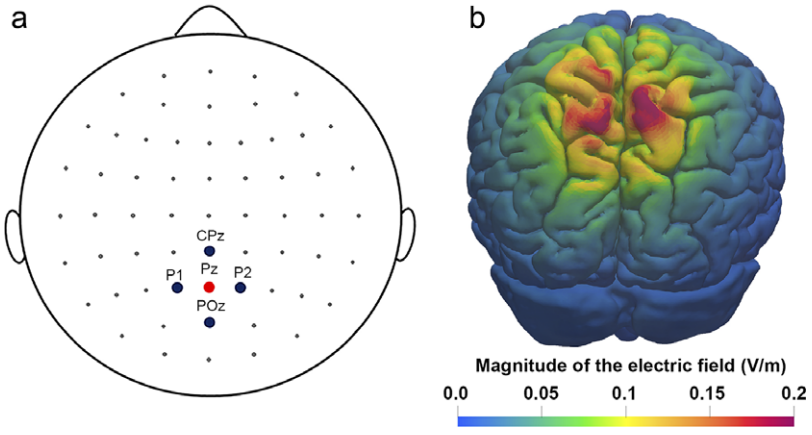

Figure 2. High-definition tACS protocol and electric field model. *Note*: (a) tACS was administered over the MPC with a 4 × 1 montage [one central (red) + four surrounding (blue) electrodes]. (b) Current flow modeling indicates maximal electric field intensity (0.20 V/m; with a ± 2 mA current) at the MPC (MNI coordinates: x = −13, y = −75, z = 57), relative to minimal electric fields (<0.02 V/m) in the frontal areas.

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questionnaire that assesses subjective sleep quality (Zheng, Li, Wang, & Lv, 2016). The $HDRS_{17}$ and Hamilton Anxiety Rating Scale (HARS) were used to evaluate depression and anxiety symptoms, respectively. The most available cognitive measures are neuropsychological tests. However, it is not clear to what extent the results obtained from these tests are related to patients' functioning in everyday lives. Therefore, we used the PDQ-D (Wang et al., 2019), a 20-item patient-reported questionnaire, to evaluate the impact of patients' cognitive dysfunction on their everyday lives based on their own perceptions. The rumination subscale of the Cognitive Emotion Regulation Questionnaire (CERQ) was used to evaluate feelings and thoughts towards negative experiences with a score from 1 (never) to 5 (always) (Zhu et al., 2012).

The primary outcome was the response rate at W6, defined by at least a 50% reduction in the PSQI total scores from baseline. Secondary outcomes were the response rates at W2 and W4; the remission rates (PSQI total score < 5) at each visit; changes in the PSQI and components (i.e. sleep onset latency (SOL), total sleep time (TST), sleep efficiency, sleep quality, and daily disturbance), $HDRS_{17}$, HARS, and the PDQ-D scores from baseline to the RCT end. Adverse events were recorded using an 18-item self-rated transcranial electrical stimulation adverse reaction questionnaire scored from 0 (none) to 4 (severe) (HX Wang et al., 2020). To investigate the long-term effects of the treatment, the post-RCT assessments were performed on the active group at 8 weeks, 10 weeks, and 14 weeks by evaluating the PSQI.

Statistical analysis of clinical data

The SPSS (version 25.0; IBM) was used for the analysis of demographic and clinical data. The continuous variables were compared between groups using the t-test if normally distributed and the Mann-Whitney test if not. The categorical variables were compared using χ^2 or the Fisher exact test.

Treatment outcomes were analyzed using R, version 3.4.0 based on an intention-to-treat (ITT) sample. The categorical variables (i.e. response rate, remission rate, and adverse reactions) were analyzed by calculating the relative risk (RR) and 95% confidence interval (CI) using a log-binomial model. The treatment-attributable changes in outcome measures were determined by linear mixed effect models, with time (W0–W6) and group (active and sham) × time as fixed factors and participants as a random intercept. The effect size was represented as a mean difference (95% CI) (Cohen'd). Blindness was assessed using the chi-square test. A two-tailed $P < 0.05$ was used to determine statistical significance.

MRI acquisition and data analysis

Imaging data were acquired with a 3.0 T MRI system (Union Medical uMR770, Beijing, China) within three days before the first treatment. The resting-state scans were performed for 10 minutes with echo-planar imaging sequence [repetition time (TR) s/echo time (TE) ms, 2/30; 90° flip angle; matrix, 64×64; thickness/gap, 3.0 mm/0.6 mm; 36 slices]. A high-resolution T1-weighted magnetization-prepared rapid gradient-echo structural image was obtained.

Images were analyzed using SPM 12 and DPABI (http://rfmri.org/DPABI). Preprocessing included correction for slice timing differences and head motion. Several nuisance signals including linear trends and head-motion parameters, and signals from the cerebrospinal fluid, white matter, and the global brain were regressed. Subsequent analyses included normalization to the MNI space (3 mm^3) and band-pass filtering (0.01–0.1 Hz). Scrubbing (Power et al., 2012) was used; the volumes with a frame-wise dependent (FD) value over 0.5, along with the previous and the next two volumes excluded. Participants were excluded if > 33% of the volumes were removed.

We analyzed the functional connectivity with the PCC used as a seed to explore the predictive effect of DMN function on therapeutic efficacy. The ventral and dorsal PCC were selected as the seeds separately rather than with the PCC as a whole based on increasing evidence suggesting a dissociable network connectivity between the subregions of PCC (Leech, Kamourieh, Beckmann, & Sharp, 2011). Functional connectivity was analyzed seeded with the ventral (MNI coordinates: x=0, y=−34, z=40; 8 mm radius) and dorsal (MNI coordinates: x=0, y=−58, z=28; 8 mm radius) PCC rather than with the PCC as a whole, based on the dissociable connectivity between the ventral and dorsal PCC (Leech, Kamourieh, Beckmann, & Sharp, 2011). Seed-based connectivity was calculated by performing Pearson correlation analysis between the mean time series of the seeds and that of each voxel. The images were Fisher's z-transformed and smoothed with a 4 mm full-width half-max kernel.

To identify neural correlates of treatment response, correlation analyses were performed between seed-based connectivity and changes (week 2 minus baseline) in primary outcome measures (PSQI) within the active group, sham group, and all participants, controlling for age, sex, baseline scores, and mean FD values. Correlations with changes in the $HDRS_{17}$, HARS, PDQ-D, and CERQ rumination subscale were also calculated for hypothesis generation purposes. A voxel-level $p<0.001$ and a cluster size of 20 voxels were used (two-tailed $p<0.05$, corrected). The cluster size was determined using a Monte Carlo simulation (Ledberg, Akerman, & Roland, 1998) using the DPABI AlphaSim utility (Yan, Wang, Zuo, & Zang, 2016). Multiple comparisons were corrected at the voxel level for each ROI, but not the numbers of ROI/correlation, since these corrections would lead to a too strict threshold of $p<0.001/5/2=0.0001$ for the correlation analysis.

Results

Baseline sample characteristics

Of the 63 eligible participants, seven were excluded due to various reasons (Figure 1). A total of 56 participants were randomly assigned to treatment, of whom 54 (96.4%) completed the whole study, with only two in the sham group discontinuing treatment due to mild side effects or loss of interest. The active and sham groups did not differ in baseline demographic and clinical data (Table 1). In Table 1, 'duration' is similar to an episode of depression, where 'current' is the duration of current insomnia, and 'total' is the duration of insomnia since the patients met the diagnosis.

Response rate

The response rate at W6, rather than W2, was used as the primary outcome measure because what we and patients mostly expect is that the treatment is effective and can be maintained for a period of time. On the primary outcome, a significantly higher proportion of participants in the active group responded to treatment at W6 compared with the sham group (71.4% versus 3.6%), with an RR value of 20.0 (95% CI 2.9 to 139.0, P = 0.0025); such superiority had emerged at W2 (RR 23.0, 95% CI 3.3 to 158.8, P = 0.0015) and W4

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Table 1. Baseline demographics and clinical characteristics

Characteristics	Active (n=28)	Sham (n=28)	*P*
Age, *y*, mean±SD	50.2±11.0	48.6±14.7	0.645
Female, *n* (%)	23 (82.1%)	20 (71.4%)	0.342
Married, *n* (%)	23 (82.1%)	22 (78.6%)	0.737
Education above high school, *n* (%)	22 (78.6%)	20 (71.4%)	0.537
Being in regular work, *n* (%)	18 (64.3%)	16 (57.1%)	0.584
BMI, kg/m^2, mean±SD	21.6±1.8	22.2±1.7	0.244
Total duration, m, median (IQR)	60.0 (67.4)	42.0 (100.5)	0.902
Current duration, m, median (IQR)	7.0 (6.0)	7.0 (6.0)	0.456
Familial insomnia disorder, n (%)	0 (0%)	0 (0%)	–
Alcohol or drug abuse, n (%)	0 (0%)	0 (0%)	–
PSQI-total, mean±SD	14.4±2.4	14.7±2.1	0.557
$HDRS_{17}$-total, mean±SD	10.3±3.1	10.1±3.8	0.909
HARS-total, mean±SD	10.6±4.4	11.0±3.9	0.725
PDQ-D-total, mean±SD	17.3±6.3	18.8±10.0	0.515
CERQ-rumination, mean±SD	12.6±1.9	11.8±2.7	0.213

Note: y, 'year'; BMI, 'body mass index'; IQR, 'inter-quartile range'; m, 'month'; PSQI, 'Pittsburgh Sleep Quality Index'; HDRS, 'Hamilton Depression Rating Scale'; HARS, 'Hamilton Anxiety Rating Scale'; CERQ, 'Cognitive Emotion Regulation Questionnaire'; PDQ-D, 'Perceived Deficits Questionnaire-Depression'.

(RR 20.0, 95% CI 2.9 to 139.0, P = 0.0025) (Figure 3a). See Supplementary Material S3 – Supplementary Table S1 for details. The post-RCT follow-up for the active group showed a noticeably lowered response rate at week 8 (57.1%), week 10 (46.4%), and week 14 (42.9%).

Remission rate

A significantly higher proportion of participants in the active group achieved remission at W2 compared with the sham group (53.6% versus 3.6%) (RR 15.0, 95% CI 2.1 to 106.0, P = 0.0066). The treatment effects were sustained at 4- and 6-week follow-ups. See Supplementary Table S1 for details.

Changes in sleep symptoms

Mixed model analysis revealed a significant and sustained effect of tACS on subjective sleep quality in the active versus sham group. Specifically, the active therapy led to significant reductions in total PSQI scores relative to the sham therapy at W2 (mean difference 8.0, 95% CI 6.6 to 9.4, P < 0.001) (Cohen's d −3.0) (Figure 3a). The superiority of active therapy was reflected in a shorter SOL (mean difference 52.5, 95% CI 35.2 to 69.7, P < 0.001) (Cohen's d −1.6), longer TST (mean difference −1.8, 95% CI −2.3 to −1.3, P < 0.001) (Cohen's d 2.1), increased sleep efficiency (mean difference −0.2, 95% CI −0.3 to −0.1, P < 0.001) (Cohen's d 1.8), improved sleep quality (mean difference 1.6, 95% CI 1.2 to 2.0, P < 0.001) (Cohen's d −2.3), and less daily disturbance (mean difference 1.5, 95% CI 1.0

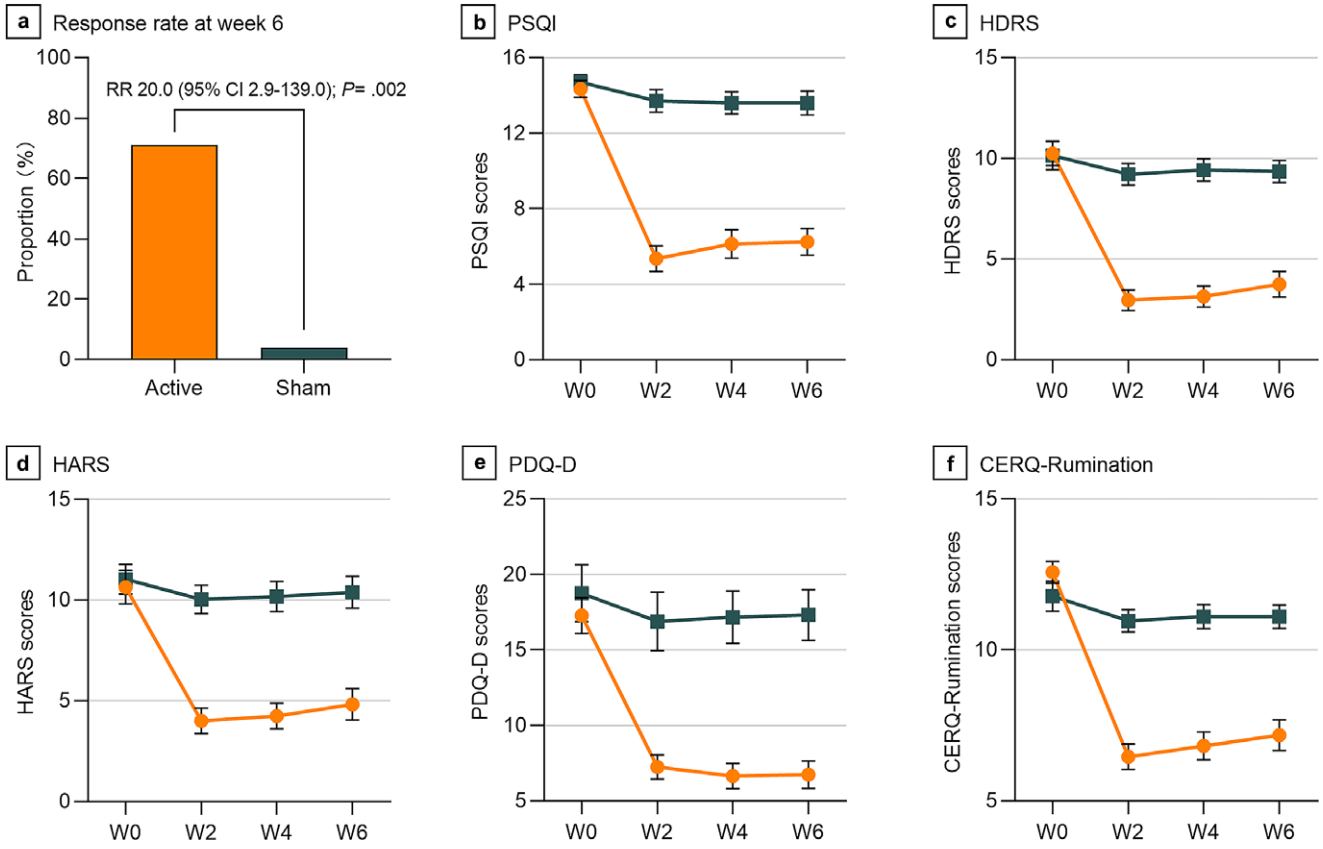

Figure 3. The response rate and symptom trajectories in the active and sham groups. *Note*: (a) The response rate at week 6 in the active and sham groups, as evaluated by the Pittsburgh Sleep Quality Index (PSQI). (b–f) The mean reductions in the symptoms scores in the active and sham groups from baseline to week 6 based on the intent-to-treat dataset (n = 56), as evaluated by the PSQI (b), 17-item Hamilton Depression Rating Scale (HDRS) (c), Hamilton Anxiety Rating Scale (HARS) (d), Perceived Deficits Questionnaire-Depression (PDQ-D) (e), and Cognitive Emotion Regulation Questionnaire (CERQ) rumination subscale (f). Error bars represent 1 SE. RR, risk ratio; W0: baseline, W2: week 2, W4: week 4, and W6: week 6.

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to 2.0, p < 0.001) (Cohen's d −1.6). The effects lasted into W4 and W6. See Supplementary Material S3 – Supplementary Figure S1 and Supplementary Table S2 for details.

Changes in emotional and cognitive deficits

As shown in Figure 3b and c, the active group showed significantly greater improvements (versus sham) in the measures of depression ($HDRS_{17}$) (mean difference 6.4, 95% CI 4.8 to 7.9, P < 0.001) (Cohen's d −2.2) and anxiety (HARS) symptoms (mean difference 5.6, 95% CI 3.9 to 7.4, P < 0.001) (Cohen's d −1.7) at W2. Active therapy was also superior to sham in improving perceived cognitive deficits (PDQ-D) (mean difference 8.2, 95% CI 5.7 to 10.6, P < 0.001) (Cohen's d −1.8) (Figure 3d) and rumination (CERQ) (Cohen's d −2.84; 95% CI −3.58, −2.09; *P* < 0.0001) (Figure 3e). The differences were sustained into W4 and W6. See Supplementary Material S3 – Supplementary Table S2 for details.

Safety and blinding

In the active group, one participant experienced discomfort at the stimulating site, and the other experienced drowsiness during the treatment. One participant in the sham group discontinued treatment due to tinnitus. These adverse effects were mild and disappeared after the completion of treatment. Serious adverse events were not observed. The adverse events did not differ between the two groups (RR 2.0, 95% CI 0.2 to 20.8, P = 0.562).

Eleven (39%) participants in the active group and 13 (46%) in the sham group correctly guessed their allocation ($\chi^2 = 0.292$, P = 0.589). The correct guess of assessors was 14 (50%) for the sham group and 12 (43%) for the active group ($\chi^2 = 0.297$, P = 0.592). See Supplementary Material S3 – Supplementary Table S3 for details.

Neural correlates of treatment response

Figure 4a shows the seed locations of PCC. The analysis conducted within the active group showed significant correlations between ventral PCC and treatment response. Specifically, a trend towards negative connectivity between the vPCC and the right superior frontal gyrus (SFG) (x = 21, y = 12, z = 60; peak intensity = −0.826; 24 voxels) (Figure 4b) and the right inferior parietal lobule (IPL) (x = 45, y = −33, z = 48; peak intensity = −0.786; 73 voxels) (Figure 4c) was associated with stronger responses in sleep symptoms, as evaluated by the PSQI. A stronger positive connectivity between the vPCC and right middle frontal gyrus (MFG) (x = 24, y = 48, z = 27; peak intensity = 0.855; 32 voxels) was associated with improvements in cognitive deficits (PDQ-D) (Figure 4d), while stronger positive connectivity between the vPCC and ventromedial PFC (vmPFC) (x = −3, y = 21, z = −12; peak intensity = 0.814; 25 voxels; Figure 4e) (x = 0, y = 63, z = −3; peak intensity = 0.800; 22 voxels; Figure 4f) was associated with alleviation in rumination (CERQ).

Discussion

To the best of our knowledge, this study is the first to evaluate the efficacy and safety of medial parietal alpha-frequency tACS in patients with chronic insomnia. The results corroborate the hypothesis by showing a substantial and lasting improvement in sleep symptoms and associated functional deficits. Uncommon adverse events and high retention rates indicate a good acceptability of the treatment. Neuroimaging analysis underscores an association between treatment efficacy and vPCC connectivity.

Although the response rate at post-tACS (82%) is similar to that (77.2%) of the previous study (HX Wang et al., 2020) which delivered 15 mA–75.5 Hz tACS over insomniacs, the response rate at 6-week follow-up (71.4%) seems to be higher than that study (53.4%), suggesting a more stable effect. The striking effect may be attributed to the core role of the MPC played in sleep, emotional, and cognitive function. A more precise stimulation with HD-tACS may also contribute to the optimization of therapeutic effects. The previous studies (Donde et al., 2021; Herrero Babiloni et al., 2021; Ma et al., 2021; Zhou et al., 2020) of tES delivered stimulation in a non-focal manner using a pair of electrodes with a large size (5–10 cm). Under a 1×1 configuration, a wide range of areas between the electrodes are affected and the peak appears between the electrodes. The multi-electrode protocol consists of one central and multiple surrounding electrodes with small size, which constrains the physiological effects within the annular area, with the peak appearing below the central electrode. The 4×1 HD-tACS has shown a stronger effect in the motor cortex than the 1×1 configuration (Kuo et al., 2013). However, the post-RCT follow-up from weeks 8–14 showed a significant decrease in response rate, suggesting that the inflection point for the efficacy may be 4–6 weeks after the treatment ended. A consolidation therapy after 2-week intervention may promote the maintenance of therapeutic effects.

In contrast, we observed a low response rate of sham therapy, which was weaker than the placebo effect reported in many studies (Frase et al., 2019; HX Wang et al., 2020; Zhou et al., 2020). This may be attributed to methodological issues, such as stimulation techniques, number of sessions, or duration. We noticed that there were also studies (Harvey et al., 2017; Sheng et al., 2018) showing a placebo effect similar to ours and one (Sheng et al., 2018) of them utilized a 4×1 HD configuration. We also examined the relationships between treatment guesses and response rate at 6 weeks and found that in the active group, 10/11 patients guessed as 'active' and 10/12 patients guessed as 'not sure' were all responders, while 5/5 patients guessed as 'sham' were all non-responders. In the sham group, most subjects (25/28) guessed as 'not sure' or 'sham'. This phenomenon hints that blind guessing may be biased by therapeutic effects. There is controversy regarding the appropriate sham control of tES (Davis, Gold, Pascual-Leone, & Bracewell, 2013). Sham therapy usually involves turning on stimulation for a few seconds so that subjects have sensation, and then turning it off when sensation is absent (Ambrus et al., 2012). The ideal sham control is inactive to minimize the stimulation effect, but the subjects cannot distinguish it from the active condition. This may be unreliable as the active stimulation may elicit more persistent effects that make it distinguishable, which becomes prominent when the current intensity increases (O'Connell et al., 2012), especially under high-definition stimulation where the current is concentrated within a local area to improve the focality of stimulation. The development of more reasonable sham controls is required.

Given the significant therapeutic effect, it is meaningful to speculate on the neural mechanism underlying tACS treatment. The psychological and physiological hyperarousal contributes to insomnia (Krause et al., 2017). The precuneus and surrounding posteromedial areas are among the structures displaying the highest resting activity and are engaged in a wide-spectrum mental process involving self-reference and episodic memory (Cavanna & Trimble, 2006). Alpha oscillations modulate large-scale neural networks and drive the shutting of arousal-promoting systems (Hillebrand et al.,

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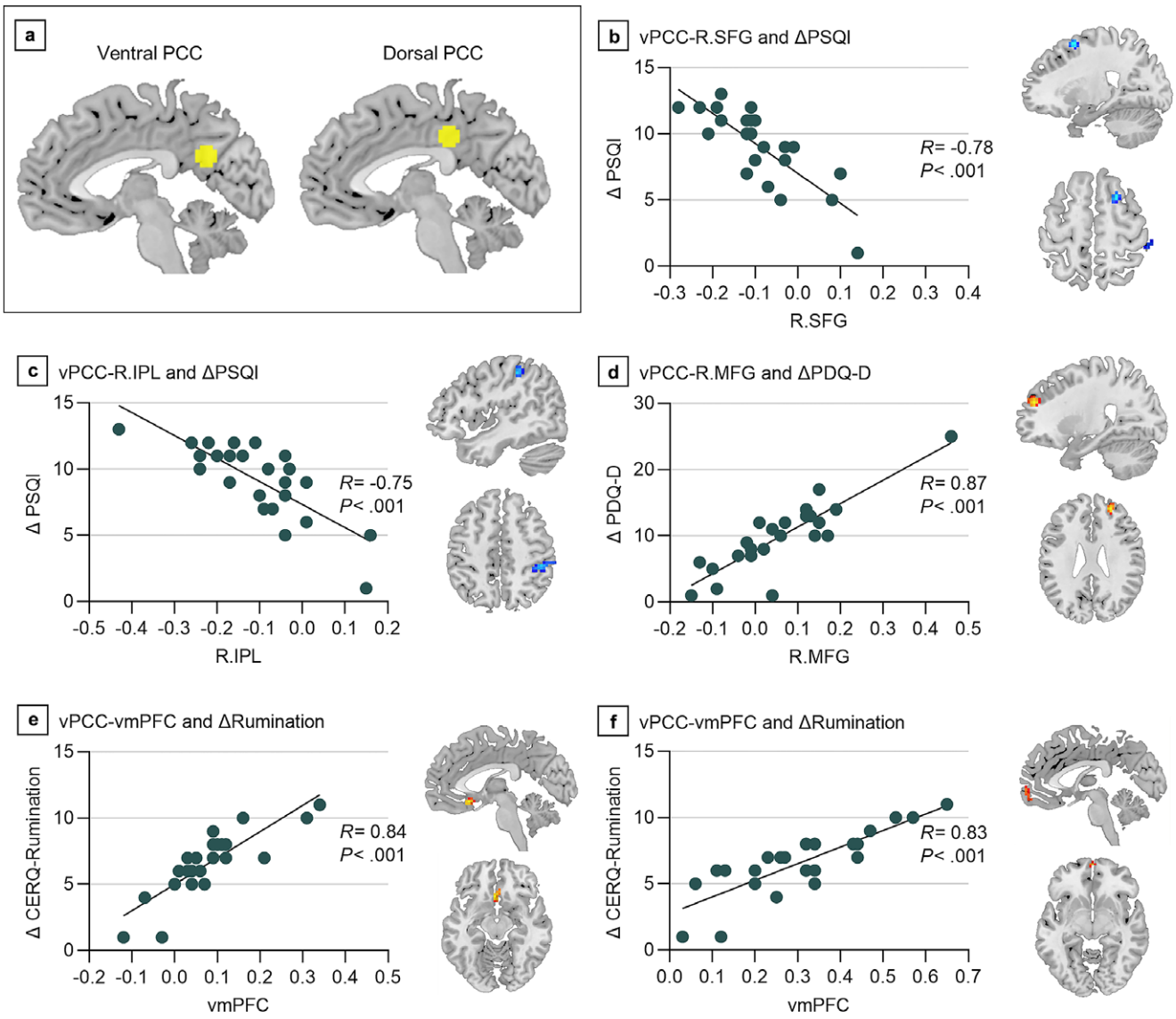

Figure 4. Correlations between vPCC connectivity and treatment response. *Note*: (a) The location of the ventral and dorsal posterior cingulate cortex (PCC) seeds. (b–f) The scatter plots and brain images show a correlation between vPCC-right superior frontal gyrus (R.SFG) connectivity and changes in Pittsburgh Sleep Quality Index (PSQI), a correlation between vPCC-right inferior parietal lobule (R.IPL) connectivity and changes in PSQI, correlation between vPCC-right middle frontal gyrus (R.MFG) connectivity and changes in Perceived Deficits Questionnaire-Depression (PDQ-D), and correlations between vPCC-ventromedial prefrontal cortex (vmPFC) connectivity and changes in Cognitive Emotion Regulation Questionnaire (CERQ) rumination subscale. The clusters survived with a voxel-wise P < 0.001 and cluster size of 20 voxels (P < 0.05, AlphaSim corrected). Δ: week 2 minus baseline.

2016; Kalauzi, Vuckovic, & Bojic, 2012). Researchers reported decreased alpha activity after SD and anterior-posterior dissociation within the DMN (Gujar, Yoo, Hu, & Walker, 2010; YJ Wang et al., 2020; Wu et al., 2021). Patients with insomnia had a reduced degree of centrality in the precuneus and an association between its cortical thickness with sleep quality (Yan et al., 2018) (Montesino-Goicolea et al., 2020). Further, DMN connectivity was modulated after repetitive transcranial magnetic stimulation (rTMS) was applied to regulate sleep (Diefenbach et al., 2019). Therefore, we surmise that tACS may mitigate insomnia, and associated emotional and cognitive deficits by enhancing the alpha inhibitory control and functional integration within the DMN. This assumption may be partially supported by research in healthy volunteers that showed increased within-DMN connectivity and reduced anxiety arousal following alpha-frequency tACS over the parietooccipital cortex (Clancy et al., 2018; Clancy et al., 2022).

Neuroimaging analyses revealed several features of vPCC connectivity associated with treatment response. Sleep improvement was associated with vPCC connectivity to the SFG and IPL, whereas cognitive benefit was associated with vPCC-MFG connectivity, and alleviation of rumination was associated with vPCC-vmPFC connectivity. The frontoparietal network carries the most individual variability among the various networks (Mueller et al., 2013); which increases at high relative to low-level arousal (Lee et al., 2022). This variability may mediate the association between vPCC-frontoparietal connectivity and the tACS response in sleep symptoms. Correlation between vPCC-MFG connectivity and cognitive enhancements may be ascribed to the integrative role of these structures in cognitive function (Busler et al., 2019). The vmPFC is engaged in self-relevant processing (Satpute & Lindquist, 2019), and excessive activity in this region underlies maladaptive rumination (Hamilton, Farmer, Fogelman, & Gotlib, 2015). Consistent

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with our results, vmPFC activity has been used to predict the response to rTMS (Liston et al., 2014) and antidepressant treatment (Phillips et al., 2015). These connectivity features may inform personalized treatments. On the one hand, individual connectivity helps to predict which individual would benefit from a given approach, informing the selection of treatment strategy. On the other hand, individual connectivity can be used to optimize the electrode layout. This is especially meaningful for the high-definition configuration which allows for unique combinations of electrode locations to target individual networks.

The advantages of this study include the inclusion of drug-naive patients, sham-controlled, and sufficient blindness. However, several issues still need to be addressed. First, we used the PSQI to assess subjective sleep symptoms. Future studies combining objective monitoring such as polysomnography, will allow for a more intensive evaluation of sleep. Second, we cannot exclude the possibility that improvements in emotional and cognitive symptoms promote sleep. Given that the MPC plays a common role in sleep, emotion, and cognition (Samann et al., 2011; Satpute & Lindquist, 2019), it is possible that tACS improves all these domains. However, perhaps we should consider this issue from a more practical perspective. An ideal target should possess the ability to modulate multi-dimensional functions, which is especially important for insomniacs that involve symptoms of multiple domains. Third, the efficacy of tACS could be affected by stimulating targets and a series of parameters. Comparing the therapeutic effects of distinct stimulation targets and parameters as well as the patient's responsiveness to treatments will optimize treatment strategy. A fixed instead of individual frequency was used in our study. Personalized stimulation of alpha frequency has been shown to be more effective in entertaining intrinsic neural oscillations (De Koninck, Guay, Blais, & De Beaumont, 2021). Finally, developing a personalized closed-loop tACS system integrating individual differences in neural oscillations and the state of the brain is required for future treatment optimization.

Conclusions

In conclusion, this study showed that alpha-frequency tACS applied over the MPC is an effective and safe treatment in improving sleep symptoms and associated functional deficits for patients with chronic insomnia. Capitalizing on the vPCC connectivity may provide a way towards personalized treatment. Against the extensive use of the PFC as a target, this study provides a new target and stimulation approach for non-invasive neuromodulation of chronic primary insomnia.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/S0033291725000625.

Data availability. The data that support this study are available from the corresponding author upon reasonable request.

Author contribution. L. Wang and K. Wang designed the research; L. Wang, K. Wang, Z. Piao, X. Gu, H. Liu, D. Wang, Z. Yan, Y. Liu, G. Shi, Y. Chen, Z. Xiao, T. Liu, and Q. Cui performed the experiment; L. Wang, W. Meng, and T. Yan wrote the paper.

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Competing interests. The authors declare none.

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