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Effect of add-on transcranial alternating current stimulation (tACS) in major depressive disorder: A randomized controlled trial

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ABSTRACT

Background: The effect of transcranial alternating current stimulation (tACS) on major depressive disorder (MDD) was not confirmed.
Objective: To evaluate the feasibility, safety, and efficacy of tACS as an add-on treatment for the symptoms of depression and to understand how tACS affects brain activity.
Methods: The 4-week, double-blind, randomized, sham-controlled trial was performed from January 29, 2023 to December 22, 2023. Sixty-six participants were recruited and randomly assigned to receive 20 40-min sessions of either active (77.5Hz, 15 mA) or sham stimulation, with one electrode on the forehead and two on the mastoid, each day (n = 33 for each group) for four weeks (till Week 4). The participants were followed for 4 more weeks (till Week 8) without stimulation for efficacy/safety assessment. During the 4-week trial, all participants were required to take 10–20 mg of escitalopram daily. The primary efficacy endpoint was the change in HAMD-17 scores from baseline to Week 4 (with 20 treatment sessions completed). Resting-state electroencephalography (EEG) was collected with a 64-channel EEG system (Brain Products, Germany) at baseline and the Week 4 follow-up. The chi-square test, Fisher's exact test, independent-sample *t*-test, or Wilcoxon rank-sum test were used, as appropriate, to compare the differences in variables between groups. The effect of the intervention on the HAMD-17 score was also evaluated with linear mixed modeling (LMM) as sensitivity analysis. The correlation between the mean reduction in EEG and the mean reduction in the HAMD-17 total score was evaluated using Spearman correlation analysis.
Results: A total of 66 patients (mean [SD] age, 28.4 [8.18] years; 52 [78.8 %] female) were randomized, and 57 patients completed the study. Significant differences were found in the reductions in the HAMD-17 scores at Week 4 ($t = 3.44$, $P = 0.001$). Response rates at Week 4 were significantly higher in the active tACS group than in the sham tACS group (22 out of 33 patients [66.7 %] versus 11 out of 33 [33.3 %], $P = 0.007$). In the active tACS group, a correlation between the mean change in alpha power and HAMD-17 scores at Week 4 was found ($r = 2.38$, $P = 0.024$), and the mean change in alpha power was significantly bigger for responders ($Z = 2.46$, $P = 0.014$). No serious adverse events were observed in this trial.
Conclusion: The additional antidepressant effect of tACS is significant, and the combination of tACS with antidepressants is a feasible and effective approach for the treatment of MDD. The antidepressant mechanism of tACS may be the reduction in alpha power in the left frontal lobe. Future research directions may include exploring more appropriate treatment parameters of tACS.

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1. Introduction

Major depressive disorder (MDD) is a common disease affecting more than 300 million people. It is a leading cause of disability worldwide and a major contributor to the overall global burden of disease (World Health Organization, 2018). Therefore, the development of effective, accessible interventions for MDD is a high priority for the improvement of public health. First-line, evidence-based treatment options for MDD include psychopharmacology and psychotherapeutic approaches. However, 30–50 % of patients do not adequately respond to first-line treatments. which generally involve a combination of antidepressants and cognitive-behavioral therapy [1], so there is an urgent need for new treatment options.

Transcranial alternating current stimulation (tACS) is a neuromodulation technique that applies electrical currents with changing intensity to the scalp to regulate cortical excitability and spontaneous brain activity. It has been used for over a decade in different fields (for instance, cognitive neuroscience) [2,3]. However, it has only been applied in psychiatric clinical research in recent years [4,5]. At present, most clinical studies on depression used tACS with frequencies of 10 Hz [6], 40 Hz [7], or 77.5 Hz [8] and stimulation sites selected in the frontal lobe. One study has proved that tACS with a current of 15 mA and a frequency of 77.5 Hz can deliver electrical currents to deep brain tissues [9]. It was also found that tACS (frequency 77.5 Hz) enhanced the levels of endorphins and neurotransmitters (including serotonin) in the CSF, brainstem, hypothalamus, and cortex β [10,11]. Some of endorphins and neurotransmitters changes are believed to be the neurobiological mechanisms for improving depressive symptoms [12,13].

A study examining tACS's role in treating MDD revealed that tACS with 15 mA and 77.5 Hz was effective in alleviating depressive symptoms in MDD [8]. However, because only first-episode drug-naive patients with MDD were included in the study, the generalizability of its findings was limited. Another study examined the efficacy of tACS combined with SSRIs, but it did not limit the type and dose of the antidepressants used in the study [14]. As the antidepressant efficacy of different SSRIs varied [15], it is still unknown whether the combination of antidepressants and tACS could enhance the efficacy of antidepressants and bridge the gap in the first few weeks when antidepressants have not taken effect. In addition, the antidepressant mechanism of tACS is complex and currently unclear.

Depression is related to a complex picture of altered brain oscillations [16]. The resting-state low-frequency bands (delta, beta, and alpha) in electroencephalography (EEG), especially the alpha band, were enhanced in patients with depression in terms of either power or coherence. Moreover, the enhancement persisted even after an individual changed from an eye-closed to an eye-open state [17–20]. Patients with MDD exhibit elevated oscillatory activity, specifically in the alpha frequency band (8–12 Hz) [21]. Although alpha oscillations serve important functions in the healthy brain [22,23], increased alpha oscillation in patients with depression represents a state of neuronal hypoactivity leading to disrupted affective processing. Researchers found that the left prefrontal cortex was inhibited, indexed by increased alpha frequency power, during the processing of positive emotions in individuals with depression [24]. Since the elevated amplitude of left frontal alpha oscillations is theorized to correspond to a reduction in approaching positive experiences [24,25], we hypothesized that a stimulation may produce a selective decrease in left frontal alpha oscillations towards images rated as positive.

Therefore, we conducted a double-blind study to evaluate the feasibility, safety, and efficacy of tACS as a treatment for the symptoms of depression. To understand how tACS affects brain activity, we measured alpha power changes as our secondary outcome using high-density EEG.

2. Methods

2.1. Study Design and participants

The 4-week, double-blind, randomized, sham-controlled trial was performed at Beijing Anding Hospital, Capital Medical University, from January 29, 2023 to December 22, 2023. The trial received institutional review board approval, was performed in accordance with ethical principles originating in the Declaration of Helsinki [26], and was reported in accordance with CONSORT guidelines [27]. The study was registered on the Chictr.org.cn website before enrollment (ChiCTR2300067443, https://www.chictr.org.cn/index.html). There was no change in the protocol during the study. All patients provided written informed consent prior to enrollment. The trial was completed on reaching predetermined target enrollment numbers. After the 4-week trial, all patients entered the depression cohort and were followed up for 8 weeks.

2.2. Sample size calculation

Previously, there is only one randomized controlled trial investigating the effectiveness of tACS as an add-on to antidepressants in treating depression [14]. However, we found that the effect size derived from this study was extremely large. The sample size calculated based on this effect size was 3, which would be too small to verify the effect statistically. Therefore, we used a conservative estimate of 0.8, which was considered the criteria for large effects, to calculate our sample size instead. PASS 2021 was applied to calculate the sample size. We set effect size = 0.8, α (two-sided) = 0.05, power = 0.8, and β = 0.2 and found after calculation that each group would require 33 participants, with a 20 % dropout rate. Therefore, the experimental and control groups would need 33 participants each, making a total sample size of 66.

2.3. Inclusion/exclusion criteria

Participants were recruited through physician referrals and posters. The inclusion criteria were: (1) being 18–55 years old; (2) being diagnosed with MDD by a psychiatrist using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5); (3) having a total score of 17 or more on the 17-item Hamilton Rating Scale for Depression (HAMD-17) and a HAMD-17 Item 1 (Depression) score of 2 or more; (4) having not received any antidepressant medications for the current depressive episode; (5) being able to understand and sign the informed consent. Some of the exclusion criteria were: (1) having a current or history of seizures, epilepsy, hydrocephalus, central nervous system tumors, or acute brain injury and infection; (2) having a significant risk of suicide indicated by a score of 3 or 4 on the HAMD-17 Item 3 or with a history of suicidal behavior; (3) having been exposed to electroconvulsive therapy (ECT), modified electroconvulsive therapy (MECT), transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), tACS, or other neurostimulation treatments in one month before enrollment; (4) being pregnant or breastfeeding; (5) patients with any severe organic diseases or were in an unstable condition because of an organic disease. The trial protocol, which contains additional inclusion and all exclusion criteria, is available in Supplement 1.

2.4. Randomization, concealment, and blinding

A computer-generated randomization schedule using randomly permuted blocks randomly assigned eligible patients to the active and sham tACS groups in a 1:1 ratio. First, a random number table containing randomization sequences was generated with the PLAN step in the SAS 9.4 software by a statistician not involved in conducting this trial. Second, a nurse (also not involved in conducting this trial) put

group assignment results generated from the random number table in identical, sequentially numbered, opaque, sealed envelopes. Third, each patient received a sealed envelope at enrollment. Finally, on the patient's first day of enrollment, or the day the patient received the first stimulation session, the envelope with group assignment information would be opened by a researcher.

In the whole randomization process and throughout the trial, the active or sham groups, as well as the active or sham stimulation devices, were represented with the letters A or B (only the device operators got the information on the letter assigned to a patient), so that all individuals involved in the trial were blinded to the type of stimulation (active or sham) they gave or received. Also, there was no difference between the active and sham stimulation devices in terms of appearance and the way they influence the patient's senses, so the patient and the operator could not distinguish which instrument was the active stimulation device based on the appearance of the device or the subjective feelings of the patients. After statistical analyses in this study were completed, unblinding was performed.

2.5. Procedures

Participants were asked to sit comfortably in reclining chairs while receiving FDA/NMPA (National Medical Products Administration) approved tACS (Nexalin Technology, Inc.) administered by trained nurses in accordance with standardized instructions. A 4.45 × 9.53 cm electrode was placed on the forehead at Fpz, Fp1, and Fp2 in the 10/20 international placement system. Two 3.18 × 3.81 cm electrodes were placed on each side of the mastoid. The tACS stimulation waveforms include ramp-up and ramp-down periods of 180 and 12 s, respectively. The waveforms were square waves with an average amplitude of 15 mA and were distributed equally from the frontal region to the mastoid areas (amplitudes were reported as zero-to-peak).

All participants received 20 sessions of stimulation at 77.5 Hz and 15 mA, while the sham tACS had no active stimulation. From Monday to Friday, one 40-min session was administered at a fixed time each day. During the 4-week trial, all participants were also asked to take 10–20 mg of escitalopram each day.

This study involved the combined use of escitalopram throughout the 4-week period. All medications were taken orally after breakfast (once daily). The medication used in this study was 10-mg escitalopram tablets. Dose titration was performed by the researchers based on side effects and/or clinical course. The initial dose of escitalopram was 5 mg/day, which could be increased to 10 mg/day after 2 weeks based on the patient's condition. The dose could be further increased to 20 mg/day if necessary. Each increase in dose should be spaced about 2 weeks apart and not less than 4 days apart.

2.6. EEG

Resting-state EEG data were collected at baseline and the Week-4 follow-up using a 64-channel EEG system (BrainProducts, Germany). The electrodes were positioned according to the standard international 10/20 system. The sampling frequency was 5000 Hz, and electrode impedance was kept below 10 KΩ. Participants had their eyes open for 5 min, then had their eyes closed for 5 min. During the eyes-open condition, participants were instructed to fixate on a cross-hair. Participants also completed a face-word Stroop task, the results of which are not presented here.

The EEGLAB [28] toolbox in Matlab was used to preprocess the EEG data. The steps of EEG data preprocessing were: (1) channel selection (removed IO channel); (2) FIR band pass filter (0.1–50 Hz); (3) segmentation of epochs into 2-s segments; (4) bad channels rejection; (5) resampling to 500 Hz; (6) re-reference to bilateral mastoid; (7) Independent Component Analysis (ICA) and ICA-based manual artifact removal. After preprocessing, the power spectral density (PSD) of EEG was estimated with the fast Fourier transform method, and the PSD of the alpha frequency band (8–12 Hz) was calculated to compare the changes in EEG. Channels of the left frontal lobe were selected and averaged to represent the alpha power in the left frontal lobe.

2.7. Outcome measures

The primary efficacy endpoint was the change in HAMD-17 [29] scores from baseline to Week 4 (with 20 treatment sessions completed).

Secondary efficacy endpoints included: Clinical Global Impression of Improvement (CGI-I) at Weeks 2 and 4; the changes from baseline to Week 4 (with 20 treatment sessions completed) in the scores on the HAMD-17 reflecting depression (Items 1, 2, 3, 7, 8), anxiety (Items 9, 10, 11, 15, 17), insomnia (Items 4, 5, 6), and somatic symptoms (Items 12, 13, 14, 16) [30], Generalized Anxiety Disorder-7 (GAD-7) [31], 16-item Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR16) [32], Pittsburgh Sleep Quality Index (PSQI) [33], Clinical Global Impressions-Severity of Illness Scale (CGI-S) [34]; the proportions of responders (defined with a reduction of 50 % or more from baseline in the HAMD-17 total score) at each visits; and epileptiform activities revealed by EEG recordings.

Safety and tolerability were evaluated with adverse events (AEs), vital signs, clinical laboratory evaluations, and electrocardiogram parameters. Serious AEs were defined as any untoward medical occurrence that resulted in death, was life threatening (at the time of the event), required inpatient hospitalization, resulted in persistent or significant disability.

2.8. Statistical analysis

The main analyses were completed on an intent-to-treat basis, meaning all randomized patients were included. Missing data for HAMD-17 scores were imputed using the last observation carried forward. Descriptive data at baseline were reported with mean (standard deviation) or median and interquartile range (IQR) for continuous variables and count (percentage) for categorical variables.

The primary endpoint was assessed with an independent-sample *t*-test based on data with the last observation carried forward (LOCF) imputation. We performed three sensitivity analyses for the primary outcome to assess the robustness of the results. In Sensitivity Analysis 1, multiple imputation for monotone missing data, we fitted a regression model from observed data and potential predictors (i.e., age, sex, baseline score, first episode) to generate imputed values. We used SAS multiple imputations (PROC MI) to impute 25 values for each missing observation and combined estimates using PROC MI ANALYZE in SAS. Sensitivity Analysis 2, a per-protocol analysis, was also performed to examine whether the reductions in the scores on the HAMD-17 and the response rates differed between the two groups. Sensitivity Analysis 3 evaluated the effect of the intervention on the HAMD-17 scores with linear mixed modeling (LMM) based on all available data without imputation, with the treatment group, visit, and their interaction (group × visit) as fixed effects and the participant as a random effect.

A secondary outcome, the response rate, was compared using the chi-square test. The reductions in the scores of each factor of the HAMD-17 and the scores of CGI and CGI-S were compared using the Wilcoxon rank-sum test. An independent-sample *t*-test was used to compare the differences between the reductions in the scores on the QIDS-SR16, GAD-7, and PSQI in the active and sham tACS groups. The correlation between the mean reduction in EEG and the mean reduction in the HAMD-17 total score from baseline to Week 4 was evaluated with Spearman correlation analysis.

All data were analyzed using SAS for Windows, version 9.4 (SAS Institute, Cary, NC) and R4.3.2 (R Foundation for Statistical Computing, Vienna, Austria). All P values were two-sided, and the differences were considered statistically significant when the P value was <0.05.

3. Results

3.1. Participants

A total of 152 patients with MDD were assessed for eligibility, and 66 patients met the inclusion criteria and were randomly allocated to the active tACS group (n = 33) or sham tACS group (n = 33). After randomization, seven participants in the sham tACS group were lost at week 2, and two participants in the active tACS group did not complete the study (Fig. 1). The participants' demographic and clinical characteristics are summarized in Table 1. More than half of the participants were female (78.8 %); mean values for other demographics included 28.42 ± 8.18 years for age, 22.25 ± 4.44 kg/m^2 for BMI, and 3 (1–12) months for the duration of the recent episode. Of all participants, 50 % were first episode, and 9.1 % had a family history of mental disorders.

Of the 66 patients, 64 started at a dose of 5 mg/day of escitalopram and increased to 10 mg/day after 4 days, with two patients in each group increasing to 15 mg/day after 2 weeks. In addition, one patient in the active tACS group did not take escitalopram, and one patient in the sham tACS group maintained a dose of 5 mg/day.

3.2. Primary outcomes

In the intention-to-treat analysis, significant differences were found in the mean reduction of the HAMD-17 scores at Week 4 (t = 3.44, P = 0.001). There were also statistically significant differences in the reduction of the HAMD-17 scores between the two groups at both weeks 2 and 8 (week 2: t = 3.48, P < 0.001; week 8: t = 3.19, P = 0.002) (Fig. 2). The raw and reduction mean scores of all outcomes at all time points are shown in Supplementary Materials Table S1.

3.3. Secondary outcomes

Significantly more participants in the active tACS group (n = 22/33, 66.7 %) responded (defined with a reduction of 50 % or more from

Table 1
Basic information.

Variables	Active tACS	Sham tACS
Sex		
Male	8(24.24)	6(18.18)
Female	25(75.76)	27(81.82)
Educational level		
Graduate	24(72.73)	23(69.70)
High school	4(12.12)	4(12.12)
Master/Doctor	5(15.15)	6(18.18)
Residence		
City	32(96.97)	32(96.97)
Country	1(3.03)	1(3.03)
Marriage status		
Unmarried	25(75.76)	27(81.82)
Married	8(24.24)	6(18.18)
Monthly income (Chinese Yuan)		
More than 10000	13(39.39)	13(39.39)
1001-5000	2(6.06)	3(9.09)
5001-10000	18(54.55)	17(51.52)
Work status		
Unemployed/other	9(27.27)	5(15.15)
Employed	12(36.36)	15(45.45)
Student	12(36.36)	13(39.39)
Smoking history	5(15.15)	5(15.15)
Alcohol history	8(24.24)	11(33.33)
First episode	15(45.45)	18(54.55)
Family history of mental disorder	4(12.12)	2(6.06)
Age (Year)	29.36(8.76)	27.48(7.58)
Body mass index	23.29(5.32)	21.21(3.08)
Total course of MDD (months)	49.00 (10.00–104.00)	30.00(6.00–79.00)
Duration of current episode (months)	3.00(1.00–19.00)	3.00(1.00–10.00)
Total score of HAMD-17 at baseline	20.00(18.00–22.00)	20.00 (18.00–22.00)
Frequency of episode	2.00(1.00–3.00)	1.00(1.00–3.00)

Note: n (%) or mean (standard deviation) or median (interquartile range).

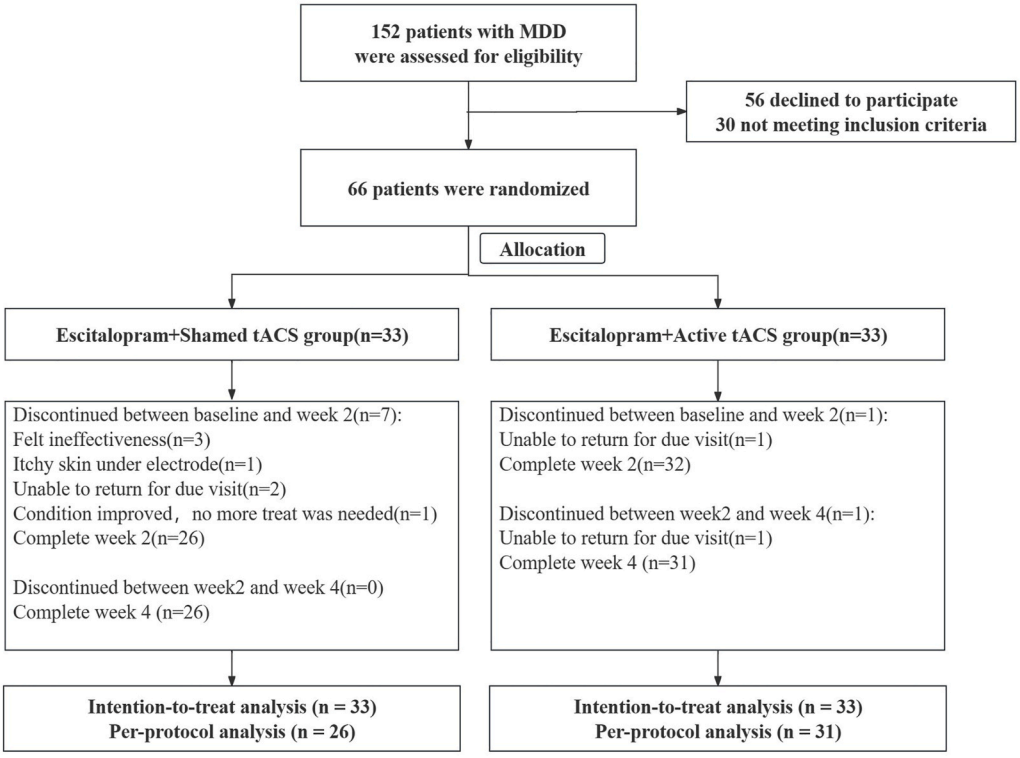

Fig. 1. Flow Chart.

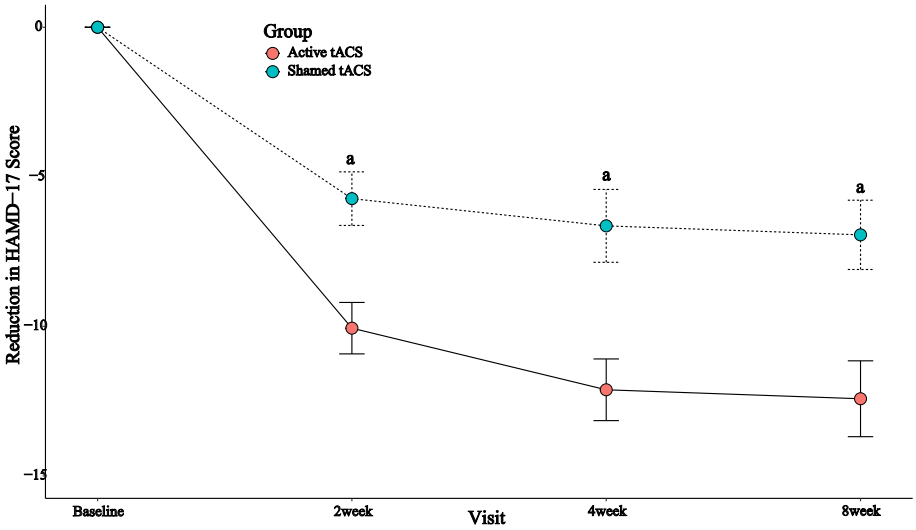

Fig. 2. The Mean Reductions of the 17-item Hamilton Rating Scale for Depression (HAMD-17) Scores from Baseline to Weeks 2, 4, and 8 in the Active tACS and Sham tACS Groups

Note: HAMD-17 (the 17- item Hamilton Rating Scale for Depression; range: 0–51; higher scores indicate more severe depressive symptoms). The error bars indicate SEs. The missing data of the HAMD-17 scores for 1 patient in Week 4 and 8 patients in Week 8 were imputed using the last observation carried forward.
a represents $P < 0.05$.

baseline in the HAMD-17 total score) at Week 4 compared with those in the sham tACS group (n = 11/33, 33.3 %; $\chi^2 = 7.33$, $P = 0.007$). This difference was also observed at Week 2 (active tACS: n = 14/33, 42.4 %; sham tACS: n = 6/33, 18.2 %; $\chi^2 = 4.59$, $P = 0.032$) and Week 8 (active tACS: n = 22/33, 66.7 %; sham tACS: n = 11/33, 33.3 %; $\chi^2 = 7.33$, $P = 0.007$) (Fig. 3). Compared with those in the sham tACS group, the reductions in the scores on the depression and insomnia subscales of the HAMD-17 in the active tACS group at Week 2 were significantly larger ($P < 0.05$). At Week 4, the reductions in the scores on the depression, insomnia, and somatic subscales of the HAMD-17 in the active tACS group were significantly larger (Supplementary materials Table S2). At Week 4, the CGI-S score reduction in the active tACS group was significantly higher ($Z = -2.37$, $P = 0.018$) (Supplementary materials Table S3). The differences between the reductions in the QIDS-SR16, GAD-7, and PSQI scores in the active and shamed tACS groups were not statistically significant ($P > 0.05$) (Supplementary Materials Table S4).

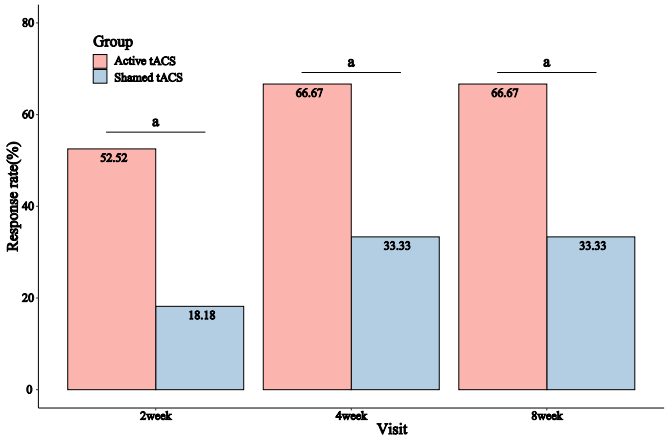

Fig. 3. The Response Rates at Different Visits in the Active tACS and Sham tACS Groups

Note: Response was defined as a 50 % reduction in the 17-item Hamilton Rating Scale for Depression (HAMD-17, range: 0–51; higher scores indicating more severe depressive symptoms). Missing data of the HAMD-17 scores for 1 patient in Week 4 and 8 in Week 8 were imputed using the last observation carried forward.
a represents $P < 0.05$.

3.4. Sensitivity analysis

The results of the multiple imputation were consistent with those of the primary analysis. The results showed that the estimated mean HAMD-17 reduction in the active tACS group was larger than in the sham tACS group ($t = 2.19$, $P = 0.031$) at week 4. The per-protocol analysis also supported this result (Supplementary Materials Table S5).

In addition, a mixed-effects model analysis with the treatment group, visit, and their interaction (group × visit) as fixed effects and the participant as a random effect revealed a significant treatment group-by-time interaction ($F = 5.75$, $P = 0.004$). The improvement over visits in the study (baseline, Week 2, and Week 4) was significantly greater in the active tACS group. The least-squares mean reduction in the HAMD-17 score from baseline to Week 4 was 12.70 (se 0.75) in the active tACS group and 8.77(se 0.81) in the sham tACS group (between-group difference 3.93 [se 1.11], 95 % CI 1.94 to 6.12; p = 0.001). (Supplementary materials Table S6).

3.5. Blinding integrity

To test the quality of the blinding in our study, we paid return visits to all patients. In the active stimulation group, 25 patients thought they received active stimulation, 6 thought they received sham stimulation, and 2 were lost to follow-up; in the sham stimulation group, 21 thought they received active stimulation, 9 thought they received sham stimulation, and 3 were lost to follow-up. In both the active and sham stimulation groups, most patients (80.6 % and 70 %, respectively) believed they received active tACS. Also, there was no statistical difference between the two groups in the number of patients who believed they received active or sham stimulations. (p = 0.563).

3.6. Mechanism exploration

To verify whether tACS was effective in changing alpha oscillations, we assessed the changes in resting-state alpha power at the Week-4 follow-up in the PP sample. Baseline alpha power was not different between the two groups. We compared the changes in alpha power

between the treatment groups but found no significant difference (Supplementary materials Fig. S1). Then, we conducted an in-depth exploratory analysis. In the active tACS group, we found a correlation between the mean reduction of PSD in eye-closed state EEG and the mean reduction in the HAMD-17 total score from baseline to Week 4 (r = 2.38, $P = 0.024$). Also, in the active tACS group, the mean reduction of PSD from baseline to Week 4 in eye-closed state EEG was significantly larger in the responders than in the non-responders (Z = 2.46, P = 0.014). On the other hand, in the sham tACS group, no consistent results were found (Fig. 4). A similar analysis of the eye-open state did not reveal any significant effect of the stimulation on changing alpha power. Taken together, our results indicate that tACS was effective in targeting alpha oscillations in the left frontal regions, and this change had a relationship with clinical symptoms.

3.7. Safety

No serious adverse events were observed in this trial. The reported general side effects in the active tACS group (compared with the sham tACS group) included headache (3/33 compared with 0/33), drowsiness (3/33 compared with 0/33), and dizziness (0/33 compared with 2/33).

4. Discussion

In this randomized, double-blind, controlled trial strictly restricting the type and dose of antidepressant involved, we confirmed the effect of tACS used as an adjunct to treatments of patients with MDD to improve the efficacy of antidepressants. Compared with those of patients receiving the sham add-on treatment, almost all domains of depressive symptoms of the patients receiving the active add-on treatment significantly improved. Self-reported and serious adverse events did not significantly differ between the groups. These findings indicate that compared to antidepressant monotherapy, the add-on tACS can enhance the efficacy in acute treatment.

Regarding the primary outcome, our study found that tACS combined with escitalopram was significantly more effective than escitalopram alone, indicating that tACS had a promising antidepressant efficacy. We also found a significant add-on antidepressant effect after 4 weeks of treatment, and the mentioned effects persisted for 4 weeks after the end of the tACS treatment. Clinical studies on tACS in the field of MDD involved frequencies of 10 Hz, 40 Hz, and 77.5 Hz, and all three frequencies had shown antidepressant effects. Studies on tACS at 40 Hz include a case report [35] and a clinical trial in 6 patients with MDD [7]; participants in both studies improved after 2 weeks of treatment and had improved cognitive function. After 2 weeks of 40-Hz tACS combined

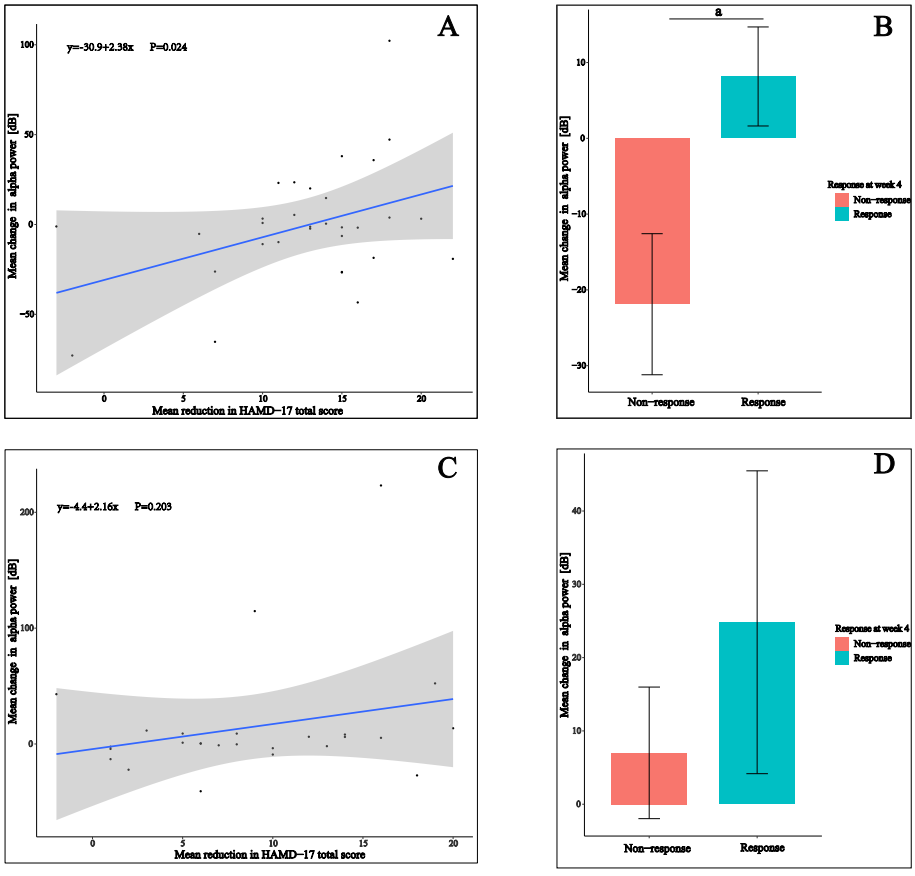

Fig. 4. Relationship between changes in EEG alpha power and HAMD-17
Note: A: In the active tACS group, the correlation between the mean reduction in EEG and the mean reduction in the HAMD-17 total score from baseline to Week 4, evaluated with Spearman (r = 2.38, P = 0.024)
B: In the active tACS group, the difference in the mean reductions from baseline to Week 4 in EEG between responders and non-responders at Week 4, evaluated using the Wilcoxon Rank Sum Test (Z = 2.46, P = 0.014)
C: In the active tACS group, the correlation between the mean reduction in EEG and the mean reduction in the HAMD-17 total score from baseline to Week 4, evaluated with Spearman (r = 2.16, P = 0.203)
D: In the active tACS group, the difference in the mean reductions from baseline to Week 4 in EEG between responders and non-responders at Week 4, evaluated using the Wilcoxon Rank Sum Test (Z = 0.62, P = 0.533)
a represents $P < 0.05$.

with antidepressants, the average reduction rate of the HAMD scores reached 73.5 %. Alexander et al. [6] randomized 32 patients with MDD into three study groups of 10-Hz tACS, 40-Hz tACS, and sham stimulation and administered one 40-min intervention session each day for 5 consecutive days along with antidepressants. The response rate of the 10-Hz tACS group at Week 2 was significantly higher than the 40-Hz and sham stimulation groups, suggesting that 10-Hz tACS had a better antidepressant efficacy. The most reliable evidence in MDD is for tACS with 15 mA, 77.5 Hz: An RCT of tACS in 100 drug-naïve patients with MDD [8] showed a response rate of 70 % and a remission rate of 62 % after 4 weeks of tACS treatment, which were significantly higher than the response and remission rates after sham stimulation (42 % and 26 %). However, this study only included first-episode drug-naïve patients, and the more significant treatment effect may be because of that. Another RCT studied tACS combined with antidepressants in 62 patients [14] and found a promising clinical efficacy, with a reduction of 74.29 % in the HAMD scores in the active group and 32.54 % in the sham group at the end of Week 4. Although this study had limitations and the use of antidepressants was not limited, tACS as an add-on to antidepressants may be a good option for patients who need a fast effect. Along with other neuromodulations, rTMS also enhances the clinical response to antidepressants [36] and significantly accelerates the alleviation of depressive symptoms [37] in patients with MDD. A study of 2-week rTMS combined with citalopram found that the response rates in the active group versus the sham group were 39 % versus 29 % at Week 2 and 46 % versus 36 % at Week 4 [38]. A study of 4-week rTMS in combination with paroxetine found a response rate of 95.5 % and a remission rate of 68.2 % in the active group, which were significantly higher than those in the sham group (71.4 % and 38.1 %) at Week 4, although there was no significant difference at Week 8 [39]. Studies of tDCS as an add-on treatment to antidepressants also demonstrated the synergistic effect of combination therapy. One study found that participants receiving 4 weeks of tDCS combined with sertraline had a response rate of 53.3 % and a remission rate of 23.3 %, significantly higher than those in the sertraline-only group (26.7 % and 13.3 %) [40]. In another study, patients with MDD were divided into three groups: 30-min, 20-min, and sham tDCS, combined with sertraline. After ten days of tDCS stimulation, the 30-min, 20-min, and sham groups showed response rates of 89 %, 68 %, and 50 % and remission rates of 70 %, 27 %, and 35 %, respectively. The improvement in depressive symptoms was more substantial in the active stimulation groups, and the improvement in the 30-min group was significantly larger than in the 20-min group [41]. In summary, tACS is expected to be an effective add-on antidepressant treatment comparable to rTMS and tDCS. However, considering that rTMS and tDCS have been evaluated in large-scale multi-center trials, whereas tACS has only been studied in small-scale trials, it should be noted that there is a risk of false-positive findings and our findings need to be confirmed by larger trials in the future.

The QIDS-SR16 scores did not reveal any significant treatment advantage in the active tACS stimulation group over the sham stimulation group. Some studies have found that patients scored themselves higher on self-report measures than the clinicians rated them. Explanations for this phenomenon include the differences in the focus of the clinician and patient, overestimation of symptom severity by the patients, high levels of anxiety, need for approval (especially social desirability), and high levels of self-transcendence (especially self-forgetfulness) [42]. Furthermore, after comparing each factor in the HAMD-17, we found that the factors depressed mood, insomnia, and somatization showed more pronounced improvements, whereas these symptoms were lighter weighted in the QIDS-SR16; this difference may be part of the reasons why the changes in the total score were not significant. Previous studies examining the concordance between self-report and clinician-rated measures were inconsistent, and this is the main reason why most clinical trials would use both self-report and clinician-rated measures as outcome instruments, with the latter serving as the measurement tool for the primary outcome [42,43].

The CGI was also used to assess the severity of the patient's depressive symptoms and the degree of improvement. The CGI-S scores at Week 2 suggested that the tACS group had more improvement than the sham group. The results of the CGI-S revealed the positive impact of tACS on the overall clinical impression of patients with MDD. Although the CGI is an instrument relying on the subjective judgment of the evaluators, it provides important information on the effectiveness of treatment, especially for the evaluation of practical clinical significance.

The safety of using high currents is a concern. In this study, 86.4 % (57/66) of the participants completed the 4-week study. The dropout rate was lower than the estimation of 20 %, suggesting that the tACS used in this study was safe and well tolerated. All patients were followed up for adverse events, and most side effects in this study were mild (some patients experienced dizziness, headache, and daytime sleepiness). More importantly, there was a difference between the adverse events in the two groups. Previous studies did not report side effects of daytime sleepiness [8,14]. However, we observed prolonged daytime sleepiness that was clearly related to the treatment, with sleepiness being the most pronounced at the end of tACS (although it should be noted that this finding still needs to be validated in future studies). Therefore, it may be necessary to notify patients who drive vehicles. In addition, no manic or hypomanic symptoms, seizures, neurologic complications, optical illusions, deaths, or other serious adverse events were observed in our study. Overall, the safety of tACS in combination with antidepressants for the treatment of MDD was confirmed, suggesting that future clinical trials with tACS are feasible.

The physiological target of the current study was left frontal alpha oscillations. EEG alpha activity is more pronounced with eyes closed [44], and alpha power asymmetry has been found to be more reliable with eyes closed than with eyes open [45]. The alteration of alpha power in our study also occurred only in the eye-closed state. This alteration was thought to reflect reduced neuronal activity in the left frontal lobe, one of several key regions where abnormalities have been found in brain imaging studies of depression [46]. One article has examined EEG changes after receiving tACS in patients with MDD; it found that 10-Hz tACS resulted in a significant reduction in alpha oscillations in the left frontal region with eyes closed, whereas no changes were found with 40-Hz tACS. In addition, 10-Hz tACS showed better antidepressant effects [6]. Another study found that tACS with individualized alpha frequency (IAF) could reduce resting-state left frontal alpha power in patients with MDD. Furthermore, the reduction of left frontal alpha oscillation by tACS was specific for stimuli with positive valence [47]. Our study also found a decrease in left frontal alpha frequency in patients who responded to the tACS treatment but not in patients with no response. We hypothesize that the antidepressant effect of tACS may be related to the decrease in left frontal alpha power. The exact mechanism of tACS has not been determined; studies have shown that tACS induces cortical oscillations by entrainment and spike-timing dependent plasticity [48]. Studies have consistently demonstrated the localized power enhancement after tACS and have found that immediate tACS after-effects led to an increase in resting-state alpha power [49]. The transient alpha power enhancement after a single tACS treatment may be due to a stimulus dose that is not sufficiently persistent to induce long-term plasticity [50]. The increase in transient alpha power may reflect neural induction of time-synchronized cortical oscillations by exogenous stimuli [51,52], but evidence for long-term effects remains limited. We found a decrease in alpha power after 20 sessions of tACS, which is opposite to the immediate effect, suggesting that repeated application of tACS may lead to oscillator resetting, which in turn leads to a decrease in alpha power through a homeostatic mechanism [53], producing an antidepressant effect. Therefore, the results of this study once again suggested that the intrinsic regulation of alpha oscillations may be an important mechanism for the antidepressant effect of tACS.

This study has some limitations. First, we only observed the efficacy in the acute phase, and we only included a 4-week follow-up, which is rather short compared to current best-practice RCTs in MDD. Therefore,

the maintenance effect still needs to be further investigated. Second, we used only tACS with 77.5 Hz, 15 mA, and a fixed stimulation position. The antidepressant efficacy of different frequencies, currents, and electrode combinations is unknown. Third, we only compared the changes in left frontal alpha power, and it is unclear whether the EEG at other locations and frequencies changed. Also, all patients used antidepressants, which may have affected the EEG. The growing recognition of the presence of abnormal oscillatory dynamics in the pathology of MDD has generated strong interest in the direct modulation of endogenous oscillations. Future studies on various forms of neuromodulation and EEG alterations in unmedicated patients are needed. Finally, the dropout rates were higher in the sham group, which might be related to the lack of antidepressant effect in that group. Future studies should make efforts to reduce the dropout rate in the sham group. In summary, although our trial provided preliminary evidence for the antidepressant effects of tACS, larger long-term trials are needed to derive more reliable conclusions.

Our results suggest that the additional antidepressant effect of tACS was significant and lasted for at least 4 weeks, and combining tACS with antidepressants is a feasible and effective approach for the treatment of MDD. The antidepressant mechanism of tACS may be the reduction of the alpha power in the left frontal lobe. Future research directions may include exploring more appropriate treatment parameters of tACS.

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CRediT authorship contribution statement

Jingjing Zhou: Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization. **Dan Li:** Writing – original draft, Formal analysis, Data curation. **Fukang Ye:** Investigation, Data curation. **Rui Liu:** Methodology, Data curation. **Yuan Feng:** Project administration, Investigation, Funding acquisition. **Zizhao Feng:** Investigation, Data curation. **Ruinan Li:** Data curation. **Xiaoya Li:** Data curation. **Jing Liu:** Data curation. **Xueshan Zhang:** Data curation. **Jia Zhou:** Writing – review & editing, Visualization, Formal analysis. **Gang Wang:** Supervision, Software, Resources, Funding acquisition.

Declaration of competing interest

The authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2024.06.004.

References

[1] Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatr 2006;163(11):1905–17.
[2] Antal A, Boros K, Poreisz C, Chaieb L, Terney D, Paulus W. Comparatively weak after-effects of transcranial alternating current stimulation (tACS) on cortical excitability in humans. Brain Stimul 2008;1(2):97–105.
[3] Marshall L, Helgadóttir H, Mölle M, Born J. Boosting slow oscillations during sleep potentiates memory. Nature 2006;444(7119):610–3.
[4] Wang HX, Wang L, Zhang WR, Xue Q, Peng M, Sun ZC, et al. Effect of transcranial alternating current stimulation for the treatment of chronic insomnia: a randomized, double-blind, parallel-group, placebo-controlled clinical trial. Psychother Psychosom 2020;89(1):38–47.
[5] Elyamany O, Leicht G, Herrmann CS, Mulert C. Transcranial alternating current stimulation (tACS): from basic mechanisms towards first applications in psychiatry. Eur Arch Psychiatr Clin Neurosci 2021;271(1):135–56.
[6] Alexander ML, Alagapan S, Lugo CE, Mellin JM, Lustenberger C, Rubinow DR, et al. Double-blind, randomized pilot clinical trial targeting alpha oscillations with transcranial alternating current stimulation (tACS) for the treatment of major depressive disorder (MDD). Transl Psychiatry 2019;9(1):106.
[7] Haller N, Senner F, Brunoni AR, Padberg F, Palm U. Gamma transcranial alternating current stimulation improves mood and cognition in patients with major depression. J Psychiatr Res 2020;130:31–4.
[8] Wang H, Wang K, Xue Q, Peng M, Yin L, Gu X, et al. Transcranial alternating current stimulation for treating depression: a randomized controlled trial. Brain 2022;145(1):83–91.
[9] Shan Y, Wang H, Yang Y, Wang J, Zhao W, Huang Y, et al. Evidence of a large current of transcranial alternating current stimulation directly to deep brain regions. Mol Psychiatr 2023:1–9.
[10] Lebedev VP, Malygin AV, Kovalevski AV, Rychkova SV, Sisoev VN, Kropotov SP, et al. Devices for noninvasive transcranial electrostimulation of the brain endorphinergic system: application for improvement of human psycho-physiological status. Artif Organs 2002;26(3):248–51.
[11] White NE, Richards LM. Nexalin and related forms of subcortical electrical stimulation. In: Rhythmic stimulation procedures in neuromodulation. Elsevier; 2017. p. 131–57.
[12] Hegadoren K, O'donnell T, Lanius R, Coupland N, Lacaze-Masmonteil N. The role of β-endorphin in the pathophysiology of major depression. Neuropeptides 2009;43(5):341–53.
[13] Mayberg HS, Brannan SK, Tekell JL, Silva JA, Mahurin RK, McGinnis S, et al. Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response. Biol Psychiatr 2000;48(8):830–43.
[14] Jiong Luo CS, Pan Weigang, et al. Efficacy and safety of transcranial alternating current stimulation combined with antidepressants in depressive episodes. Journal of Capital Medical University 2022;43(2):244–8.
[15] Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet 2018;391(10128):1357–66.
[16] Fingelkurts AA, Fingelkurts AA. Altered structure of dynamic electroencephalogram oscillatory pattern in major depression. Biol Psychiatr 2015;77(12):1050–60.
[17] Smart OL, Tiruvadi VR, Mayberg HS. Multimodal approaches to define network oscillations in depression. Biol Psychiatr 2015;77(12):1061–70.
[18] Olbrich S, Arns M. EEG biomarkers in major depressive disorder: discriminative power and prediction of treatment response. Int Rev Psychiatr 2013;25(5):604–18.
[19] Northoff G. How do resting state changes in depression translate into psychopathological symptoms? From 'Spatiotemporal correspondence' to 'Spatiotemporal Psychopathology'. Curr Opin Psychiatr 2016;29(1):18–24.
[20] Newson JJ, Thiagarajan TC. EEG frequency bands in psychiatric disorders: a review of resting state studies. Front Hum Neurosci 2018;12:521.
[21] Leuchter AF, Cook IA, Hunter AM, Cai C, Horvath S. Resting-state quantitative electroencephalography reveals increased neurophysiologic connectivity in depression. PLoS One 2012;7(2):e32508.
[22] Jensen O, Mazaheri A. Shaping functional architecture by oscillatory alpha activity: gating by inhibition. Front Hum Neurosci 2010;4:186.
[23] Klimesch W. α-band oscillations, attention, and controlled access to stored information. Trends Cognit Sci 2012;16(12):606–17.
[24] Harmon-Jones E, Gable PA. On the role of asymmetric frontal cortical activity in approach and withdrawal motivation: an updated review of the evidence. Psychophysiology 2018;55(1).
[25] Davidson RJ. Anterior cerebral asymmetry and the nature of emotion. Brain Cognit 1992;20(1):125–51.
[26] World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Bull World Health Organ 2001;79(4):373–4.
[27] Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. Ann Intern Med 2008;148(4):295–309.
[28] Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods 2004;134(1):9–21.
[29] Zheng YP, Zhao JP, Phillips M, Liu JB, Cai MF, Sun SQ, et al. Validity and reliability of the Chinese Hamilton depression rating scale. Br J Psychiatry 1988;152:660–4.

[30] Lin J, Wang X, Dong F, Du Y, Shen J, Ding S, et al. Validation of the Chinese version of the Hamilton rating scale for depression in adults with epilepsy. Epilepsy Behav 2018;89:148–52.
[31] Shih YC, Chou CC, Lu YJ, Yu HY. Reliability and validity of the traditional Chinese version of the GAD-7 in Taiwanese patients with epilepsy. J Formos Med Assoc 2022;121(11):2324–30.
[32] Liu J, Xiang YT, Wang G, Zhu XZ, Ungvari GS, Kilbourne AM, et al. Psychometric properties of the Chinese versions of the Quick inventory of depressive Symptomatology - clinician rating (C-QIDS-C) and self-report (C-QIDS-SR). J Affect Disord 2013;147(1–3):421–4.
[33] Liu X. Reliability and validity of the Pittsburgh sleep quality index. Chinese journal of psychiatry 1996;29:103.
[34] Berk M, Ng F, Dodd S, Callaly T, Campbell S, Bernardo M, et al. The validity of the CGI severity and improvement scales as measures of clinical effectiveness suitable for routine clinical use. J Eval Clin Pract 2008;14(6):979–83.
[35] Wilkening A, Kurzeck A, Dechantsreiter E, Padberg F, Palm U. Transcranial alternating current stimulation for the treatment of major depression during pregnancy. Psychiatr Res 2019;279:399–400.
[36] Berlim MT, Van den Eynde F, Daskalakis ZJ. High-frequency repetitive transcranial magnetic stimulation accelerates and enhances the clinical response to antidepressants in major depression: a meta-analysis of randomized, double-blind, and sham-controlled trials. J Clin Psychiatry 2013;74(2):e122–9.
[37] Rumi DO, Gattaz WF, Rigonatti SP, Rosa MA, Fregni F, Rosa MO, et al. Transcranial magnetic stimulation accelerates the antidepressant effect of amitriptyline in severe depression: a double-blind placebo-controlled study. Biol Psychiatr 2005;57 (2):162–6.
[38] Huang ML, Luo BY, Hu JB, Wang SS, Zhou WH, Wei N, et al. Repetitive transcranial magnetic stimulation in combination with citalopram in young patients with first-episode major depressive disorder: a double-blind, randomized, sham-controlled trial. Aust N Z J Psychiatr 2012;46(3):257–64.
[39] Wang YM, Li N, Yang LL, Song M, Shi L, Chen WH, et al. Randomized controlled trial of repetitive transcranial magnetic stimulation combined with paroxetine for the treatment of patients with first-episode major depressive disorder. Psychiatr Res 2017;254:18–23.
[40] Brunoni AR, Valiengo L, Baccaro A, Zanão TA, de Oliveira JF, Goulart A, et al. The sertraline vs. electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. JAMA Psychiatr 2013;70(4): 383–91.
[41] Pavlova EL, Menshikova AA, Semenov RV, Bocharnikova EN, Gotovtseva GN, Druzhkova TA, et al. Transcranial direct current stimulation of 20- and 30-minutes combined with sertraline for the treatment of depression. Prog Neuro-Psychopharmacol Biol Psychiatry 2018;82:31–8.
[42] Corruble E, Legrand JM, Zvenigorowski H, Duret C, Guelfi JD. Concordance between self-report and clinician's assessment of depression. J Psychiatr Res 1999; 33(5):457–65.
[43] Sousa S, Robinson L, Franklin M, Watson S. Patient-reported and clinician-rated outcome measures: complementary evidence from two different perspectives. J Affect Disord 2020;276:848–9.
[44] Barry RJ, Clarke AR, Johnstone SJ, Magee CA, Rushby JA. EEG differences between eyes-closed and eyes-open resting conditions. Clin Neurophysiol 2007;118(12): 2765–73.
[45] Metzen D, Genç E, Getzmann S, Larra MF, Wascher E, Ocklenburg S. Frontal and parietal EEG alpha asymmetry: a large-scale investigation of short-term reliability on distinct EEG systems. Brain Struct Funct 2022;227(2):725–40.
[46] Koenigs M, Grafman J. The functional neuroanatomy of depression: distinct roles for ventromedial and dorsolateral prefrontal cortex. Behav Brain Res 2009;201(2): 239–43.
[47] Riddle J, Alexander ML, Schiller CE, Rubinow DR, Frohlich F. Reduction in left frontal alpha oscillations by transcranial alternating current stimulation in major depressive disorder is context dependent in a randomized clinical trial. Biol Psychiatr: Cognitive Neuroscience and Neuroimaging 2022;7(3):302–11.
[48] Vogeti S, Boetzel C, Herrmann CS. Entrainment and spike-timing dependent plasticity–a review of proposed mechanisms of transcranial alternating current stimulation. Front Syst Neurosci 2022;16:827353.
[49] Clancy KJ, Baisley SK, Albizu A, Kartvelishvili N, Ding M, Li W. Lasting connectivity increase and anxiety reduction via transcranial alternating current stimulation. Soc Cognit Affect Neurosci 2018;13(12):1305–16.
[50] Kasten FH, Dowsett J, Herrmann CS. Sustained aftereffect of α-tACS lasts up to 70 min after stimulation. Front Hum Neurosci 2016;10:245.
[51] Reato D, Rahman A, Bikson M, Parra LC. Effects of weak transcranial alternating current stimulation on brain activity-a review of known mechanisms from animal studies. Front Hum Neurosci 2013;7:687.
[52] Helfrich RF, Schneider TR, Rach S, Trautmann-Lengsfeld SA, Engel AK, Herrmann CS. Entrainment of brain oscillations by transcranial alternating current stimulation. Curr Biol 2014;24(3):333–9.
[53] Leuchter AF, Cook IA, Jin Y, Phillips B. The relationship between brain oscillatory activity and therapeutic effectiveness of transcranial magnetic stimulation in the treatment of major depressive disorder. Front Hum Neurosci 2013;7:37.