Efficacy and Safety of tDCS and tACS in Treatment of Major Depressive Disorder: A Randomized, Double-Blind, Factorial Placebo-Controlled Study Design

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Background: Transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS) are regarded as promising antidepressant treatments.

Objective: To compare the efficacy and safety of tDCS, tACS, escitalopram, and placebo/sham stimulation controls.

Design: Randomized, parallel, double-blind, placebo-controlled study.

Methods: Sample sizes were calculated based on data from previous similar studies. Eligible non-treatment-resistant depressive outpatient subjects with moderate-to-severe depression (HRDS ≥17) are randomized to receive (1) tDCS + placebo; (2) tACS + placebo; (3) escitalopram + placebo; or (4) sham stimulation + placebo. The intensity of electricity is 2 mA, lasting for 30 minutes over two consecutive working days (10 sessions in total). The medication lasts for 6 weeks. The primary outcome measure was the response rates within 6 weeks (week 6 is also the endpoint of the study), and secondary outcome measures included changes in other clinical measurements. Safety and acceptability are measured by adverse event rates and dropout rates. Exploring outcome consist of the performance of cognitive battery as well as neurophysiology results.

Conclusion: To the best of our knowledge, the present study is the first double-blind controlled study comparing tDCS, tACS, and clinically used antidepressants, which will provide further evidence for their efficacy and safety in possible clinical applications.

Keywords: transcranial direct current stimulation, tDCS, transcranial alternating current stimulation, tACS, electrical stimulation, major depressive disorder, MDD

Introduction

Major depressive disorder (MDD) is a widespread neuropsychiatric disorder with an estimated 12-month prevalence of 2.1% and a lifetime prevalence of 3.4% in China1. Currently, the predominant treatment for MDD is antidepressant drugs, which only brings about 1/3 clinical remission rate2.3 Meanwhile, antidepressant drugs usually result in undesirable side effects and undergo 2–4 weeks to achieve clinical efficacy. Therefore, it is necessary to explore other alternative efficient approaches.

Non-invasive physical therapy interventions, including transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS), have attracted the researchers’ attention. Both tDCS and tACS stimulate the brain...
through scalp electrodes to modulate cortical activity, whose benefits include painlessness, causing few adverse events, portable, easy to operate, and economic.

**Transcranial Direct Current Stimulation (tDCS)**

TDCS delivers direct currents (0.5–2 mA) to the scalp to modulate the neural activity of the cerebrum. Its exact mechanism has yet to be defined. The stimulatory effect of tDCS is characterized by polarity regulation: the anode current promotes depolarization of neuronal membrane potentials to enhance cortical excitability, and the cathode current induces hyperpolarization changes to inhibit cortical excitability.

TDCS potentially improves cognitive performances, such as reduction in response time and vigilance to threat, and improved emotion recognition. However, there is insufficient evidence to state that tDCS has a positive or negative effect as a treatment for depression cognitive dysfunction and should therefore be further investigated.

Evidence of tDCS’ efficacy on a depressive episode remains inconsistent, in part due to various confounding variables (ie, tDCS parameter settings, outcome measures, etc.) that are not under control. The effects of tDCS varying by individuals may also contribute to the heterogeneous results. The structural traits and functional states of individuals neural systems are considered the main sources of the individual sensitivity to tDCS. In addition, the baseline phenotypic predicts the response to tDCS. In other words, although several meta-analyses and systematic reviews suggest that the efficacy of tDCS is promising, the quality of the evidence is generally poor along with the unclear risk of bias. Therefore, it is necessary to further confirm its therapeutic efficacy and explore the predetermined factors of response to treatment through routine clinical and neuropsychological assessments.

**Transcranial Alternating Current Stimulation (tACS)**

TACS, another newly emerging neurological intervention, works by regularly oscillating electrical currents alternating between positive and negative voltages to modulate neural activity and phasic.

The alpha frequency (8–12 Hz) appears increased oscillatory activity in the frontal lobe of MDD patients, indicating that its regulation of mood, the processing of affective information, and emotional stimuli are disturbed. The increase in left hemisphere alpha activity is also associated with a lack of approach behavior.

An RCT study found that 40 minutes 10 Hz-tACS for 5 consecutive days can effectively target alpha oscillations in the frontal area, with its response rates significantly outperformed sham stimulation at the 2-week follow-up. Therefore, successful reshaping of disrupted oscillations may have changed the symptoms of MDD.

The tACS may have potential antidepressant effects, but relevant RCTs are very limited, with only one study exploring the efficacy of tACS and no studies comparing the effects of tACS with other common treatments.

**Safety of tDCS and tACS**

A meta-analysis has reported that low-intensity transcranial electrical stimulations, including tDCS and tACS, are safe. TDCS was also well tolerated in the treatment of MDD and there was no significant difference in the rates of adverse event and drop-out between active and sham stimulation groups.

Common adverse reactions to stimulation are itching, tingling sensation, burning sensation, headache, and discomfort at the stimulated region. Researchers can moisten the sponge by avoiding rubbing the skin where the electrodes stimulate, stimulating uneven (eg scarring) or inflamed skin areas, or using saline instead of tap water to reduce common adverse skin reactions. All these adverse events are brief and minor. Similar results are observed in tACS treatment. Active tES treatment strategies are at least as acceptable as sham treatment.

Several studies have reported episodes of hypomania/mania in patients with major depression after active tDCS stimulation. And tDCS in combination with sertraline may cause hypomania/mania episodes. A meta-analysis revealed that even though the incidence of hypomania/mania episode was higher in the active stimulation group than in the sham group, the difference was not statistically significant. Overall, the causal relationship between tDCS and hypomania/mania episodes is difficult to prove given the low incidence and the limited number of subjects in a controlled trial.

Previous studies often have some limitations, they include: (1) Small sample size; (2) Mixed samples with bipolar disorders or patients with treatment-resistant depression; (3) The stimulation protocol (stimulation target and time, current intensity, frequency, and the number of sessions as well as sham-stimulation) differs
for one RCT to another; and (4) Fail to control other confounding factors, such as concurrent medications and psychotherapy, that may make it difficult to identify the main source of efficacy. As a review suggests medications that influence various neurotransmitter systems (GABA, dopamine, serotonin, etc.) may have an impact on tDCS effects on tissue excitability.\(^{31}\) Moreover, most of the previous evidence present a risk of low-quality or nebulous bias,\(^{19}\) which requires more precise estimates of the effect of treatment.

**Aims of the Study**

To verify the efficacy of tDCS and tACS, this study plans to conduct a randomized, double-blind, placebo-controlled clinical trial. We will compare the efficacy and safety of tDCS, tACS, sham stimulus/placebo, and one anti-depression drug, escitalopram. We choose the escitalopram because it shows relatively good efficacy and acceptability for the acute treatment of MDD\(^{32}\) and is commonly used in clinical practice in China.\(^{33--37}\) This drug should be adequate to be an active comparator as well as reflect real-world clinical practice. We will also identify the cognitive enhancement effect of tDCS and tACS.

**Methods**

**Participants**

Participants are recruited by outpatient psychiatrists and advertisement posters in Shanghai Mental Health Center. Written informed consent is obtained from all the participants. Men and women age between 18 and 65 who meet the following criteria could be enrolled.

The inclusive criteria include:

1. Diagnosed with major depressive disorder (MDD) following DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th edition) criteria by psychiatrists. The diagnosis is conducted by Structured Clinical Interview (SCID) for DSM-V.
2. The presence of a depressive episode of at least moderate intensity, referring to Hamilton Depression Rating Scale (17-items) (HDRS-17) score \(\geq 17\).
3. Participants with middle school and above education to ensure their ability to understand and complete the necessary measurements in the study;

Exclusive criteria:

1. Participants who meet the diagnostic criteria of other severe mental disorders including bipolar disorder, schizophrenia, alcohol and substance use disorders, personality and developmental disorders;
2. Patients with treatment-resistant depression (TRD), defined as who did not respond (eg, HDRS score reduction rate <50% after treatment) to two successive antidepressant treatment of adequate dose and duration;\(^{38}\) patients using or who used escitalopram in the current acute depressive episode are also excluded because escitalopram is not comparable in such cases. However, those who used escitalopram in previous episodes and presented clinical responses can be included.
3. High risk of suicide and self-injury (ie score \(\geq 3\) in the Hamilton suicide question);
4. Patients with the severe or unstable physical disease within 3 months or stroke within 30 days;
5. Pregnancy and lactation;
6. The subjects had attended any other clinical trials within 30 days before the baseline.
7. The subjects had taken any psychopharmacological drugs seven days before baseline. If the subjects are taking any pharmacological medication, there should be a wash-out period of at least 5 times the half-life of the drug. Specifically, a stable dosage of eszopiclone and zolpidem is allowed during the trial. Psychotherapy or any other systematic antidepressant treatment is not allowed during the screening and intervention phases.

Patients will withdraw from the study for the following reasons:

1. The patient requests for withdrawal for any reason;
2. The occurrence or deterioration of medical condition (eg, increased suicide risk, sudden onset of serious physical illness which would not allow the patient to continue the study, or participation in the study presents a significant burden to the patient);
3. The occurrence of serious adverse events that cannot be tolerated by the patient,
4. Violation of the treatment protocol (eg, the patient requests for hospitalization or other approaches of treatment);

The reasons for withdrawal will be recorded factually in time. Participants who complete the study or
withdraw from the study will be referred to an outpatient psychiatrist.

Sample Size
Since previous studies suggested that tDCS is more suitable for the initial treatment of depression, the response rate was chosen as the main endpoint measurement in this study. Our null hypothesis is that there is no significant difference in response rate between tDCS, tACS, Escitalopram, and sham/placebo groups. The study’s primary aim is to prove the alternative hypothesis. Data for calculating the sample size for this study were obtained from comparable studies. The response rate for tACS, escitalopram, tDCS and sham/placebo is 77.8%, 47%, 39% and 22% respectively. Power Analysis and Sample Size (PASS) software were used for a priori power analysis with a statistical power of 80%, using a two-tailed test at the 5% level of significance, indicating that 88 subjects will be adequate to detect the difference in response rate. Taking 20% drop-out rate into account, a sample size of 112 with 28 subjects in each group was determined.

Intervention Design
Before the start of the study, we use a table of block random numbers generated by SPSS. Participants will be assigned to the corresponding intervention group according to their entry number (Please see Figure 1 for the study flow chart). The intervention groups include: active tDCS + placebo, active tACS + placebo, sham stimulus + escitalopram and sham stimulus + placebo. Physical

Figure 1 Study flow chart.
stimulation starts at baseline and ends at week 2, and medication starts at baseline and ends at week 6. During the last 4 weeks of our study, the pharmacological intervention alone, but without tDCS/tACS/sham stimulations, was used and we wanted to observe if there was a delayed improvement in symptoms during this time, as previous studies have found that the behavioural effects of 20 to 30 minutes of tDCS stimulation lasted for approximately 90 minutes and the effects of 5 stimulation sessions were still detectable after 3 months.  

The visit windows are baseline, week 2, 4, and endpoint (week 6). There will be a clinical assessment at each visit. Cognitive assessments are at baseline and week 2. Functional imaging scanning is performed at baseline and week 6. Safety assessments are at week 2, 4 and 6. Measurement arrangements are shown in Table 1. Study measurement timetable

| Table 1 The Study Measurement Schedule |
|----------------------------------------|
|                                      |
| **Clinical Assessment**                |
| HDRS        | × | × | × | × | × |
| HAMA        | × | × | × | × | × |
| MADRS       | × | × | × | × | × |
| CGI         | × | × | × | × | × |
| YMRS        | × | × | × | × | × |
| ASRM        | × | × | × | × | × |
| tDCS/tACS   | ❌ |  |  |  |  |
| adverse events |     |  |  |  |  |
| SERS        | × | × | × | × | × |
| Clinic lab  | × | × | × | × | × |
| blood       |                                      |
| **Cognitive Tests**                    |
| WSCT        | × | × |                     |
| Stroop color-word test                 | × | × |                     |
| **Neurophysiological Measurements**   |
| EEG         | × | × |                     |
| fMRI        | × | × |                     |

**Abbreviations:** HDRS, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; CGI, Clinical Global Impression; YMRS, Young Mania Rating Scale; ASRM, Altman Self-Rating Mania Scale; SERS, Asberg Side-effect Rating Scale for Antidepressant; WCST, Wisconsin Card Classification Test.

**Procedures**

The optimal protocol of tDCS (current intensity, stimulation target, duration, treatment frequency, etc.) is still being explored. The Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the treatment of adult major depressive disorder recommended a minimum “dose” of tDCS stimulation: the current intensity of 2 mA for 30 min/day, once a day for a total of 10 times.  

In this study, we follow the mentioned protocol. All stimulations are performed using the standard device (Starstim, Neuroelectrics Barcelona SL, Spain). The anode electrode is placed over the left dorsolateral prefrontal cortex (F3 in the International EEG System 10–20) and the cathode electrode over the right dorsolateral prefrontal cortex (F4). The electrodes are 5x5cm round sponges moistened with saline solution. There are 10 sessions for tDCS, tACS, and sham stimulation, with each session lasting for 30 minutes. To improve adherence and minimize dropouts, the study schedule is flexible, allowing participants to choose 10 days freely without intervention within 14 days.

For tDCS, the current intensity ramps up from 30 seconds to 2 mA and steadily lasts for 30 minutes, and ramps down to zero in the last 30 seconds. For tACS, one electrode serves as the anode while the other serves as the cathode during half cycle of an oscillation and then reverses at the peak intensity of 2 mA. The sham group only receives the currents of 30 s ramp-up to 2 mA at the beginning of the session and 30 s ramp-down at the end, to mimic typical initial sensations of an active stimulus (eg, tingling, itching at the electrode sites) while minimizing potential neuromodulatory effects. The effect of this sham-protocol is similar to that of active stimulation, but less distinct.

The escitalopram/placebo drugs are prescribed to the patient at baseline at a dosage of 10mg/d.

**Blinding**

Different stimulation protocols are pre-programmed on the computer by a dedicated person and the operator only follows the protocol codes, thus ensuring that neither the subject nor the operator is aware of the stimulation protocol being performed. Both escitalopram and placebo tablets are of the same appearance. The subjects and all study members involved in the enrolment, intervention operation, or assessment of participants are blinded to the study group. Blinding is also tested at the follow-up visit and endpoint of the study by asking subjects and raters to guess to which group they were assigned.
Ethic Issues
The trial has registered in the Chinese Clinical Trial Registry (ChiCTR number: ChiCTR1800018063) on August 28, 2018. The study has been approved by the ethics committee at Shanghai Mental Health Center (registration approval number 2018–74R). Written informed consent is obtained from all participants. The study will comply with the Declaration of Helsinki.

Outcome Measures
Clinical Assessment
All clinical assessments will be administered by trained raters with established inter-rater reliability. In this study, categorical outcome (percentage of responders) is chosen as the primary outcome for it probably better reflects clinical practice. Response rate refers to the number of participants who achieved at least a 50% reduction in scores measured by the Montgomery-Asberg Depression Rating Scale (MADRS) compared to baseline. Specifically, participants who meet the criteria for clinical response at any of the 2, 4 and 6 week follow-up windows will be considered responders. We choose MARDS instead of HRDS as primary outcome measurement because the HRDS was not designed for use in intervention studies and should therefore only be used during screening visits as one of the inclusion criteria, whereas the MARDS is more sensitive to treatment effects and is more suitable as an indicator of efficacy. Secondary outcomes consist of clinical remission (MARDS≤10) rates and score change of other measurements, including Hamilton Anxiety Rating scale (HAMA), self-report Quick Inventory of Depressive Symptomatology (QIDS-SR) and Clinical Global Impression (CGI). All these measures have satisfactory psychometric properties in depression measurement.

Safety Assessment
Safety is measured by a standard adverse event (AE) scale for tES, on which we record the frequency and severity of adverse events (eg headaches, tingling, itching, burning sensations, and any other phenomenon such as phosphene). Asberg Side-effect Rating Scale for Antidepressant (SERS) is used to track adverse events of medications. Also, the Young Mania Rating Scale (YMRS) is used to monitor possible hypomanic and manic symptoms during the intervention. We also take blood samples as one of the safety indicators, mainly for monitoring Complete Blood Count (CBC) and liver and kidney function.

Cognitive Assessment
We chose two easily administered cognitive tests based on previous recommendations which are Wisconsin Card Sorting Test (WSCT) and Stroop test. WSCT is a neuropsychological test reflecting subjects’ abstract generalization, working memory, cognitive transfer, and other aspects. Subjects are asked to sort 128 cards based on three possible categories (colors, number, and shape). After six consecutive correct responses, the sorting principle alerts us to another category. The test ends when subjects complete all six categories correctly or use all 128 cards. The preservative errors, the number of correct responses, the number of wrong responses, the total response time, and other of the total 13 indexes data before and after the intervention will be used for statistical analysis. Stroop Color-Word Test aims to test selective attention function and inhibition capacity and the performance of which improved significantly after antidepressant treatment. 120 characters will be randomly presented with identical color (such as red “red”), contradictory color (such as green “red”), irrelevant color (such as green “middle”), irrelevant color semantics (such as blue “yellow”) and neutral stimulus (color block), each stimulus presented for 1 s. The subjects are asked to click on the corresponding color button for the four colors. The response time, the correct number, the number of errors, and the number of omissions are variables to be analyzed in this study.

Functional MRI
Functional magnetic resonance imaging (fMRI) will be carried out at baseline and endpoint (week 6). Functional MRIs are set as below. Siemens 3T magnetic resonance scanner is used to complete the scanning, including structure image, resting state, task state and DTI sequence. Structural image: scanning parameters are as follows: TR = 2500ms, TE = 3.5ms, TI = 1200ms, voxel size: 1.0×1.0×1.0mm, Flip angle = 8, 45 slices, FOV = 256mm, Grappa = 2; the whole scanning process lasts 5 minutes. Resting functional imaging: scanning parameters are as follows: TR = 1400ms, TE = 30ms, Flip angle = 80, 64 slices, matrix = 112×112, FOV = 224, acquisition voxel size = 2.0×2.0×2.0mm; the whole scanning process lasts 10 minutes. The subjects are given gaze points during the scanning, and all the subjects are required to keep their
eyes open during the scanning process. Diffusion tensor imaging: scanning parameters are as follows: TR = 1400ms, TE = 60ms, 112×112 matrix, FOV = 224mm, voxel size: 2.0×2.0×2.0mm, B1 = 1000, 64 slices, 137 non-collinear; the whole scanning process lasts 7 minutes.

We apply fMRI because it may provide critical information for response prediction and acts as an outcome measure of functional response to tDCS. Several studies have revealed the reductions of prefrontal gray matter volumes of the bilateral anterior cingulate cortices (ACC) and DLPFC in MDD. Gray matter volumes of the ACC and PFC at baseline predicted treatment response. And the volumes of these regions increased after successful antidepressant treatment. Therefore, we will analyze voxel-based gray matter volumes of PFC and ACC region at baseline and endpoint using parcellation approaches.

Statistical Analysis

The statistician will analyze the information collected in an intention-to-treat (ITT) dataset and impute missing follow-up observation caused by poor compliance using the last observation carried forward (LOCF) design because missing data are presented to be minimal and thus can be considered at random in similar study. We will also compare the baseline characteristics of participants with missing follow-up data and those without missing data using ANOVA, χ² or Kruskal–Wallis test for continuous variables and categorical variables, respectively. Although our main endpoint is response rates, the remission rates will be presented too.

Multiple comparison issues of post hoc analysis will be carried out using Bonferroni adjustment. Specifically, although in our speculation, these variables would not be normally distributed, we will apply parametric tests because the Central Limit Theorem states that this approach in more than 30 observations is permitted. The Fisher’s exact test will be used to compare the frequency of adverse events in each group. A mixed ANOVA will be performed with one dependent within-subject variable (eg, score change of MADRS and HRDS), one independent within-subject variable (visit time – four levels), and one independent between-subject variable (group – four levels). General linear models will also be constructed to identify whether the demographics, descriptive and cognitive test variables predict individual response to tDCS. A two-sided 5% significance level will be considered statistically significant.

Discussion

To the best of our knowledge, the current study is the first parallel double-blind placebo-controlled trial exploring tACS, tDCS, and escitalopram in the treatment of MDD. Confounding factors such as concurrent medication, psychotherapy, and other treatment approaches are strictly controlled to probe the pure effect of tDCS and tACS. Considering that our sample size is not large enough to enroll an excessively heterogeneous sample, we also exclude participants with treatment-resistant depression (TRD), as TRD has been established as a negative predictor of treatment response. In general, we expect patients with ongoing, moderate to severe depressive episodes with a history of treatment of only 1–2 medications or no previous medication. This study is currently being conducted. Ideally, we will complete and conclude the study within the original sample size plan and within the timeframe of the grant.

There were only two previous studies that compared tDCS with antidepressant drugs and were both conducted in the cultural context of Latin America. Previous research has found that active tDCS (2mA, 30min, 12 sessions) and 50mg/d sertraline had similar efficacy over 6 weeks, while one other study presented that tDCS (30-minute, 2mA, 15 sessions) did not show non-inferiority to escitalopram over a 10-week period. It should be noted that depression symptoms vary from cultures and requires various treatment approaches, for example, somatization is more severe and common in China. It is necessary to provide more evidence of tDCS and tACS treating MDD in the cultural context of China.

The limitations of this trial are the relatively short duration of the trial (6 weeks) and the low dose of escitalopram (10mg/d) or active tDCS (2mA, 30 minutes, 10 sessions), as symptoms may improve over 2 to 3 months. And we failed to combined active tDCS/tACS with medications, which is a promising field since the former study has found the sertraline combined with tDCS shows significantly better efficacy than tDCS only or sertraline only. These limitations are the result of financial and feasibility constraints. Also, our trial lacked a blank control or waiting group. As tDCS/tACS is a new type of treatment, the research staff will take a relatively long time to explain the procedure to the patient and obtain informed consent. During the first two weeks of intervention, patients return to the hospital daily. The raters will follow a patient for 6 weeks and there will be frequent contact (eg to make appointments to return to the
hospital or to answer questions from the patient). Active participation in the experiment itself can have a therapeutic effect because patients may develop a good doctor–patient relationship with friendly researchers, have time to talk and feel supported by the researcher during the engagement process.64 These may result in confounding factors for evaluating the effectiveness of the treatment. Another limitation of the trial is that we are unable to confirm the physiological effects of sham-stimulation using EEG due to various limitations, since the sham stimulation itself may have enhanced effects due to the cumulative effect of repeated delivery.65

In summary, we expect the results of our trial to provide more evidence that may potentially advance our advances in physical stimulation intervention and benefit clinical practice in the treatment of MDD. These would include: 1) whether the non-invasive physical therapy interventions (tDCS) and (tACS) could be a safe and useful intervention for MDD; 2) Any difference of efficacy between tDCS and tACS in treating MDD; 3) comparing to medications, whether the tDCS and tACS may have comparable efficacy in symptom improvement; and 4) whether the treatment of tDCS or tACS would also improve the cognitive function in MDD.

Funding
The study was funded by the Municipal Hospital Clinical Research Cultivating Project of Shanghai Shenkang Hospital Development Center (SHDC12018X24).

Disclosure
The authors report no conflicts of interest in this work.

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