Research Protocol

（Version：1.0　Date：　2025-06-06　）

Project Title：A comparative study of the clinical efficacy of transcranial direct current stimulation targeting the DLPFC versus DMPFC in the treatment of depression

Research Institution：The Second Affiliated Hospital of Anhui Medical University

Department in Charge：Department of Psychology and Sleep Medicine

Principal Investigator：Yanghua Tian

Participating Institutions：The Second Affiliated Hospital of Anhui Medical University

Researcher Declaration

As the principal investigator of this research project, I will adhere to the ethical principles outlined in the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (2023), the WMA Declaration of Helsinki (2013), the CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002), and the ethical principles of GCP. Under the guidance of Good Clinical Practice (GCP) for drug clinical trials, I will conduct the research in accordance with the protocol approved by the ethics committee and its requirements to ensure scientific rigor and protect the health and rights of participants.

Protocol Summary

Project Title	A comparative study of the clinical efficacy of transcranial direct current stimulation targeting the DLPFC versus DMPFC in the treatment of depression
Version Number/Version Date	Version：1.0 Date： 2025-06-06
Participating Institutions	The Second Affiliated Hospital of Anhui Medical University
Principal Investigator	Yanghua Tian
Research Objectives	This study aims to investigate the differential effects of different transcranial direct current stimulation (tDCS) targets on emotional regulation in patients with depression
Sample Size	This study is a randomized controlled trial. Based on relevant research literature, it is planned to enroll 50 participants.
Research Subjects	Patients with depression
Inclusion Criteria	(1) Meets the diagnostic criteria for depression outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5); (2) Patient age is between 18 and 65 years; (3) Education level exceeding 5 years, with no significant hearing or visual impairments; (4) Voluntary signing of informed consent and ability to cooperate with general demographic data collection and neuropsychological scale testing.
Exclusion Criteria	(1) Age under 18 or over 65; (2) Patients with neurological disorders such as epilepsy or severe physical illnesses; (3) Patients with comorbid neuropsychiatric disorders, such as schizophrenia or obsessive-compulsive disorder; (4) Patients unable to undergo tDCS treatment for any reason, including presence of ferromagnetic metal in

	the head or implanted medical devices in the head/neck region; (5) Pregnant or lactating women.
Trial Termination Criteria	All subjects enrolled in the study completed all study protocol-required visits.
Disqualification/Withdrawal Criteria	(1) The subject experiences a serious adverse reaction, and the principal investigator and ethics review committee determine continued participation is inappropriate; (2) The subject exhibits mania, delirium, or severe suicidal behavior during the study period; (3) A major protocol violation occurs; (4) The subject requests termination of participation.
Criteria for Early Termination	(1) Occurrence of a serious adverse event deemed inappropriate for continuation of the study by the principal investigator and the ethics review committee; (2) Other circumstances deemed necessary for study termination by the investigator.
Primary Efficacy Measures	17-item Hamilton Depression Rating Scale (HAMD), Positive and Negative Affect Scale (PANAS)
Secondary Efficacy Measures	the association memory test, Self-Rating Depression Scale (SDS), Hamilton Anxiety Rating Scale (HAMA), 15-item Somatic Symptom Severity Scale of the Patient Health Questionnaire (PHQ-15), Insomnia Severity Index (ISI), and Ruminative Responses Scale (RRS)
Safety Indicators	Adverse Events
Statistical Analysis Methods	Statistical analysis was performed using SPSS 25.0 (IBM SPSS Inc., Illinois, USA) and GraphPad Prism 8.0.2 (GraphPad Software, Inc., USA). For baseline demographic and clinical characteristics, continuous variables were expressed as mean ± standard deviation. Intergroup comparisons were conducted using independent samples

	t-tests or Mann-Whitney U tests based on data normality. Categorical variables were expressed as frequencies, with group differences assessed using chi-square tests. Repeated measures analysis of variance (ANOVA) was then employed to examine changes in clinical scales over time and between groups, with time (baseline, post-treatment) as the within-subject factor and group (DLPFC group, DMPFC group) as the between-subject factor. Simple effects analysis was conducted for variables showing significant time × group interactions. Finally, based on data normality, Pearson or Spearman correlation analyses explored associations between PANAS improvement and HAMD improvement, as well as correlations between clinical symptoms and neurophysiological changes. Effect sizes were reported alongside p-values. A p-value < 0.05 was considered statistically significant.
Forms of Research Publication	Academic Journal Articles

1. Background:

Depression is a common mental disorder characterized by persistent low mood and anhedonia[1, 2]. Pharmacological and psychotherapeutic treatments demonstrate only moderate efficacy[3]. Non-invasive brain stimulation techniques offer novel therapeutic approaches. Among these, transcranial direct current stimulation (tDCS) holds advantages due to its simplicity, low cost, and minimal side effects, exhibiting good efficacy and tolerability in depression treatment[4-6]. The dorsolateral prefrontal cortex (DLPFC), a core region of the cognitive control network, serves as a traditional target for non-invasive brain stimulation in depression and plays a crucial role in positive affect (PA) processing[7, 8]. Conversely, the dorsomedial prefrontal cortex (DMPFC), a central region of the default mode network, participates in negative self-referential processing and negative affect (NA) regulation, demonstrating potential as a novel therapeutic target[9-11].

2. Objective:

Given the distinct roles of DLPFC and DMPFC in separate affective regulation networks, this study aims to investigate the differential effects of different tDCS targets on emotional regulation in patients with depression.

3. Research Methods:

3.1 Study Population

Individuals diagnosed with depression

3.2 Inclusion Criteria

(1) Meets the diagnostic criteria for depression outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5); (2) Patient age is between 18 and 65 years; (3) Education level exceeding 5 years, with no significant hearing or visual impairments; (4) Voluntary signing of informed consent and ability to cooperate with general demographic data collection and neuropsychological scale testing.

3.3 Exclusion Criteria

(1) Age under 18 or over 65; (2) Patients with neurological disorders such as epilepsy or severe physical illnesses; (3) Patients with comorbid neuropsychiatric disorders, such as schizophrenia or obsessive-compulsive disorder; (4) Patients unable to undergo tDCS treatment for any reason, including presence of ferromagnetic metal in the head or implanted medical devices in the head/neck region; (5) Pregnant or lactating women.

3.4 Specific Research Content

(1) Screening Period: Depression patients were screened based on inclusion and exclusion criteria.

(2) Treatment Period: This study employed a randomized, single-blind controlled clinical trial. Depression patients were recruited from the inpatient department of the Department of Psychiatry and Sleep Medicine and randomly assigned to two groups: the tDCS stimulation of the DLPFC group and the tDCS stimulation of the DMPFC group. Both groups will receive tDCS treatment twice daily for 5 consecutive days. Each session lasts 20 minutes at 2mA, with a minimum 4-hour interval between sessions. Prior to initiating tDCS treatment and following completion of all treatment sessions, patients

underwent standardized assessments administered by clinical psychologists. These included tests of associative memory, the Self-Rating Depression Scale (SDS), the 17-item Hamilton Depression Rating Scale (HAMD), Hamilton Anxiety Rating Scale (HAMA), 15-item Somatic Symptom Severity Scale of the Patient Health Questionnaire (PHQ-15), PHQ-15), the Insomnia Severity Index (ISI), the Positive and Negative Affect Scale (PANAS), and the Ruminative Responses Scale (RRS). Follow-up was conducted after one month, during which only the HAMD scale was assessed. Primary clinical outcomes included changes in HAMD scores at baseline, post-treatment, and 1-month follow-up; number of responders and remitters post-treatment (response defined as >50% reduction in HAMD score at endpoint; remission defined as HAMD score ≤7 at endpoint); improvement in PANAS scores post-treatment; correlation between HAMD improvement and PANAS improvement. Secondary outcomes included post-treatment changes in associative memory scores, SDS scores, HAMA scores, PHQ-15 scores, ISI scores, and RRS scores.

(3) Follow-up Period: Patients underwent follow-up one month after treatment completion. HAMD scale data were collected to evaluate symptom improvement.

3.5 Statistical Analysis Methods

Statistical analysis was performed using SPSS 25.0 (IBM SPSS Inc., Illinois, USA) and GraphPad Prism 8.0.2 (GraphPad Software, Inc., USA). For baseline demographic and clinical characteristics, continuous variables were expressed as mean ± standard deviation. Intergroup comparisons were conducted using independent samples t-tests or Mann-Whitney U tests based on data normality. Categorical variables were expressed as frequencies, with group differences assessed using chi-square tests. Repeated measures analysis of variance (ANOVA) was then employed to examine changes in clinical scales over time and between groups, with time (baseline, post-treatment) as the within-subject factor and group (DLPFC group, DMPFC group) as the between-subject factor. Simple effects analysis was conducted for variables showing significant time × group interactions. Finally, based on data normality, Pearson or Spearman correlation analyses explored associations between PANAS improvement and HAMD improvement, as well as correlations between clinical symptoms and neurophysiological changes. Effect sizes were reported alongside p-values. A p-value < 0.05 was considered statistically

significant.

3.6 Criteria for Subject Withdrawal/Termination from the Study

A subject must withdraw/terminate from the study if one or more of the following conditions occur: Severe adverse events occur, and the study principal investigator and ethics review committee determine continued participation is inappropriate; Other circumstances deemed necessary by the investigator to terminate the study.

References

1. Marx, W., et al., *Major depressive disorder.* Nat Rev Dis Primers, 2023. 9(1): p. 44.
2. Rice, F., et al., *Adolescent and adult differences in major depression symptom profiles.* J Affect Disord, 2019. 243: p. 175-181.
3. Mutz, J., et al., *Comparative efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults: systematic review and network meta-analysis.* Bmj, 2019. 364: p. l1079.
4. Sauvaget, A., et al., *Hospital production cost of transcranial direct current stimulation (tDCS) in the treatment of depression.* Neurophysiol Clin, 2019. 49(1): p. 11-18.
5. Nikolin, S., et al., *Safety of repeated sessions of transcranial direct current stimulation: A systematic review.* Brain Stimul, 2018. 11(2): p. 278-288.
6. Jog, M.A., et al., *Personalized High-Definition Transcranial Direct Current Stimulation for the Treatment of Depression: A Randomized Clinical Trial.* JAMA Netw Open, 2025. 8(9): p. e2531189.
7. Hauser, T.U., E. Eldar, and R.J. Dolan, *Separate mesocortical and mesolimbic pathways encode effort and reward learning signals.* Proc Natl Acad Sci U S A, 2017. 114(35): p. E7395-e7404.
8. Erhardt, A., et al., *Repetitive transcranial magnetic stimulation increases the release of dopamine in the nucleus accumbens shell of morphine-sensitized rats during abstinence.*

Neuropsychopharmacology, 2004. 29(11): p. 2074-80.

9. Eickhoff, S.B., et al., *Functional Segregation of the Human Dorsomedial Prefrontal Cortex.* Cereb Cortex, 2016. 26(1): p. 304-21.

10. Hamilton, J.P. and I.H. Gotlib, *Neural substrates of increased memory sensitivity for negative stimuli in major depression.* Biol Psychiatry, 2008. 63(12): p. 1155-62.

11. Disner, S.G., et al., *Neural mechanisms of the cognitive model of depression.* Nat Rev Neurosci, 2011. 12(8): p. 467-77.

Informed Consent Form for Participants

Project Title: A comparative study of the clinical efficacy of transcranial direct current stimulation targeting the DLPFC versus DMPFC in the treatment of depression

Informed Consent Form Version Number and Date: 1.0 2025-06-06

Dear Participant:

We invite you to participate in a comparative study of the clinical efficacy of transcranial direct current stimulation targeting the DLPFC versus DMPFC in the treatment of depression, approved by the Second Affiliated Hospital of Anhui Medical University. This study is led by Chief Physician Tian Yanghua of the Department of Neurology and is expected to enroll 50 voluntary participants. The study has been reviewed and approved by the Ethics Committee of the Second Affiliated Hospital of Anhui Medical University (Ethics Approval Number: YX2025-222).

This information sheet provides details to assist you in deciding whether to participate in this clinical study. Participation is entirely voluntary and will not affect your regular medical care or treatment at our hospital. Please rest assured! Should you choose to participate, our research team will make every effort to ensure your safety and protect your rights throughout the study.

Please read this information sheet carefully. If you have any questions, please ask the researcher responsible for explaining the informed consent form.

1. Background:

Depression is a common mental disorder characterized by persistent low mood and anhedonia. Pharmacological and psychotherapeutic treatments demonstrate only moderate efficacy. Non-invasive brain stimulation techniques offer novel therapeutic approaches. Among these, transcranial direct current stimulation (tDCS) holds advantages due to its simplicity, low cost, and minimal side effects, exhibiting

good efficacy and tolerability in depression treatment. The dorsolateral prefrontal cortex (DLPFC), a core region of the cognitive control network, serves as a traditional target for non-invasive brain stimulation in depression and plays a crucial role in positive affect (PA) processing. Conversely, the dorsomedial prefrontal cortex (DMPFC), a central region of the default mode network, participates in negative self-referential processing and negative affect (NA) regulation, demonstrating potential as a novel therapeutic target.

2. Objective:

Given the distinct roles of DLPFC and DMPFC in separate affective regulation networks, this study aims to investigate the differential effects of different tDCS targets on emotional regulation in patients with depression.

3. Research subjects

Inclusion Criteria: (1) Meets the diagnostic criteria for depression outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5); (2) Patient age is between 18 and 65 years; (3) Education level exceeding 5 years, with no significant hearing or visual impairments; (4) Voluntary signing of informed consent and ability to cooperate with general demographic data collection and neuropsychological scale testing.

Exclusion Criteria: (1) Age under 18 or over 65; (2) Patients with neurological disorders such as epilepsy or severe physical illnesses; (3) Patients with comorbid neuropsychiatric disorders, such as schizophrenia or obsessive-compulsive disorder; (4) Patients unable to undergo tDCS treatment for any reason, including presence of ferromagnetic metal in the head or implanted medical devices in the head/neck region; (5) Pregnant or lactating women.

If a subject withdraws due to non-compliance with criteria, the investigator should maintain open communication with the subject, explaining the withdrawal procedures and consequences, and ensuring

they understand their rights and options. Provide necessary psychological support and counseling to the subject, particularly when withdrawal is related to adverse reactions or psychological distress.

4. Research Process

This study is a randomized, single-blind controlled clinical trial. We plan to enroll 50 participants in this study.

(1) Screening Period: Depression patients were screened based on inclusion and exclusion criteria.

(2) Treatment Period: This study employed a randomized, single-blind controlled clinical trial. Depression patients were recruited from the inpatient department of the Department of Psychiatry and Sleep Medicine and randomly assigned to two groups: the tDCS stimulation of the DLPFC group and the tDCS stimulation of the DMPFC group. Both groups will receive tDCS treatment twice daily for 5 consecutive days. Each session lasts 20 minutes at 2mA, with a minimum 4-hour interval between sessions. Prior to initiating tDCS treatment and following completion of all treatment sessions, patients underwent standardized assessments administered by clinical psychologists. These included tests of associative memory, the Self-Rating Depression Scale (SDS), the 17-item Hamilton Depression Rating Scale (HAMD), Hamilton Anxiety Rating Scale (HAMA), 15-item Somatic Symptom Severity Scale of the Patient Health Questionnaire (PHQ-15), PHQ-15), the Insomnia Severity Index (ISI), the Positive and Negative Affect Scale (PANAS), and the Ruminative Responses Scale (RRS). Follow-up was conducted after one month, during which only the HAMD scale was assessed. Primary clinical outcomes included changes in HAMD scores at baseline, post-treatment, and 1-month follow-up; number of responders and remitters post-treatment (response defined as >50% reduction in HAMD score at endpoint; remission defined as HAMD score ≤7 at endpoint); improvement in PANAS scores post-treatment; correlation between HAMD improvement and PANAS improvement. Secondary outcomes included post-treatment changes in associative memory scores, SDS scores, HAMA scores, PHQ-15 scores, ISI scores, and RRS scores.

(3) Follow-up Period: Patients underwent follow-up one month after treatment completion. HAMD scale data were collected to evaluate symptom improvement.

5. Alternative Treatment

If you choose not to receive any treatment during the trial, you may continue with routine psychological and sleep medicine care.

6. Potential Risks and Discomfort

Skin sensations under electrodes may include prickling, mild fatigue, burning, or itching. Should skin damage occur, it will be treated with medications such as burn ointments. Maintain local cleanliness and disinfection to prevent infection. Contact relevant medical staff for evaluation and management if necessary.

7. Expected Benefits

Depression patients may experience clinical symptom improvement, though no significant effect may occur. This study also aims to provide additional clinical evidence for future treatment strategies for depression.

8. Free Treatment

Patients are responsible for standard hospitalization costs incurred during routine inpatient care. All expenses related to tDCS treatment during the study will be covered at no cost.

9. Compensation

Participants undergoing follow-up examinations at Anhui Medical University Second Affiliated Hospital two months post-treatment will receive a transportation subsidy of 200 RMB.

10. Indemnification

Should any research-related harm or injury occur during your participation, we will immediately provide necessary medical treatment. We will conduct a fair and reasonable assessment of any harm or injury you sustain in strict accordance with current laws and regulations, and determine the corresponding compensation amount. The compensation amount will be borne by the research institution, ensuring the entire compensation process is transparent and fair. We commit that compensation decisions will fully consider your rights and interests, following legally prescribed procedures and standards.

11. Pre-, During-, and Post-Study Considerations

First, fully understand the study's purpose, process, and potential risks to ensure clear awareness of participation. Second, assess your own condition to ensure suitability for participation. During the study, follow the researchers' guidance for proper use of equipment, pay attention to any discomfort, and report it promptly. Avoid activities or substances that may affect the results, maintain communication with the researchers, understand the compensation policy, and ensure your personal privacy is protected. Finally, avoid participating in other interventional studies that may affect the research results during the study period. Pay attention to medication management and ensure timely communication with the researchers when taking medications that may affect your mental state or emotions.

12. Confidentiality

Information obtained about you during the study will be kept strictly confidential and used solely for this research. Personal details such as participant phone numbers, addresses, and ID numbers will be recorded in a participant identification code table. Study-related metrics will be entered into the CRF form and used exclusively for scientific publication purposes, without disclosing any participant personal information during publication.

No public report on this study's findings will disclose your personally identifiable information. We

will make every effort within legal boundaries to protect the privacy of your personal medical data. When necessary, researchers, regulatory authorities, ethics committees, and supervisory bodies may access your medical records and related information only after signing confidentiality agreements. By signing this informed consent form, you agree to the use of your personal and medical information for the purposes described above.

13. Re-obtaining Informed Consent

You will be contacted to re-sign the informed consent form under the following circumstances: 1. Changes to the research protocol, scope, or content; 2. Research utilizing previously identified samples used for diagnosis or treatment; 3. Re-use of identified human biological samples or related clinical history data from the biobank database for research; 4. Other changes occurring during the research process.

14. Voluntary Participation

You may choose not to participate in this study or notify the investigator at any time to withdraw. Your data will not be included in the study results, and your medical care and rights will not be affected. The study physician may terminate your participation if you require alternative treatment, fail to comply with the study protocol, experience study-related harm, or for any other reason. You may access information materials and progress updates related to this study at any time. Should new safety information related to this study arise, we will promptly notify you.

15. Subject Rights and Responsibilities

As a subject in this study, you have the following responsibilities: (1) Provide truthful information regarding your medical history and current physical condition; (2) Inform the study physician of any discomfort experienced during the study period; (3) Inform the study physician if you have recently participated in other studies or are currently participating in other studies.

16. Contact Information

If you have questions about this study, experience any discomfort or injury during participation, or have concerns regarding participant rights, please contact Duan Nanxue at +86-18326962052.

Should you have any concerns or complaints regarding the research personnel during the study, you may contact the Ethics Committee of the Second Affiliated Hospital of Anhui Medical University at 0551-63806061 or 0551-63806098.

Subject Signature Page

Subject Consent Statement:

I have read the above introduction to this study, and the study physician has thoroughly explained the research content to me. Prior to signing this informed consent form, I have no further questions regarding the study that require consultation. On this basis, I voluntarily participate in the clinical research described herein, and my decision is based on a full understanding of the potential risks and benefits of participating in this study. Furthermore, the investigator has not used deception, inducement, coercion, or any other means to compel my consent to participate in the study. I understand that I may withdraw from the study at any time without condition.

This informed consent is signed on behalf of the subject due to the subject's lack of legal capacity or limited legal capacity.

Subject Signature: _____ Date: _____

Subject Contact Information:_____

Guardian Signature: _____ Impartial Witness Signature:_____

Date:_____ Date:_____

Guardian Contact Information: _____ Impartial Witness Contact Information:_____

Investigator's Declaration:

I confirm that I have explained the details of this study to the patient, particularly the potential risks and benefits of participating.

Investigator Signature: _____

Date: _____

Investigator Contact Information:_____

Note: This page is the subject's signature page. The study physician shall provide the subject with a detailed explanation of the study content and related information. Informed consent shall be signed by the subject themselves/guardian/legal representative and the study physician who provided the explanation. If the subject has questions about the study content, the investigator shall immediately provide a detailed explanation in person. After signing, both the investigator and the subject shall retain one original copy each.