INFORMED CONSENT FORM

Official Title: Efficacy and Mechanisms of Time-Domain Interferential Transcranial Electrical Stimulation in Treating Depression Associated With Childhood Trauma

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Informed Consent Form Version: 02

Study Protocol Version: 02 (December 1, 2025)

Study Site: Shanghai Mental Health Center

Document Type / Subtitle: Informed Consent Form

Public posting copy: participant names and signatures are not included. The signature fields below are blank template fields.

1. Introduction

You are invited to participate in a clinical research study. This informed consent form provides information to help you decide whether to participate. Please read it carefully. If you have any questions, please ask the investigator responsible for the study.

Participation is voluntary. This study has been reviewed and approved by the Ethics Committee of the study institution.

2. Study Objectives

- To investigate the mediating role of childhood trauma in depressive disorders.
- To elucidate the neuroimaging and immunological mechanisms of childhood trauma-related depressive disorders.
- To investigate the mechanisms by which temporal interference transcranial electrical stimulation improves mood through modulation of thalamocortical circuits.

3. Significance of the Study

Depressive disorders are common psychiatric conditions associated with a high suicide rate and a substantial social burden. Childhood trauma may be a major contributing factor in the development of mental disorders in 28.9% of patients, and its effects on physical and mental health can persist throughout life. At least one form of childhood trauma is reported in 45.59% of individuals with depressive disorders. However, there are currently no effective medications with a high level of safety specifically for the treatment of childhood trauma, and the overall quality of the existing evidence is low. Studies have shown that psychological interventions can reduce depressive symptoms among patients with depressive disorders and childhood trauma histories, but the evidence base remains insufficient. Therefore, nonpharmacological interventions that are effective, free of adverse effects, acceptable, and accessible are important for treating depressive disorders associated with childhood trauma.

By integrating central neuroimaging (functional magnetic resonance imaging, fMRI) and peripheral immune biomarkers, this study seeks to systematically investigate, for the first time, the mechanisms by which temporal interference transcranial electrical stimulation (TI) treats childhood trauma-related depressive disorders by modulating thalamocortical circuits. This work may provide direct evidence regarding the brain–body pathophysiological mechanisms linking childhood trauma to depression and offer new insights into the biological effects of TI, an emerging neuromodulation technique, thereby advancing the theory of noninvasive brain stimulation.

The study aims to provide a safe, effective, and precise new nonpharmacological intervention for this high-risk, treatment-resistant subtype of depressive disorder associated with childhood trauma. Its findings may be translated into clinical practice to improve outcomes through individualized targeted stimulation and offer a new approach to addressing limitations of existing treatments, including adverse effects and limited efficacy, with substantial potential clinical and social value.

The project plans to recruit 200 participants in the intervention group at Shanghai Mental Health Center. The project duration is one year and it is funded by the Shanghai Key Discipline Program of Traditional Chinese Medicine. This study has received approval from the Ethics Committee of Shanghai Mental Health Center.

4. Study Procedures

4.1 Screening

If you agree to participate, we will discuss the study in detail with you or your family and explain relevant information. You will be asked to provide information relating to your illness, including personal information,

the course of your illness, medication use, family history, previous medical visits, and findings from previous examinations. Each participant will be assigned an identification number and a study record will be created.

Before formal participation, you will complete a general information questionnaire covering name, age, sex, years of education, marital status, ethnicity, number of illness episodes, and medication use, as well as the Childhood Trauma Questionnaire–Short Form (CTQ-SF), 17-item Hamilton Depression Rating Scale (HAMD-17), 14-item Hamilton Anxiety Rating Scale (HAMA-14), Connor–Davidson Resilience Scale (CD-RISC), and other questionnaires. Only individuals meeting the eligibility requirements based on examinations and assessments may enter the formal study. Even if you agree to participate, you may not be eligible; the research staff will explain the reason.

We will invite 74 patients with depressive disorders to participate in this study.

Inclusion Criteria

- A psychiatrist diagnoses a depressive episode according to ICD-11 criteria.
- The participant meets ICD-11 diagnostic criteria for a depressive episode, has an HAMD-17 score ≥17 and <25, and has a history of childhood trauma, with at least one CTQ-SF subscale meeting the following threshold: emotional abuse >13; physical abuse >10; sexual abuse >8; emotional neglect ≥15; or physical neglect ≥10.
- Male or female outpatient aged 18–65 years, inclusive.
- At least a junior high school education and the ability to complete self-report scales.
- No psychiatric medication treatment within one month before enrollment (including antipsychotics, antidepressants, mood stabilizers, antiepileptic drugs, central nervous system stimulants, etc.).
- Voluntary participation and provision of signed informed consent.

Exclusion Criteria

- Severe cardiac, hepatic, or renal disease; organic brain disease; severe cardiovascular disease; a history of tumors, hematologic disease, rheumatic disease, malnutrition, or neurodegenerative disease; or a depressive episode secondary to another psychiatric or physical disease.
- History of tobacco, alcohol, or other psychoactive substance abuse.
- Pregnancy.
- Previous participation in another drug clinical trial before enrollment.

4.2 Study Groups

Study group: escitalopram oxalate plus temporal interference transcranial electrical stimulation, 37 participants.

Control group: escitalopram oxalate plus sham stimulation, 37 participants.

4.3 Intervention Plan

Experimental group: This study uses temporal interference transcranial electrical stimulation (TI) to treat patients. The stimulation plan will be individually tailored based on each patient’s magnetic resonance imaging (MRI) data to precisely target the intended brain region. Before the intervention, a physician will comprehensively explain its purpose, procedures, and precautions. During treatment, the patient will sit or lie in a comfortable position and remain relaxed. A trained physician will administer treatment using the TI device.

Participants will receive three stimulation sessions each day, with each session lasting 30 minutes and a 30-minute rest between sessions, for 14 consecutive days. Throughout stimulation, participants must remain awake and relaxed and minimize body and head movement to maintain stimulation stability.

During TI treatment, all patients will also receive standard antidepressant therapy (escitalopram oxalate, 10 mg/day, taken in the morning). Throughout the study, concomitant antipsychotics, other antidepressants, and mood stabilizers are prohibited unless permitted by the protocol.

Participants will undergo questionnaires, rating scales, and laboratory assessments, including the Childhood Trauma Questionnaire, HAMD-17, HAMA, Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Treatment Emergent Symptom Scale (TESS), MRI, and immunological indicators (IL-2, IL-6, IL-10, IL-17A, IL-22, and TNF-α).

5. Risks and Discomforts

As a healthy control participant in this study, you should be informed in advance of the possible risks and discomforts of participation. You will need to complete a one-time baseline questionnaire assessment and a multimodal MRI scan. The entire procedure will take approximately 1.5–2 hours and may interfere to some extent with your personal schedule. Some rating scales (such as the Childhood Trauma Questionnaire and depression and anxiety scales) ask about personal upbringing and emotional status and may evoke brief emotional reactions or psychological discomfort.

Risks Associated with the Temporal Interference Device

The overall risk of using the temporal interference stimulation device in this study is assessed as low to moderate. Physical risks (such as skin irritation) are generally mild, transient, and manageable. Neuropsychiatric risks, particularly for individuals with childhood trauma-related depressive disorders, require careful attention and mainly include transient mood fluctuations and potential reactivation of traumatic memories.

Risk management measures: A comprehensive risk management system has been developed, including strict screening, detailed informed consent, close monitoring by a multidisciplinary team (psychiatrists and clinical psychologists), and a defined adverse-event emergency response plan, to safeguard participants' well-being and safety.

Risks and Discomforts Associated with MRI

During the scan, you must lie still in the scanner for approximately 45 minutes, which may cause stiffness or fatigue. The scanner produces continuous noise (professional hearing protection will be provided), which may cause irritability or anxiety in sensitive individuals. The scanning environment is relatively narrow and enclosed, and a small number of individuals may experience transient claustrophobic discomfort.

Risk management measures: We will strictly follow MRI safety screening procedures before scanning to exclude absolute contraindications, such as magnetic metallic implants or cardiac pacemakers. If you experience anxiety, fear, or other discomfort during scanning, we will stop the examination immediately and provide reassurance; severe cases may receive oral medication for symptomatic management under professional supervision.

Confidentiality Risks

All personal information and research data collected in this study will be coded and de-identified and stored in an encrypted, access-controlled system. Although strict confidentiality procedures have been established, there remains a theoretically very small possibility of inadvertent disclosure.

6. Benefits

The assessments may help with diagnosis and provide recommendations for your treatment, or yield useful information for research on the disease. Escitalopram oxalate used in this trial will not be provided free of charge; however, there will be no treatment fee for temporal interference transcranial electrical stimulation provided as part of the study.

7. Alternative Treatments

You may choose other antidepressants or traditional Chinese medicine decoctions for symptomatic treatment. Antidepressants can improve depressive symptoms relatively quickly but may cause adverse drug reactions, such as gastrointestinal reactions. Traditional Chinese medicine decoctions may have fewer adverse drug reactions but may require a longer course of treatment, have a slower onset of effect, and carry a risk of inadequate symptom control.

8. Restricted Medications

If you choose to follow the study treatment plan, your antidepressant medication will be restricted during the intervention period, and only escitalopram oxalate may be used. Escitalopram oxalate is widely used in clinical practice and is recommended by guidelines as a first-line antidepressant.

9. Participant Responsibilities

As a study participant, you are responsible for providing truthful information about your medical history and current physical condition; informing the study physician of any discomfort experienced during the study; refraining from restricted medications, foods, etc.; and informing the study physician whether you have recently participated in or are currently participating in another study.

10. Privacy and Confidentiality

If you decide to participate, your participation and personal information collected during the trial will be kept confidential. The responsible study physician and other research staff will use your medical information for research. This may include your name, address, telephone number, medical history, and information obtained during study visits. Your behavioral and MRI data will be labeled with a numerical study identifier rather than your name. Identifying information will not be disclosed outside the research team without your permission. All study team members and the study sponsor are required to maintain the confidentiality of your identity. Your records will be kept in locked filing cabinets accessible only to research personnel. To ensure the study is conducted in accordance with applicable requirements, members of government regulatory authorities or the Ethics Committee may, when necessary and as permitted by regulations, review your personal information at the study institution. No personal information identifying you will be disclosed when study results are published.

11. Reimbursement / Compensation

You will receive RMB 30 as a subsidy for local transportation expenses.

If you are injured as a result of participating in this study, you may receive free medical treatment and/or appropriate compensation for injury related to this clinical research.

You may choose not to participate or may notify the investigator and withdraw at any time. Your data will not be included in the study results, and your medical care and rights at this center will not be affected.

The study physician may discontinue your participation if you need other treatment, do not follow the research plan, experience study-related injury, or for any other reason.

12. Expected Costs of Participation

There will be no additional charges for any rating scale assessments or MRI examinations conducted as part of this study.

13. Legal Rights

Nothing in the preceding sections limits your right to seek legal assistance. By signing this informed consent form, you do not waive any of your legal rights.

14. Contact Information

You may request information and updates about the study at any time. For questions about the rights of research participants, contact the Ethics Committee of Shanghai Mental Health Center at 021-34773308.

INFORMED CONSENT FORM — SIGNATURE PAGE

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Study Site: Shanghai Mental Health Center

Principal Investigator (Responsible Study Physician): Lanying Liu

- I have read this informed consent form.
- I have had an opportunity to ask questions, and all my questions have been answered.
- I voluntarily agree to participate in this study and consent to providing my information to investigators for analysis.
- If I meet the inclusion criteria and agree to participate, the physician will enroll me in the study.
- I have been informed of the duration of participation in the study.
- I have been informed of the procedures and examinations that will be performed during the study.
- I understand the possible risks and benefits of participating in the study.
- By signing this form, I do not waive any of my legal rights.
- Before joining this study, I sign this informed consent form voluntarily.
- I may choose not to participate or may withdraw after notifying the investigator at any time without discrimination or retaliation; my medical care and rights will not be affected.
- The study physician may discontinue my participation if I need other treatment, fail to follow the research plan, experience a study-related injury, or for any other reason.
- I will receive a signed copy of this informed consent form.

Participant Name (Print): _____

Participant Signature: _____

Date: Year _____ Month _____ Day _____

Legal Guardian Name (Print): _____

Legal Guardian Signature: _____

Date: Year _____ Month _____ Day _____

I have accurately explained this document to the participant. He/she has read this informed consent form and has had an opportunity to ask questions. I confirm that he/she has voluntarily consented.

Investigator Name (Print): _____

Investigator Signature: _____

Date: Year _____ Month _____ Day _____