Clinical Research Protocol

Project Title: Efficacy and Mechanisms of Time-Domain Interferential Transcranial Electrical Stimulation in Treating Depression Associated With Childhood Trauma
Sponsor: Shanghai Mental Health Center
Study Department: Department of Traditional Chinese Medicine
Funding Source: Shanghai Key Discipline Project of Traditional Chinese Medicine
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Statement of Compliance

This study will be conducted in strict accordance with the Good Clinical Practice (GCP) guidelines for drug clinical trials, the Administrative Measures for Investigator-Initiated Clinical Research Conducted by Medical and Health Institutions, and the Declaration of Helsinki. We undertake to conduct this study in accordance with this protocol. Investigators must be trained, and the study may only be initiated after written approval by the Ethics Committee and written informed consent from the subjects has been obtained. Any amendment to the protocol must be approved again.

Protocol Title:

Efficacy and Mechanisms of Time-Domain Interferential Transcranial Electrical Stimulation in Treating Depression Associated with Childhood Trauma

1. Research Background:

Depressive disorder is a common mental illness characterized by a high suicide rate and a heavy social burden. According to the WHO global health assessment report on depressive disorders, there were 350 million patients with depressive disorder worldwide in 2021, and it has become the second leading cause of death among people aged 15-29 years. Depressive disorder is characterized by persistent low mood and loss of interest or pleasure, often accompanied by cognitive, behavioral and physiological symptoms, and significantly affects the individual's daily life, social and occupational functioning; some patients may also develop self-harm or suicidal behavior [1,2]. It has a major impact on the global

burden of disease and imposes a heavy burden on patients, their families and society.

Existing studies indicate that childhood trauma is a major risk factor for depressive disorder. Epidemiological studies show that individuals who have experienced childhood trauma are at higher risk of depressive disorder, anxiety disorder, or both. Childhood trauma may be the main cause of mental disorders in 28.9% of patients, and its impact on physical and mental health extends throughout the life course. 45.59% of patients with depressive disorder have experienced at least one type of childhood trauma. Patients with a history of childhood trauma are 2.66-3.73 times more likely to develop depressive disorder in adulthood than those without such trauma.

Some studies suggest that environmental stress can induce depression-like behavior in adolescent female rats, accompanied by elevated corticosterone (CORT) and cholecystokinin (CCK) and decreased

neuropeptide Y (NPY) [3,4,5,6]. However, no effective and safe medication is yet available in clinical practice for childhood trauma, and the overall quality of existing evidence is low. Studies have shown that psychological intervention can reduce depressive levels in patients with depressive disorder who have experienced childhood trauma, but evidence-based medical evidence remains insufficient. Therefore, effective, side-effect-free, acceptable and easily

accessible non-pharmacological treatments are essential in the treatment of depressive disorder accompanied by childhood trauma. Studies have attempted to explain the intrinsic physiological pathogenesis of childhood trauma, involving neuroendocrinology, neuroinflammation and neuroimaging, but no clear and definitive explanation has yet been established.

Time-domain interferential electrical stimulation is an emerging non-invasive brain stimulation technique that uses two high-frequency carrier currents to generate interferential fields in vivo. Existing studies have found that it has certain clinical efficacy for depressive disorder and trauma. The following summarizes the research progress and prospects of time-domain interferential electrical stimulation in depressive disorder accompanied by childhood trauma.

2. Study Rationale

2.1 Preclinical Animal Studies and Literature Basis

2.1.1 Association between childhood trauma and depressive disorder: A large body of epidemiological and clinical studies has confirmed that childhood trauma is an important risk factor for depressive disorder. About 45.59% of patients with depressive disorder have experienced at least one type of childhood trauma, and their risk of the disorder is 2.66-3.73 times that of individuals without trauma. Childhood trauma is closely associated with abnormalities in brain structure (such as the hippocampus, amygdala and prefrontal cortex) and functional connectivity, and can cause hypothalamic-pituitary-adrenal (HPA) axis dysfunction and systemic inflammatory responses (such as elevated IL-6 and TNF-α).

2.1.2 Neuromodulatory potential of time-domain interferential transcranial electrical stimulation (TI): As a non-invasive deep brain stimulation technique, TI was first proposed by Grossman et al. in 2017 and was shown in mouse experiments to precisely modulate neural

activity in deep brain regions such as the hippocampus, inducing c-fos expression and behavioral changes. Subsequent studies in rhesus monkeys and human models have further verified the safety of TI and its ability to effectively modulate deep brain regions (such as the amygdala, nucleus accumbens and prefrontal cortex), showing particular potential in improving depressive and anxiety symptoms and cognitive function.

2.1.3 Mechanism of action of TI: TI generates a low-frequency envelope electric field in deep brain regions through two high-frequency currents, and mainly affects neuronal activity through subthreshold modulation rather than directly eliciting action potentials. Studies in non-human primates and humans have confirmed that it can modulate neural oscillations and improve emotional and cognitive function, with mild adverse reactions (such as fatigue and headache), indicating good safety and feasibility for blinding.

2.2 Basis for Subject Selection

The study population is patients with depressive disorder accompanied by childhood trauma: Given the high prevalence of childhood trauma in depressive disorder and its impact on treatment response, this study specifically focuses on this subgroup in order to investigate its distinctive neural circuit and immune mechanisms.

For patients with depressive disorder accompanied by childhood trauma, the traditional single-drug treatment model often faces multiple challenges. On the one hand, such patients often have complex trauma-related psychopathological mechanisms, resulting in a low response rate to conventional antidepressants and incomplete symptom improvement; on the other hand, traumatic experiences may affect their trust in treatment and sense of self-efficacy, resulting in generally poor medication adherence. Together, these factors often prolong the overall treatment process, increase the relapse rate and lead to unsatisfactory prognosis. In recent years, with a deeper understanding of the neural

circuit mechanisms of depression, non-invasive neuromodulation techniques have offered new approaches to overcoming this dilemma. As an emerging physical treatment modality capable of targeting deep brain regions with good tolerability, TI shows unique advantages. It may act directly at the level of neural circuits that are difficult to adequately address with pharmacotherapy by modulating the activity of core brain networks involved in emotional processing and traumatic memory. Therefore, an integrated intervention strategy combining pharmacotherapy with time-domain interferential transcranial electrical stimulation is of important clinical value. This combined regimen is expected to produce synergistic effects: medication provides foundational support at the level of neurochemical transmitters, while TI provides precise modulation at the level of neural circuit function. Theoretically, this may not only accelerate emotional improvement during the acute phase and reduce the risk of dropout due to slow onset of

action, but may also more effectively promote the recovery and stabilization of long-term neural function, thereby fundamentally improving long-term prognosis and offering a better path toward the dual goals of symptom remission and functional recovery.

2.3 Basis for Dose Selection / Intervention Regimen

Previous studies have investigated TI in major depressive disorder (MDD). In one such study, TI was applied to 15 patients with MDD. Each participant received five weeks of treatment, during which one 20-minute stimulation session was applied. The Hamilton Depression and Anxiety Rating Scales (HAMD/HAMA) decreased significantly after a single stimulation of the DLPFC/amygdala, and all 15 patients showed marked symptom remission after 5 weeks of treatment. No obvious adverse reactions were observed in any case.

2.3.1 TI intervention parameters: With reference to previous animal and clinical studies, TI uses an individualized electrode configuration, and the

electric field distribution is optimized based on each subject's structural MRI data. Three sequences per day, each sequence lasting 30 minutes, with a 30-minute interval, for 14 consecutive days. This regimen has shown good tolerability and neuromodulatory effects in previous studies, and the current intensity is kept within a safe range (<2 mA) to avoid tissue damage or obvious discomfort.

2.3.2 Concomitant medication: All patients receive escitalopram oxalate 10 mg/d uniformly as the background treatment, in order to control drug confounding effects and highlight the add-on efficacy and mechanistic effects of TI.

2.4 Basis for Endpoint Selection

2.4.1 Primary efficacy endpoint: the reduction rate of the HAMD-17 score at baseline and after 2 weeks of treatment. This scale is an internationally recognized tool for assessing depressive symptoms and has good reliability, validity and clinical relevance.

2.4.2 Secondary endpoints:

(1) Neuroimaging indicators: resting-state fMRI is used to assess changes in functional connectivity of the thalamo-cortical circuit, revealing the remodeling effect of TI on central circuits;

(2) Immune indicators: serum levels of inflammatory factors such as IL-2, IL-6, IL-10, IL-17A, IL-22 and TNF-α are measured to explore the "central-peripheral" immunomodulatory pathway;

(3) Cognitive and emotional scales: BAI, BDI and other scales are used to assist in assessing emotional and cognitive improvement.

2.5 Basis for Risk and Benefit Assessment

2.5.1 Risk control: TI is a non-invasive stimulation, and clinical studies have reported that its adverse reactions are mild and transient (such as fatigue and scalp tingling). This study will strictly follow safe operating procedures, monitor subjects' responses in real time, and establish

dropout and discontinuation criteria to ensure the rights and safety of subjects.

2.5.2 Benefit analysis:

(1) For subjects: free professional assessment and the opportunity to receive a novel non-pharmacological treatment are provided, which may bring about symptom relief and functional improvement;

(2) For science and society: the mechanisms of TI in childhood trauma-related depression will be elucidated, promoting the development of individualized neuromodulation therapy, which is of important clinical and scientific value.

3. 3. Study Objectives

This study plans to recruit patients with depressive disorder accompanied by childhood trauma, conduct a mechanistic exploratory study, and, through multimodal integrated analysis of central fMRI and peripheral body-fluid markers, systematically elucidate the mechanism

by which time-domain interferential transcranial electrical stimulation improves mood through modulation of the thalamo-cortical system.

4. 4. Study Overview

4.1 Study Design

4.1.1 Overall Design

4.1.1.1 Study Hypotheses

This study proposes the following core hypotheses:

Primary hypothesis: Time-domain interferential transcranial electrical stimulation (TI) combined with escitalopram oxalate, compared with pharmacotherapy alone, can more significantly improve depressive symptoms in patients with depressive disorder accompanied by childhood trauma (with a HAMD-17 score reduction rate ≥50% as the criterion for response).

Mechanistic hypothesis: TI exerts antidepressant effects by modulating the functional connectivity of the thalamo-cortical circuit and by affecting the levels of peripheral inflammatory factors (such as IL-6

and TNF-α), thereby forming a "central-peripheral" bidirectional regulatory pathway.

4.1.1.2 Type of Study Design

This study adopts a randomized, double-blind, sham-stimulation-controlled, parallel-group design.

4.1.1.3 Randomization Method

A block randomization method is used, with random sequences generated by computer to ensure balance of sample sizes between the two groups.

The random sequence is generated and kept by independent research staff who do not participate in subject recruitment and assessment.

After signing the informed consent form and completing the baseline assessment, subjects are assigned to the corresponding group by the investigators according to the randomization number.

4.1.1.4 Blinding Design

This study adopts a double-blind design.

4.1.1.5 Study Site Setting

This is a single-center study, and all subjects are recruited from outpatients and inpatients of Shanghai Mental Health Center.

4.1.2 Study Procedures and Methods

4.1.2.1 Study Duration

Total study duration: approximately 12 months (including subject recruitment, intervention, follow-up and data analysis).

Participation duration for each subject: 4 weeks in total.

4.1.2.2 Study Process and Stage Arrangements

(I) Stage 1: Screening and Baseline Period (Day -7 to Day 0)

(1) Study content and procedures:

(1) Recruitment and informed consent: 74 patients with depressive disorder accompanied by childhood trauma will be recruited from the outpatient and inpatient departments of Shanghai Mental Health Center.

Investigators will explain the study content, potential risks and benefits in detail, and subjects will sign a written informed consent form.

(2) Screening assessment:

1) Diagnosis will be confirmed by a psychiatrist according to ICD-11 criteria; 2) assessments will be performed using the Childhood Trauma Questionnaire (CTQ-SF), HAMD-17, HAMA-14, BAI, BDI, the Connor-Davidson Resilience Scale (CD-RISC) and other scales; 3) demographic data (age, sex, years of education, marital status, etc.) and clinical data (number of episodes, medication history, etc.) will be collected.

(3) Baseline examinations:

Imaging examination: multimodal MRI scanning (3D T1WI, DTI, rs-fMRI).

Blood sample collection: approximately 5-10 mL of peripheral venous blood will be collected for baseline measurement of inflammatory factors (IL-2, IL-6, IL-10, IL-17A, IL-22, TNF-α).

(2) Samples and data collected:

(1) Data: signed informed consent forms, demographic and clinical data questionnaires, and all baseline scale scores.

(2) Samples: baseline blood samples.

(3) Collection methods: face-to-face interviews, paper/electronic questionnaires, venous blood sampling and MRI scanning.

(II) Stage 2: Intervention Period (Day 1 to Day 14)

(1) Study content and procedures:

(1) Randomization: based on the screening results, 74 subjects with depressive disorder accompanied by childhood trauma will be selected and randomly assigned in a 1:1 ratio to the "TI active stimulation + medication group" or the "TI sham stimulation + medication group".

(2) Interventions:

1) All subjects: escitalopram oxalate 10 mg will be taken every morning.

2) TI stimulation: physicians will perform time-domain interferential transcranial electrical stimulation based on the subject's individualized head model. Three sequences per day, each sequence lasting 30 minutes, with a 30-minute interval between sequences, for 14 consecutive days. TI intervention parameters: with reference to previous animal and clinical studies, TI uses an individualized electrode configuration, and the electric field distribution is optimized based on each subject's structural MRI data. Three sequences per day, each sequence lasting 30 minutes, with a 30-minute interval, for 14 consecutive days. This regimen has shown good tolerability and neuromodulatory effects in previous studies, and the current intensity is kept within a safe range (<2 mA) to avoid tissue damage or obvious discomfort.

(3) Interim assessment (around Day 7): a brief HAMD-17 assessment may be performed to monitor symptom changes (optional according to protocol flexibility).

(2) Samples and data collected:

Data: medication adherence records, TI stimulation treatment records, adverse event record forms, and interim scale scores (if any).

(3) Follow-up method: outpatient. Subjects are required to visit the hospital daily to receive TI stimulation treatment and medication management.

(III) Stage 3: Endpoint Assessment of Intervention (Day 14 to Day 28)

(1) Study content and procedures:

(1) Efficacy and safety assessment: HAMD-17 and HAMA-14 scale assessments will be performed again.

(2) Re-examination of mechanistic indicators:

A second multimodal MRI scan will be performed.

A second peripheral venous blood sample will be collected to measure post-intervention levels of inflammatory factors.

(3) Safety assessment: all adverse events during the intervention period will be systematically recorded.

(2) Samples and data collected:

(1) Data: endpoint scale scores and adverse event record forms.

(2) Samples: post-intervention blood samples.

(3) Collection methods: face-to-face interviews, venous blood sampling and MRI scanning.

(4) Follow-up method: outpatient.

(IV) Stage 4: Follow-up Period (Day 42 ± 3 days, i.e., 4 weeks after the end of intervention)

(1) Study content and procedures:

(1) Efficacy and safety follow-up: follow-up will be conducted by outpatient visit or telephone.

(2) Any adverse events and concomitant medications since the last visit will be inquired about and recorded.

(3) Third blood sample collection: peripheral venous blood will be collected to detect long-term changes in inflammatory factors.

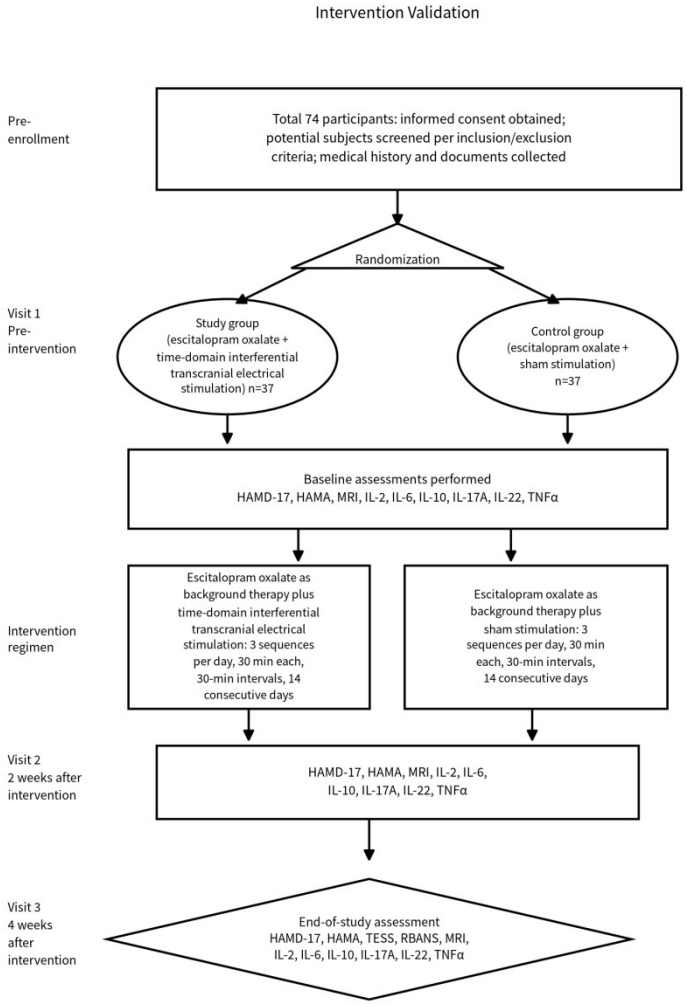
(2) Samples and data collected:

(1) Data: follow-up period scale scores, and records of adverse events and concomitant medications.

(2) Samples: follow-up period blood samples (if follow-up is conducted by telephone, the subject must be scheduled for a separate hospital visit for blood collection).

Follow-up method: outpatient visits are preferred; some assessments may be conducted by telephone as appropriate, but blood sampling must be completed at the outpatient clinic.

4.1.3 Study Flow Chart



4.1.4 Study Schedule

Study Stage	Screening Period	Baseline Period	End of Treatment	Follow-up Period
Time Point	Week 0	Week 0	Week 2	Week 4
Visit	√	√	√	√
Signing of informed consent	√			
Medical history collection	√			
Demographic data	√			
Inclusion/exclusion criteria assessment	√			
Randomization	√			
Clinical scale assessment				
• HAMD-17	√		√	√
• HAMA-14	√		√	√
• BAI	√			
• BDI	√			
• CD-RISC	√			
• CTQ-SF	√			
Imaging examination				
• Resting-state fMRI		√	√	
• Task-state fMRI (MIST)		√	√	
• 3D T1 structural imaging		√	√	
• DTI		√	√	
Laboratory tests				
• Blood sample collection	√		√	√
• Immune marker testing (IL-2, IL-6, IL-10, IL-17A, IL-22, TNF-α)			√	√
Interventions				
• TI/sham stimulation			√ (weeks 1-2, daily)	
• Escitalopram oxalate (10 mg/d)		√ (start)	√ (continued)	√ (continued)
Safety assessment	√		√	√
Concomitant medication record	√	√	√	√
Adverse event record	√	√	√	√

4.2 Study Population

4.2.1 Inclusion/Exclusion Criteria for the Imaging-Immune Mechanism Study of Childhood Trauma-Related Depressive Disorder

(1) Inclusion criteria:

(1) Diagnosis of depressive episode by a psychiatrist according to ICD-11 criteria;

(2) Meeting the ICD-11 diagnostic criteria for depressive episode, with a Hamilton Depression Rating Scale-17 item score ≥17 and <25; with a history of childhood trauma, and on the Childhood Trauma Questionnaire (CTQ-SF) emotional abuse >13, physical abuse >10, sexual abuse >8, emotional neglect ≥15, physical neglect ≥10, with at least one subscale score meeting the above conditions;

(3) Male and female outpatients aged 18-65 years (inclusive);

(4) Junior high school education or above, with the ability to complete self-rating scales;

(5) No psychiatric medication (antipsychotics, antidepressants, mood

stabilizers, antiepileptic drugs, central stimulants, etc.) within 1 month before enrollment;

(6) Voluntary participation in the study and signing of the informed consent form.

(2) Exclusion criteria:

(1) Severe heart, liver or kidney disease; brain organic disease; severe cardiovascular disease, tumor, history of hematological disease, rheumatism, malnutrition, neurodegenerative disease, etc.; depressive episodes secondary to other psychiatric or somatic diseases;

(2) History of tobacco, alcohol or other psychoactive substance abuse;

(3) Pregnant women;

(4) Participation in other drug clinical trials before enrollment.

4.2.2 Withdrawal Criteria

This study follows the principle of "voluntary participation", and subjects have the right to withdraw from the study at any time. Subjects will be withdrawn from the study if any of the following occurs:

(1) Voluntary withdrawal by the subject

For any reason, the subject or his/her legal representative is no longer willing to continue participating in the study and requests withdrawal.

(2) Discontinuation decided by the investigator

In the following circumstances, the investigator has the right to decide to discontinue the subject's participation out of consideration for the subject's safety and interests:

(1) Occurrence of a serious adverse event (SAE): the investigator judges that continued participation may expose the subject to unacceptable risk.

(2) Occurrence of an important adverse event: although not reaching the "serious" level, it occurs repeatedly or persists, seriously affecting the subject's tolerability (such as intolerable headache, dizziness, skin allergy, etc.).

(3) Emergence of a new disease or significant worsening of the condition: for example, the subject develops another serious disease (such as a

cardiovascular event or malignant tumor), or depressive symptoms worsen (such as strong suicidal ideation or behavior), making continued participation inappropriate.

(4) Pregnancy: if the subject is confirmed to be pregnant during the study, study intervention (TI stimulation and study medication) will be discontinued immediately and the subject will enter follow-up to ensure the safety of mother and child.

(3) Protocol deviation and non-adherence

(1) Serious non-adherence to the study protocol, including but not limited to:

1) Missing multiple consecutive time-domain interferential transcranial electrical stimulation treatments or study visits.

2) Failure to take the study medication (escitalopram oxalate) as prescribed, with adherence below the predefined standard (such as <80% or >120%).

3) Unauthorized use of concomitant medications explicitly prohibited in the protocol during the study period.

(2) Important protocol deviation: any deviation that may seriously affect the scientific validity of the study data or the rights of subjects.

(4) Loss to follow-up

If the subject is lost to contact and the investigator is unable to reach the subject through all contact methods provided (such as telephone, text message, e-mail, home visit, etc.), and this situation persists beyond the scheduled visit window.

(5) Administrative termination of the study

The entire study project is ordered to be terminated prematurely by the sponsor or the Ethics Committee.

4.2.3 Provisions for Suspension/Termination of the Clinical Trial

Serious safety issues occur during the trial; major errors are found in the clinical trial protocol; if the investigator believes that clinical observation results may indicate that continued research is unsafe, part

or all of the study may be terminated after consultation; the Ethics Committee requires termination of the trial;

4.2.4 Number of Subjects and Grouping Method

(1) Sample size calculation

(1) Total sample size:

This study plans to enroll 74 patients with depressive disorder who meet the criteria.

(2) Grouping and number per group:

All eligible subjects will be randomly assigned in a 1:1 ratio to the following two groups, with 37 subjects in each group.

1) Study group: escitalopram oxalate + time-domain interferential transcranial electrical stimulation (active stimulation)

2) Control group: escitalopram oxalate + sham stimulation

(3) Basis for sample size estimation:

1) This study is a high-value fMRI mechanistic study, and the sample size is estimated based on a superiority clinical study design.

2) Calculation parameters: superiority margin δ=0.2; expected response rate difference=0.27; sample standard deviation s=0.1; α=0.05, power (1-β)=0.8.

3) Calculation result: at least 26 evaluable cases are required per group.

4) Allowance for dropout: a dropout rate of 20% is expected, so the sample size for each group is expanded to 37 cases to ensure sufficient data for statistical analysis.

(2) Grouping and randomization scheme

(1) Grouping method:

This study adopts a randomized, parallel-group controlled design.

(2) Specific randomization scheme:

1) Random sequence generation: block randomization will be used, and the random allocation sequence will be generated by professional statistical software or an online randomization system (such as

http://www.trialdesign.cn/) to ensure dynamic balance of sample sizes between the two groups.

2) Random sequence concealment: the generated random sequence (i.e., the group corresponding to each subject number) will be kept sealed by independent research staff who do not participate in subject recruitment, intervention or efficacy assessment.

3) Implementation of allocation:

When a subject completes all baseline assessments and is confirmed eligible, the investigator will assign a unique randomization number according to the order of enrollment. The research staff responsible for time-domain interferential transcranial electrical stimulation will obtain the corresponding stimulation parameter regimen (active or sham stimulation) from the independent custodian according to this number, thereby completing the group allocation of the subject. This procedure ensures the unpredictability of allocation and avoids selection bias.

4.2.5 Time Commitment of Study Subjects

Total duration: approximately 4 weeks.

Total number of visits: 3 in total (including 3 outpatient visits and 1 follow-up that may be conducted by telephone).

Total time commitment: the cumulative time spent on study-related activities is approximately 40 to 50 hours (mainly concentrated in the first two weeks).

4.2.6 Recruitment Process

Subjects will be recruited by posting recruitment advertisements in the outpatient clinic and inpatient ward of the Department of Traditional Chinese Medicine of Shanghai Mental Health Center.

4.2.7 Restricted Foods, Drugs or Behaviors

(1) Lifestyle-related restrictions

Throughout the study period (from signing the informed consent form to the end of the last follow-up), subjects are required to keep their

lifestyle as stable as possible and to comply with the following requirements:

(1) Alcohol: consumption of any alcoholic beverage is prohibited. Alcohol may affect mood, sleep and cognitive function and seriously interfere with the assessment of study intervention effects.

(2) Smoking: smoking is discouraged. If abstinence is not possible, please keep the usual daily cigarette consumption stable and avoid significant increases or decreases during the study period.

(3) Diet: no special diet is required, but it is recommended to keep daily dietary habits stable. Avoid heavy consumption of caffeine-containing beverages such as coffee, tea and cola within 24 hours before a visit, so as not to affect physiological indicators and subjective feelings.

(4) Exercise: it is recommended to keep usual exercise habits stable and avoid sudden high-intensity or strenuous physical training.

(5) Others: use of any illegal psychoactive substances is prohibited.

(2) Prohibited Drugs, Treatments or Surgeries

To ensure the purity of the study data, the following drugs or treatments are prohibited throughout the study period:

(1) Prohibited concomitant medications:

1) Any antidepressant other than the study medication (escitalopram oxalate), such as SSRIs, SNRIs, NaSSAs, etc.

2) Monoamine oxidase inhibitors.

3) Any traditional Chinese medicine or Chinese patent medicine with antidepressant effects.

4) Prohibited concomitant treatments:

Other invasive or non-invasive neuromodulation treatments, such as transcranial magnetic stimulation, transcranial direct current stimulation, vagus nerve stimulation, deep brain stimulation, etc.

(2) Prohibited unnecessary surgeries: any non-emergency elective surgery should be avoided.

4.3 Study Medication

Study medication: escitalopram oxalate. Dosage: 10 mg/tablet. Administration: once daily, one tablet each time, taken orally after breakfast. Course of treatment: 4 weeks and subsequent follow-up. Storage: sealed and protected from light, placed in a cool and dry place.

4.4 Study Indicators

4.4.1 Primary Indicators and Definitions

The 17-item Hamilton Depression Rating Scale (HAMD-17) will be assessed at baseline and at 2 weeks. Post-treatment HAMD-17 reduction rate: reduction rate = (baseline HAMD-17 score - HAMD-17 score at 2 weeks/4 weeks after treatment)/baseline HAMD-17 score; a HAMD-17 reduction rate ≥50% is defined as response.

4.4.2 Secondary Indicators and Definitions

MRI will be assessed at baseline and after 2 weeks of treatment; immune indicators (IL-2, IL-6, IL-10, IL-17A, IL-22 and TNF-α) will be assessed at baseline, after 2 weeks of treatment and at the 4-week follow-up, and differences before and after treatment will be compared.

4.4.3 Safety Indicators

(1) Immune indicator testing:

Serum immune indicators (IL-2, IL-6, IL-10, IL-17A, IL-22 and TNF-α) will be measured using enzyme-linked immunosorbent assay (ELISA) kits, and the specific ELISA procedures will be performed according to the instructions.

(2) Study scales:

(1) 17-item Hamilton Depression Scale (HAMD-17): one of the most widely used clinician-rated scales for assessing depressive status in psychiatric clinical practice. Previous studies have reported good reliability and validity for this scale. The scale uses a 5-point rating method to assess the

subject's depressive symptoms; the higher the total score, the more severe the depressive symptoms. A total score above 24 indicates severe depression; above 17 indicates mild or moderate depression; below 7 indicates no depressive symptoms.

(2) Hamilton Anxiety Scale (HAMA): a clinician-rated scale used to assess the severity of anxiety symptoms in patients with neurosis and other patients. Previous studies have reported good reliability and validity for this scale. According to the assessment criteria provided by the Chinese Psychiatric Scale Collaborative Group, a total score above 29 indicates severe anxiety; above 21 indicates definite marked anxiety; above 14 indicates definite anxiety; above 7 indicates possible anxiety; below 7 indicates no anxiety symptoms. In previous studies, a cutoff of 14 has often been used, and the higher the total score, the more severe the anxiety symptoms.

(3) Repeatable Battery for the Assessment of Neuropsychological Status

(RBANS): used to assess the cognitive function of subjects. In clinical application, this scale has the advantages of short administration time, simple operation, and sensitive and valid results, and patients with depressive episodes show a high degree of cooperation. RBANS contains 5 index scores: (1) Immediate Memory Index, reflecting the subject's ability to remember information shortly after it is presented by the examiner; (2) Visuospatial/Constructional Index, reflecting the subject's ability to perceive spatial relationships and to correctly copy a figure; (3) Language Index, reflecting the subject's verbal response ability; (4) Attention Index, reflecting the subject's memory capacity and ability to retrieve information from short-term memory stores to express information visually and verbally; (5) Delayed Memory Index, reflecting the subject's anterograde memory ability.

(4) Treatment Emergent Symptom Scale (TESS): among scales of its kind, it has the most comprehensive items and the broadest coverage, including

both common adverse symptoms and signs and a number of laboratory test results. TESS requires assessment of each symptom in three aspects: severity, the relationship between the symptom and the intervention, and the measures taken.

5. Statistical Analysis

5.1 Data Analysis Sets

To ensure the rigor and scientific validity of the analysis of study results, the following three main data analysis sets will be defined according to international conventions:

5.1.1 Full Analysis Set

(1) Definition: includes all subjects who have been randomized and who have received at least one session of time-domain interferential transcranial electrical stimulation (TI) intervention and at least one post-baseline efficacy assessment.

(2) Analysis principle: the intention-to-treat principle is applied, i.e., subjects remain in the group to which they were originally randomized for data analysis, regardless of actual adherence.

(3) Main use: for the analysis of the primary efficacy indicator (HAMD-17 reduction rate). This dataset is intended to maximize the comparability of randomization and to provide an estimate that better reflects real-world clinical efficacy.

5.1.2 Per-Protocol Set

(1) Definition: a subset of the full analysis set, including subjects who meet the following criteria:

(1) No major deviation from the main parts of the study protocol.

(2) Good treatment adherence (defined as receiving at least 80% of the planned TI stimulation sessions and medication adherence between 80% and 120%).

(3) Completion of all core efficacy assessments.

(2) Main use: for the analysis of secondary efficacy indicators and mechanistic indicators. This dataset is used to assess the efficacy of the study protocol under ideal adherence.

5.1.3 Safety Analysis Set

(1) Definition: includes all subjects who have been randomized and who have received at least one study intervention (TI active or sham stimulation).

(2) Analysis principle: analysis is performed by group according to the treatment actually received by the subject.

(3) Main use: for safety analysis, including the incidence and severity of all adverse events and the assessment of their relationship to the study intervention.

5.2 Data Management and Statistical Analysis Plan

5.2.1 Study data management:

EpiData 3.1 will be used for data entry in this study, with double entry

and verification.

(1) EpiData database construction: the data manager will construct the database according to the study protocol and study medical records.

(2) Data entry: clinical investigators or data entry personnel designated by the investigators (clinical research coordinators) will enter data from the study medical records into EpiData promptly and accurately. EpiData is not the source record; its content originates from the medical records and the study visit manual.

(3) Data locking and export: after each subject completes the trial and the data have been reviewed and verified by the monitor, the data manager will lock the data. During the trial, locked data may be exported in real time as needed for interim analysis. After all trial data of all subjects have been locked, the data manager will export them to the designated database for final statistical analysis by the statistician.

SPSS 25.0 software will be used in this study. For all quantitative data,

the goodness-of-fit test (K-S test) will be used to determine whether the data are normally distributed. Normally distributed quantitative data will be described statistically as mean ± standard deviation. Levene's test will be used to assess homogeneity of variance; for between-group comparisons of two groups with homogeneous variance, the t-test will be used; between-group comparisons will be performed using the chi-square test or Fisher's exact probability method. Statistical significance is set at two-tailed $P < 0.05$.

Two independent samples t-tests will be used to compare between-group differences in nodal and circuit indicators of subjects; general linear models will be used to control for age, sex and education level as covariates; the FWE correction method will be used for multiple comparison correction, with a correction threshold of voxel-level $P<0.001$ and cluster-level $P<0.05$. Finally, software and toolkits will be used for visualization.

Pearson or Spearman correlation analysis will be used to explore brain imaging marker parameters significantly correlated with TCM syndrome element scores. After extracting values from the positive results of the two-sample t-test of ALFF between the two groups, the resulting ALFF values will be correlated with inflammatory factors and clinical scales respectively, and the correlation analysis will be performed using Spearman rank correlation.

5.2.2 Stress paradigm:

This study uses the Montreal Imaging Stress Task (MIST) to induce psychosocial stress responses in subjects. The MIST task has been widely used in functional brain imaging research and has been repeatedly shown to reliably induce individual psychosocial stress responses, with good reliability and validity. The MIST task used in this study has three different conditions: rest condition, control condition and stress condition.

The MIST mainly consists of the following components:

（1）mental arithmetic problems to be solved;

（2）a circular panel for selecting the correct answer;

（3）a feedback panel providing answer feedback on whether the answer is correct (correct/incorrect/time-out) and whether it is recorded (recorded/not recorded);

（4）a virtual average accuracy indicator bar, in which the triangle above the bar indicates the average accuracy of all subjects and the triangle below the bar indicates the subject's current average accuracy; ultimately, the average accuracy of all participating subjects is virtually set to be lower than 80% of subjects;

（5）a time progress bar.

5.2.3 Acquisition and Analysis of Imaging Data

(1) Data acquisition and processing

In this experiment, a Siemens MAGNETOM Prisma 3.0T research MRI scanner with a 64-channel phased-array coil will be used, and scanning

will be performed in the Radiology Department. Multimodal brain MRI data of all subjects will be acquired by the same trained technician with an intermediate professional title. All subjects will first undergo routine structural imaging, followed by high-resolution 3D T1WI structural imaging, diffusion tensor imaging (DTI) and resting-state blood oxygen level-dependent functional MRI (BOLD-fMRI). Before scanning, subjects will be given 30 minutes to settle into a resting state. During data acquisition, subjects will be instructed to keep their eyes closed, remain still, relax their body, not think about specific matters, but remain awake. After resting-state data acquisition, a voice system will be used to verify whether the subject maintained wakefulness as required during scanning, and any thought processes the subject may have engaged in will be recorded. After the core sequences are scanned, data quality will be evaluated immediately, and sequences judged to have excessive head motion will be re-scanned. The fMRI sequence scanning parameters are

as follows:

(1) High-resolution 3D T1WI structural imaging: TR=2530 ms, TE=3.65 ms, imaging matrix: 256×256 mm, voxel=1.0×1.0×1.0 mm3, flip angle 8°.

(2) Diffusion tensor imaging (DTI): TR=750 ms, TE=4.17 ms, imaging matrix: 256×256 mm, slice thickness=2.0 mm, voxel=2.0×2.0×2.0 mm3, b0=1000 s/mm2, number of diffusion-sensitive gradient directions=64, flip angle 70°.

(3) Blood oxygen level-dependent functional MRI (BOLD-fMRI): TR=2000 ms, TE=30 ms, imaging matrix: 256×256 mm, time point=250, slice thickness=4 mm, voxel=4.0×4.0×4.0 mm3, flip angle 90°.

(2) Data preprocessing

In the MATLAB 2020a environment (http://www.mathworks.com/products/matlab/), BOLD functional data preprocessing will be completed based on DPABI (http://rfmri.org/dpabi). The main processing steps include:

(1) Converting fMRI images from DICOM format to NIFTI format;

(2) Removing the first 10 time points to avoid instability of the magnetic field at the beginning of scanning and adaptation of subjects to the scanning environment;

(3) Slice-timing correction, i.e., correcting the acquisition time of each slice to a single time point;

(4) Head motion correction, i.e., correcting head motion occurring during scanning; subjects whose head translation exceeds 2 mm or rotation exceeds 2 degrees will be excluded; because resting-state fMRI is particularly sensitive to head motion parameters, mean framewise displacement (mFD) will also be calculated to quantify subtle head motion, and subjects with mFD >0.2 mm or mFD greater than the mean plus 2 standard deviations of all subjects' mFD will be excluded;

(5) Co-registration, registering the T1 image to the head-motion-corrected functional image;

(6) DARTEL-based image segmentation, segmenting the registered T1 image into gray matter, white matter and cerebrospinal fluid;

(7) Covariate regression, regressing out head motion parameters, white matter and cerebrospinal fluid signals to remove their influence on the observed indicators;

(8) Normalization, using information obtained from DARTEL to register the covariate-regressed images to the standard MNI space with 3×3×3 mm3 voxels;

(9) Filtering, applying band-pass filtering of 0.01-0.1 Hz to the time series of each voxel.

Through the above preprocessing steps, noise interference can be effectively reduced and the data standardized, providing a clear and accurate data basis for subsequent resting-state DCM modeling and analysis, so as to reveal the connectivity and regulatory mechanisms between brain networks.

(3) Preprocessing and analysis of functional connectivity data between the thalamus, cortex and whole-brain voxels

Functional connectivity analysis will be performed for 5 thalamic nuclei and their corresponding cerebral cortex. The cortical regions of interest include the bilateral prefrontal cortex, motor/premotor cortex, somatosensory cortex, parietal/occipital cortex and temporal cortex.

6. Adverse Events / Serious Adverse Events

6.1 Adverse Events

6.1.1 Definition of adverse events

Adverse event: an unfavorable medical event occurring in a patient or a subject participating in a human trial after receiving a drug (or product), which does not necessarily have a causal relationship with the treatment. Serious adverse event: an event occurring during a clinical trial that requires hospitalization, prolongs hospitalization, causes disability, affects working capacity, is life-threatening or results in death,

or leads to congenital anomaly, etc.

6.1.2 Classification of adverse events

Mild: tolerated by the subject, does not affect treatment, requires no special management, and has no impact on the subject's recovery.

Moderate: intolerable to the subject, requires special management, and has a direct impact on the subject's recovery.

Severe: life-threatening to the subject, fatal or disabling, and requires immediate emergency management.

6.1.3 Recording and reporting of adverse events

Clinical adverse events may occur during the treatment of subjects. Once an adverse event (including important adverse events) occurs, the time of onset, clinical manifestations, management process and duration, outcome, and relationship to the study drug (or study product) must be recorded in detail in the case report form. If a serious adverse event occurs, a serious adverse event form must be completed and reported to

the Ethics Committee of Shanghai Mental Health Center and the health administrative department within 24 hours.

Risks and their control:

At present, high-level clinical research evidence for time-domain interferential transcranial electrical stimulation is still insufficient, and its efficacy for depressive episodes has not been fully established; therefore, there is a risk that the patient's condition may not improve significantly. Accordingly, throughout the study, professional physicians will regularly monitor the patient's condition, follow up and intervene promptly when the condition changes, and ensure patient safety by discontinuing the study, changing the medication regimen, or referring the patient to another specialist's outpatient clinic. At the end of each examination, we will assess adverse reactions in the subject and keep detailed records.

6.2 Serious Adverse Events

6.2.1 Definition of serious adverse events

A serious adverse event (SAE) refers to an unfavorable medical event occurring after a subject receives the study drug, such as death, a life-threatening event, permanent or severe disability or loss of function, hospitalization or prolongation of hospitalization, or congenital anomaly or birth defect.

6.2.2 Recording and reporting of serious adverse events

The investigator must take necessary and appropriate medical measures for the subject after the occurrence of an SAE to safeguard the subject's safety. For any serious adverse event meeting the definition that occurs during the clinical trial, the investigator should report it to the sponsor and its designated personnel immediately, within 24 hours after becoming aware of it. The investigator must determine whether the serious adverse event is related to the trial itself or the study drug, keep complete records and follow-up of the serious adverse event, and provide

detailed written reports in a timely manner. For reports involving death, the investigator should provide the Ethics Committee with other required materials, such as the autopsy report and the final medical report.

6.3 Risk Prevention and Management Measures

6.3.1 Risks of time-domain interferential equipment:

The overall risk of applying time-domain interferential stimulation equipment in this study is assessed as low to moderate. Its physical risks (such as skin irritation) are usually mild, transient and controllable. Its neuropsychiatric risks, especially in the population with childhood trauma-related depressive disorder, require high vigilance, and mainly include temporary mood fluctuations and potential activation of traumatic memories. This study has designed a comprehensive risk management system, including strict subject screening, detailed informed consent, rigorous process monitoring performed by a multidisciplinary team (psychiatrists and clinical psychologists), and

clear emergency response plans for adverse events, so as to ensure that the welfare and safety of subjects are always given top priority.

6.3.2 Main risks of time-domain interferential equipment failure:

(1) Hardware failure:

(1) Abnormal stimulation output: the device may output unexpected current (such as excessively high or low current intensity, waveform distortion, or unexpected interruption).

(2) Control unit failure: the touch screen, buttons or software interface become unresponsive, making it impossible to start, adjust or stop stimulation.

(3) Power supply problems: sudden battery depletion or unstable power supply, resulting in treatment interruption or device abnormality.

(4) Accessory failure: broken electrode leads, poor contact of electrode pads/headbands, or abnormally increased impedance.

(2) Software failure:

(1) Program crash: the control software freezes, closes unexpectedly or hangs during treatment.

(2) Parameter setting errors: parameters displayed on the software interface do not match the actual output parameters, or preset parameters are accidentally reset.

(3) Data loss/errors: treatment records, parameter logs and other data are not saved correctly or appear as garbled text.

(3) Control measures:

Regularly inspect and maintain instruments and equipment to ensure power supply safety and stable power supply. Regularly inspect equipment cables and accessories to ensure their safety. Regularly arrange manufacturer maintenance of the equipment to ensure smooth operation. Save data promptly after the trial to ensure data backup.

6.3.3 MRI-related risks and discomfort:

During scanning, subjects must remain still in a supine position

inside the scanner for about 45 minutes, which may cause physical stiffness or fatigue. The operating equipment will produce continuous noise (professional hearing protection is provided throughout), and some sensitive individuals may therefore experience irritation or anxiety; the scanning environment is a relatively small and enclosed space, and a few individuals may experience transient claustrophobic-like discomfort.

Investigators will strictly perform pre-scan safety screening to rule out absolute contraindications such as magnetic metal implants and cardiac pacemakers, so as to ensure the physical safety of subjects.

6.3.4 Privacy and confidentiality risks:

All personal information and research data collected in this study will be processed with anonymized coding and stored in an encrypted controlled system. Nevertheless, a theoretically minimal probability of unintentional disclosure still exists.

7. Ethical Requirements

7.1 Ethics Committee Review

This protocol, the written informed consent form and materials directly related to subjects must be submitted to the Ethics Committee of Shanghai Mental Health Center, and the study may only be formally initiated after written approval by the Ethics Committee of Shanghai Mental Health Center. The investigator must submit an annual study report to the Ethics Committee of Shanghai Mental Health Center at least once a year (if applicable). When the study is suspended and/or completed, the investigator must notify the Ethics Committee of Shanghai Mental Health Center in writing; the investigator must promptly report all changes in the research work (such as amendments to the protocol and/or the informed consent form) to the Ethics Committee, and must not implement these changes before obtaining approval from the Ethics Committee of Shanghai Mental Health Center, except for changes made to eliminate obvious and immediate risks to subjects. In the event of the

above circumstances, the Ethics Committee of Shanghai Mental Health Center will be notified.

7.2 Informed Consent

7.2.1 Procedures for obtaining informed consent

The investigator must provide the subject or his/her legal guardian with an informed consent form that is easy to understand and approved by the Ethics Committee of Shanghai Mental Health Center, and must give the subject or his/her legal guardian sufficient time to consider participation in this study. Subjects must not be enrolled before a signed written informed consent form has been obtained. During the subject's participation, all updated versions of the informed consent form and written information will be provided to the subject. The informed consent form should be retained as an important document relating to human trials for future reference.

8. Confidentiality Measures

The results of this project may be published in journals, but we will keep subject information confidential in accordance with legal requirements; subject personal information will not be disclosed except as required by relevant laws. When necessary, government administrative departments and the Ethics Committee of Shanghai Mental Health Center and its relevant personnel may access subject data in accordance with regulations.

9. Project Milestone Plan:

Year	Annual plan and annual objectives (work milestones divided by quarter; key milestones that must be achieved shall be specified)

2025	Q3: training of project team members; refinement of standardized techniques and detailed rules for consistency assessment of scales, and consistency evaluation performed; ethics application completed. Q4: enrollment, intervention and data collection completed for 30 patients with depressive disorder; preliminary analysis of clinical data. Milestone objective: enrollment, intervention and assessment completed for 30 study subjects.
2026	Q1: enrollment, intervention and data collection completed for 30 patients with depressive disorder; related reagents purchased. Q2: enrollment, intervention and data collection completed for 14 patients with depressive disorder; data analysis, experimental report writing and manuscript submission. Milestone objective: data consolidation, project defense and final

	close-out completed.

10. Follow-up and Medical Measures after Study Completion:

10.1 Follow-up Arrangements after Study Completion

10.1.1 Routine follow-up:

This protocol already includes a 4-week follow-up period after the end of intervention. This last follow-up (Day 42 ± 3 days) is the routine endpoint of this study; thereafter, investigators will no longer conduct active, protocol-specified follow-up of subjects as part of the study plan.

10.1.2 Subsequent medical consultation:

After the end of the study, if subjects have any questions about their health status or subsequent treatment, they may contact the study physician by telephone or outpatient visit at any time, and the study team will provide professional medical consultation. Subjects are encouraged to attend routine follow-up visits at the psychiatric outpatient clinic of a

qualified medical institution after the study, so as to ensure continued management of depressive symptoms and long-term recovery.

10.2 Medical Measures after Study Completion

10.2.1 Subsequent treatment arrangements:

This study is a short-term intervention study lasting 4 weeks. At the end of the study, regardless of the extent of symptom improvement, the study team will provide each subject with a written summary of the condition and recommendations for subsequent treatment. The study physician will work closely with the subject (and the subject's attending physician, with the subject's authorization) to develop a smooth and seamless subsequent treatment plan. This usually includes continuing standard antidepressant pharmacotherapy (such as continued escitalopram oxalate or another appropriate medication) and/or psychotherapy at a community hospital or the outpatient clinic of Shanghai Mental Health Center.

11. Responsibilities of the Parties:

The research party shall conduct the clinical trial strictly in accordance with this ethics-approved protocol, promptly assess changes in subjects' symptoms and avoid the occurrence of risks. Subjects shall receive treatment strictly in accordance with the treatment regimen of the research party.

12. Planned Forms of Output Publication:

12.1 To confirm the imaging mechanisms and immunological mechanisms by which stress mediates the thalamo-cortical circuit in depressive disorder, and to elucidate the "central → peripheral physiological response" bidirectional regulatory pathway of time-domain interferential transcranial electrical stimulation;

12.2 To provide an effective treatment method for clinical practice and a theoretical basis for the mechanism of time-domain interferential transcranial electrical stimulation;

12.3 It is planned to publish 1-2 papers acknowledging the funding of this project, including 1 high-quality paper, and to train 1 doctoral student.

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