Research Proposal

Title: A Study on the Efficacy and Safety of Accelerated Transcranial Magnetic Stimulation for Obsessive-Compulsive Disorder and Its Underlying Neurological Mechanisms

Principal Investigator: Yi-jie Zhao

Protocol Number: 2.0

Protocol Version/Date: 2.0/17 June 2025

I. Research Background

Obsessive-Compulsive Disorder (OCD) is a refractory psychiatric disorder primarily characterised by obsessive thoughts (persistent rumination or doubt concerning an event) and/or compulsive behaviours (repetitive actions, often undertaken to repeatedly verify a particular matter). Its lifetime prevalence ranges from 0.8% to 2.5%[1]. The primary treatment approaches for OCD are pharmacotherapy and cognitive behavioural therapy, though their efficacy rates remain approximately 40%–65%. Physical therapies constitute secondary treatment options.

Among these, invasive physical therapies primarily involve anterior capsulotomy and deep brain stimulation. Deep brain stimulation (DBS) is a neurosurgical intervention involving electrode implantation at specific brain locations to deliver therapeutic electrical pulses. The ventral capsule/ventral striatum (VC/VS), subthalamic nucleus, and nucleus accumbens are currently common DBS targets for OCD, effectively alleviating symptoms in patients with severe, treatment-resistant OCD. Multiple randomised controlled trials targeting VC/VS demonstrate approximately 76% response rates in treatment-resistant OCD patients[2,3]. However, the surgical risks and

financial burden render this approach inaccessible for most individuals. Consequently, non-invasive neuromodulation offers greater universal applicability.

The US Food and Drug Administration (FDA) has approved the H7 coil for deep transcranial magnetic stimulation (dTMS) targeting the medial prefrontal cortex/anterior cingulate cortex for OCD treatment. Following treatment, the response rate (defined as a 30% or greater reduction in symptom severity) among 42 patients receiving active stimulation was 38%, rising to 45% at the one-month follow-up[4,5,6]. Evidently, existing targets and treatment protocols for rTMS in OCD remain suboptimal.

The inferior frontal cortex (IFC) is closely associated with OCD's characteristic functions of response inhibition, conflict resolution, and uncertainty processing. Research indicates that cognitive behavioural therapy (CBT) can alter IFC volume. This study aims to explore the efficacy of repetitive transcranial magnetic stimulation (rTMS) using novel, individualized IFC targeting combined with symptom-induction techniques.

Reference

1 Hirschtritt, M. E., Bloch, M. H. & Mathews, C. A. Obsessive-Compulsive Disorder: Advances in Diagnosis and Treatment. Jama 317, 1358-1367, doi:10.1001/jama.2017.2200 (2017).

2 Sinai, A. et al. Focused Ultrasound Thalamotomy in Tremor Dominant Parkinson's Disease: Long-Term Results. J Parkinsons Dis 12, 199-206, doi:10.3233/JPD-212810 (2022).

3 Yamamoto, K. et al. Focused Ultrasound Thalamotomy for Tremor-dominant Parkinson's Disease: A Prospective 1-year Follow-up Study. Neurol Med Chir (Tokyo) 61, 414-421, doi:10.2176/nmc.oa.2020-0370 (2021).

4 Grant, J. E. Clinical practice: Obsessive-compulsive disorder. N Engl J Med 371, 646-653, doi:10.1056/NEJMcp1402176 (2014).

5 Banks, G. P., Heilbronner, S. R., Goodman, W. & Sheth, S. A. A population-normalized tractographic fiber atlas of the anterior limb of the internal capsule: relevance to surgical neuromodulation. J Neurosurg 137, 1278-1288, doi:10.3171/2022.1.JNS211935 (2022).
6 Bonelli, R. M. & Cummings, J. L. Frontal-subcortical circuitry and behavior. Dialogues Clin Neurosci 9, 141-151, doi:10.31887/DCNS.2007.9.2/rbonelli (2007).

II. Research Objectives and Anticipated Outcomes

(1) To validate the efficacy of 20Hz rTMS targeting the right IFC in treating treatment-resistant obsessive-compulsive disorder (OCD);

(2) To investigate whether provocation techniques for obsessive symptoms can enhance treatment efficacy;

(3) To explore the effects of transcranial magnetic stimulation on cognitive function in OCD patients and its potential physiological mechanisms.

III. Research Content and Methods

3.1 Overall Study Design and Plan

This study constitutes an open-label, prospective, single-centre investigation.

The intervention employs 20Hz repetitive transcranial magnetic stimulation (rTMS) targeting the right inferior frontal cortex (rIFC). To shorten the treatment cycle, reduce dropout rates, and ensure efficacy, the study will employ the following design: six stimulation sessions per day for five consecutive days, totalling 30 therapeutic stimulation sessions. Magnetic resonance imaging (MRI) scans, cognitive function assessments, and symptom evaluations will be conducted before and after the intervention. Symptom follow-up assessments will occur at two weeks post-treatment, with both symptom and cognitive function follow-ups at four weeks post-treatment. Symptom assessments will be completed by psychiatrists (psychiatrists/psychologists), while the intervention will be administered by trained research assistants.

The study aims to investigate the cognitive regulatory effects of non-invasive interventions. Participants will undergo tailored cognitive assessments based on

individual clinical profiles, with all tasks completed via computer using keyboard or mouse input. These tasks primarily evaluate working memory whilst also assessing attention, learning and memory, executive control, reasoning ability, risk decision-making, affective decision-making, and emotional awareness. Additionally, neuroimaging techniques will be employed to investigate the neural mechanisms underlying cognitive function in OCD patients. Participants will undergo task-related functional magnetic resonance imaging (fMRI) before and after electrical stimulation, performing a series of cognitive tasks related to executive function and affective decision-making during scanning. This will enable comparison of rTMS intervention effects on cognitive function and associated imaging mechanisms.

Data to be recorded for the study include:

Behavioural data: Task-specific behavioural metrics such as accuracy rates and reaction times.

Magnetic resonance imaging data: Acquisition sequences encompass structural imaging, task-state imaging, resting-state imaging, and diffusion tensor imaging.

3.2 Case Numbers and Grouping Methodology

The study anticipates enrolling 20 subjects with obsessive-compulsive disorder (OCD), all of whom will be assigned to the intervention group for treatment. This is an exploratory clinical study conducted as an open-label trial.

Sample size calculation was performed using G-Power 3.1 with the following parameters:

Effect size d: 1.0

Significance level α: 0.05 (two-tailed)

Power (1-β): 0.95

The calculated minimum sample size required is approximately 16. Considering a 20% clinical attrition rate, 20 participants are planned for enrolment.

IV. Inclusion and Exclusion Criteria

4.1 Inclusion Criteria

1) Volunteer subjects with Obsessive Compulsive Disorders (OCD) according to the Diagnostic and Statistical Manual of Mental Disorders (DSM V) criteria;

2) Age 18–60 years, right-handed;

3) Disease severity: Yale-Brown Obsessive Compulsive Scale score ≥16 for OCD patients;

4) Medication stable for at least 4 weeks;

5) Resistant patients to standard treatments: partial but insufficient response (reduction of Y-BOCS score < 35%) or lack of response to previous well conducted treatment including: optimal tolerated dose and adequate duration (> 12 weeks) of at least 2 Serotonin Reuptake Inhibitors (selective serotonin reuptake inhibitors, clomipramine), or 1 Serotonin Reuptake Inhibitors + 1 augmentation strategy (adjunction of an antipsychotic - such as risperidone or olanzapine or aripiprazole - or lithium or buspirone)

6) No systematic rTMS therapy in the past six months;

7) Signature of informed consent form;

8) Normal vision or corrected vision;

9) Capacity to complete protocol-specified tests.

4.2 Exclusion Criteria

1) Abnormal cognitive status (assessed using MoCA with score <24);

2) Other primary diagnosis than OCD (comorbid mild depression is tolerated)

3) Comorbid diagnosis of schizophrenia/ psychotic disorder, bipolar disorder, substance abuse or dependance3)

4) Significant self-harm intent or severe suicidal tendencies within the past year;

5) Irreversible visual or auditory impairment preventing completion of scales or related assessments;

6) Presence of metallic implants, such as pacemakers or stents;

7) Any current or potential medical, psychological, social, or geographical factors compromising patient safety or study participation;

8) Poor compliance;

9) Claustrophobia;

10) History of epilepsy or familial epilepsy

11) Pregnant or lactating women (women of childbearing potential must obtain a negative pregnancy test result prior to study commencement and employ medically approved contraceptive measures);

12) Deterioration or failure of vital organ function (cardiac, pulmonary, hepatic, renal, etc.); or unstable vital signs;

13) Conditions unsuitable for this stimulation site, such as increased intracranial pressure, elevated intraocular pressure, or glaucoma

14) History of or concomitant neurological disorders: cerebrovascular disease, central nervous system infections, Creutzfeldt-Jakob disease, Huntington's disease and Parkinson's disease, Lewy body dementia, traumatic brain injury dementia, other physical/chemical factors (drugs, alcohol, CO, etc.), significant somatic diseases (hepatic encephalopathy, pulmonary encephalopathy, etc.), intracranial space-occupying lesions (subdural haematoma, brain tumours), endocrine system disorders (thyroid disease, parathyroid disease), and dementia caused by vitamin deficiency or any other cause

V. Endpoints

5.1 Primary Endpoint

Obsessive-compulsive symptom severity: Yale-Brown Obsessive Compulsive Scale (Y-BOCS)

5.2 Secondary Endpoints

Clinical Global Impression Scale (CGI)

Depressive Symptom Severity: Hamilton Depression Rating Scale (HAMD-17 items)

Anxiety Symptom Severity: Hamilton Anxiety Rating Scale (HAMA-14 items)

Impulse Control Scale (UPPS-P)

Short-Form Parenting Behaviour Questionnaire (s-EMBU-C)

5.3 Safety Endpoints

Severity of Clinical Symptoms

5.4 Exploratory Endpoints

Beck Depression Inventory (BDI)

Chinese Version State-Trait Anxiety Inventory (STAI-S, STAI-T)

Chinese Version of the Obsessive-Compulsive Inventory (Revised) (OCI-R)

Intolerance of Uncertainty Scale (IUS-12)

Intolerance of Uncertainty Questionnaire (IUI-A, IUI-B)

Stress Perception Scale

Snaith-Hamilton Pleasure Scale (SHAPS)

Aphasia Evaluation Scale (Self-Report Version) (AES-S)

Physiological Data: Imaging and EEG require signal-to-noise ratios within acceptable ranges. Excessive head motion and motion artefacts may compromise data quality. Data significantly affected (e.g., imaging head motion impacting image clarity, electrophysiological artefacts exceeding 20% of data) will be excluded.

Cognitive Behavioural Data.

All behavioural data exceeding three standard deviations above or below the mean will be excluded to prevent statistical bias.

VI. Adverse Event Collection and Reporting

6.1 Definition of Adverse Events

Adverse Event (AE): An undesirable medical occurrence in a patient or clinical trial subject following treatment, not necessarily causally related to the treatment. An adverse event may therefore be an undesirable and unexpected sign, symptom, or time-related condition associated with use, irrespective of causality to the treatment.

Serious Adverse Event (SAE):

1) Resulting in death;

2) Resulting in a serious deterioration in the subject's health:

a) Life-threatening illness or injury, or

b) Permanent impairment of a bodily structure or bodily function, or

c) Hospitalisation or prolongation of hospitalisation, or

d) Medical or surgical intervention to avert a life-threatening illness or injury, or to prevent permanent impairment of a bodily structure or bodily function

e) Fetal distress, foetal death, congenital malformation, or birth defect

Note: Hospitalisation previously planned for the current medical condition or steps required by the clinical study protocol, without significant deterioration in health, shall not be considered a serious adverse event.

When completing the adverse event form, the investigator shall use mild, moderate, or severe to describe the intensity of the adverse event. To standardise criteria, the grading of event intensity is as follows:

Mild: Subjective discomfort not requiring symptomatic treatment or intervention suspension. Examples include mild headache, fatigue, slight itching or tingling at the

stimulation site, photopsia, or minor facial muscle twitching. Such events cease upon intervention cessation.

Moderate: Subjective discomfort requiring intervention suspension but not special symptomatic treatment, as such adverse events cease shortly after intervention cessation. Examples include severe headache, significant stinging sensation or muscle twitching at the stimulation site, and other adverse events reported as intolerable.

Severe: Risk of disability or death requiring emergency treatment and immediate intervention cessation. Examples include epileptic seizures.

6.2 Recording and Reporting of Adverse Events

Adverse events occurring during clinical research must be reported by research personnel to the clinical research sponsor and the principal investigator's institution within 24 hours of becoming aware of the event. For mild or moderate adverse events, the study physician may document the event in detail and report it to the principal investigator within three days, provided the event has been adequately resolved and the subject's condition has improved and recovered. For serious adverse events, the investigator shall notify within 24 hours of becoming aware of the event and immediately complete an adverse event form, documenting the time of occurrence, severity, duration, measures taken, and outcome.

For any SAE occurring during the clinical trial (regardless of whether related to the trial or investigational device), the investigator shall immediately provide appropriate treatment to the subject while completing an SAE report form and submitting a written report to the principal investigator. The SAE must also be recorded in the AE report section of the Case Report Form (CRF).

The Principal Investigator shall submit a written report to the relevant Ethics Committee within 24 hours of receiving the SAE report form. For any fatality, the investigator shall provide all required documentation to both the Ethics Committee and the sponsor.

Adverse events (AEs) in this study specifically refer to any unfavourable medical events occurring in clinical research subjects during the intervention period, which need not necessarily have a causal relationship with the treatment. To ensure the

completeness of safety data collection, all adverse events occurring during the study must be recorded on the CRF, including those occurring during treatment and during the protocol-specified period after treatment. This encompasses all AEs not yet present prior to the initial visit and all AEs that recur or worsen after the initial visit.

Subjects may report AEs spontaneously. When documenting AEs, the investigator should use comprehensive diagnostic or standard medical terminology to describe symptoms, rather than recording individual signs or symptoms. The CRF and source documentation must be consistent. Any discrepancies between lay language in subject records (e.g., subject diaries) and corresponding medical terminology should be clarified in the source documentation.

AEs should be followed up until resolution, stabilisation, or when the investigator deems them no longer clinically significant, or until loss to follow-up. For a subject where an AE persists at the end of the study, follow-up should continue until resolution, stabilisation, or when the investigator deems it no longer clinically significant, or until loss to follow-up. If follow-up is not conducted, the investigator must provide justification. Follow-up shall typically continue for 30 days after the subject ceases intervention treatment. Where necessary, the investigator may be requested to conduct examinations to obtain supplementary measurements and/or assessments.

6.3 Risks and Adverse Reactions

To date, among tens of thousands of subjects globally who have undergone transcranial magnetic stimulation, no cases of permanent brain damage attributable to its use have been reported. However, a small proportion of subjects may experience mild headaches and fatigue during stimulation; mild tingling or itching may occur at the stimulation site; and depending on the stimulation location, photopsia or facial muscle twitching may also occur. These symptoms can be managed by adjusting stimulation parameters and are transient adverse reactions, resolving upon cessation of stimulation.

Beyond mild headaches, safety considerations for TMS encompass other factors documented in the literature. For instance, epileptic seizures may occur, typically in individuals with pre-existing brain disorders, those using medications that lower the

seizure threshold, or those with a history of alcohol abuse. Therefore, in addition to screening criteria requiring the absence of any neurological or psychiatric conditions and no family history of epilepsy, this study will also exclude any individuals at risk of seizure induction due to epilepsy medications or alcohol consumption, thereby minimising the likelihood of epileptic seizures.

The transcranial magnetic stimulation apparatus currently in our possession allows for parameter adjustment, fully conforming to the aforementioned specifications and constituting a highly safe device. Professional medical personnel will be present throughout the stimulation period. Should any participant experience a seizure during transcranial magnetic stimulation, we shall implement the following procedures:

1) Disconnect the power supply to the transcranial magnetic stimulator and immediately remove the stimulation coil from the participant's head.

2) Medical personnel will administer emergency treatment.

3) Family members will be notified.

4) Staff will accompany the subject to the nearest medical facility.

5) Medical expenses will be advanced by trial personnel and covered by the research organisation.

6) Referral to another hospital will be determined based on clinical necessity.

VII. Withdrawal Criteria

Subjects may withdraw from the study at any time for any reason. Investigators may withdraw subjects from the study at any time for any reason. If any medical condition or circumstance arises that renders continued participation in the study not in the subject's best interests, the research subject may withdraw from the study. Withdrawal from the study shall not prejudice any benefit to the subject. Following termination, no further data collection shall be conducted from the subject. Reasons for termination or withdrawal shall be documented on the Case Report Form (CRF).

Reasons for study termination include, but are not limited to:

1) Death of the subject.

2) Loss to follow-up.

3) Refusal by the subject to receive further treatment and/or follow-up, accompanied by withdrawal of informed consent.

4) Investigator termination of the subject's participation.

5) Adverse events (e.g., occurrence of intolerable adverse events or adverse event treatment necessitating withdrawal).

6) Serious protocol deviation.

7) Subject meeting exclusion criteria (newly emerging or confirmed).

Management of withdrawn subjects:

1) All original data for withdrawn subjects shall be retained. If withdrawal occurs due to reason 2, the investigator shall endeavour to contact the subject via multiple channels (e.g., telephone, text message) to ascertain the reason, conducting at least three attempts at follow-up and re-enrolment.

2) The timing and reason for trial discontinuation shall be documented in detail on the CRF.

3) For subjects withdrawing due to reason 5, adverse events must be appropriately managed, with follow-up continuing until the adverse event (AE) is resolved or stabilised.

VIII. Data Management

This project will utilise Case Report Forms (CRFs) for data recording. The CRF cover page shall display the clinical trial name, study site, subject name abbreviation and code, study start and end dates, and date of each interview to facilitate collation and organisation. The initial interview shall cover: demographic characteristics (pinyin initials, gender, age, ethnicity, etc.), general disease status (diagnosis, duration, etc.), past medical history, prior treatments (medication names, duration, dosage, etc.),

physical examination, and vital signs. Interviews shall occur during the baseline period, treatment completion period, and follow-up period. The CRF shall include clinical scales required by the study, to be assessed by a clinician. Except during the baseline period, each assessment requires recording the occurrence of adverse events on the case report form. If present, the adverse event report form must be completed in detail. Upon completion of the case report form, the investigator must enter the data into the study computer. Magnetic resonance imaging data and cognitive task data are stored on the study computer, named using the subject identification number and interview period, and saved in a specific format. Data entered into the computer may not be modified by any person during the study period.

This study protocol and data shall be accessible only to medical and statistical experts involved in this trial, participating investigators, and other trial personnel, as well as relevant institutions such as the healthcare facility conducting the trial and the ethics committee. Participants' personal information shall be strictly confidential, with data stored in encrypted computers using participant identification numbers. Data transfer shall be conducted by researchers via encrypted portable hard drives.

Findings from this project may be published in medical journals. Patient information shall remain confidential in accordance with legal requirements and shall not be disclosed unless mandated by relevant legislation. Where necessary, governmental regulatory bodies, hospital ethics committees, and their authorised personnel may access patient records as prescribed.

IX. Statistical Analysis

9.1 Definition and Selection of Statistical Analysis Datasets

All statistical tests shall employ two-tailed procedures, with $p < 0.05$ indicating statistically significant differences.

Quantitative indicators shall be described by calculating mean, standard deviation, maximum, minimum, and median values. Categorical indicators shall be described by case numbers and percentages within each category. All data processing shall be conducted using SPSS professional statistical software.

Comparisons between groups for general characteristics were analysed using appropriate methods according to indicator type. Inter-group comparisons for quantitative data employed paired t-tests (assuming equal variance and normal distribution) or Wilcoxon signed-rank tests based on data distribution; intra-group comparisons used paired t-tests (assuming normal distribution) or Wilcoxon signed-rank tests. Categorical data will be analysed using chi-square tests or exact probability methods (where chi-square is inappropriate); ordinal data will be analysed using Wilcoxon signed-rank tests or Cochran-Mantel-Haenzel (CMH) tests.

9.2 Statistical Analysis of Research Data

Magnetic resonance data will be analysed using the SPM toolkit based on MATLAB. Electrophysiological data will be analysed using the fieldtrip toolkit based on MATLAB. Behavioural data will be analysed using MATLAB. Statistical methods will be selected according to research hypotheses and experimental requirements. Statistical software utilised will include MATLAB and SPSS. The primary focus of the study is to compare changes in brain activity (magnetic resonance, electrophysiological) and behaviourally measured cognitive alterations before and after transcranial magnetic stimulation or electrical stimulation.

X. Conflict of Interest

There are no relevant conflicts of interest for this study.

XI. Privacy and Confidentiality

This study will implement stringent privacy protection policies. All information pertaining to this project and its collaborations will be securely safeguarded. No personally identifiable information concerning participants will be disclosed to any external parties under any circumstances. Even if study results are published, participants' personal details will remain confidential.

Participants retain the right to access their personal information and the final research findings. Personal data will be protected throughout all stages of collection, storage, and application (including analysis and comparison).

PI's Signature:

Date:

Informed Consent Form

Title：A Study on the Efficacy and Safety of Accelerated Transcranial Magnetic Stimulation for Obsessive-Compulsive Disorder and Its Underlying Neurological Mechanisms

Research Institution: Shanghai Pudong New Area Mental Health Centre

Protocol Number/Version: 2.0

Informed Consent Form Version/Date: 2.0/17 June 2025

Principal Investigator: Yi-jie Zhao

You have been invited to participate in a study investigating the neural mechanisms in the brains of patients with obsessive-compulsive disorder undergoing a novel transcranial magnetic stimulation treatment protocol. This research is supported by the Pudong New Area Mental Health Centre. Please read this informed consent form carefully and consider your decision to participate in this study. Participation is entirely voluntary. As a subject, you must provide written consent before joining the clinical trial. Should any part of the informed consent form be unclear during discussion with your study doctor or researcher, you may ask them to explain it to you. We encourage you to discuss your decision to participate thoroughly with your family and friends before making a choice. You have the right to decline participation in this study or withdraw at any time without penalty or loss of rights. Should you be participating in another study, please inform your study doctor or researcher. The background, purpose, procedures, and other important information regarding this study are as follows:

I. Research Background

Obsessive-Compulsive Disorder (OCD) is a refractory psychiatric disorder primarily characterised by obsessive thoughts (persistent rumination or doubt concerning an event) and/or compulsive behaviours (repetitive actions often undertaken to repeatedly verify a particular matter), with a lifetime prevalence of 0.8%–2.5%. First-line treatments for OCD comprise pharmacotherapy and cognitive behavioural therapy, yet their efficacy rates remain approximately 40%–65%. Physical therapies constitute second-line interventions, with invasive approaches primarily involving anterior insular lobotomy and deep brain stimulation. Deep brain stimulation involves neurosurgical implantation of electrodes into specific brain locations to deliver therapeutic electrical pulses. However, for most patients, the associated surgical risks and financial burden render this approach prohibitive. Consequently, non-invasive

neuromodulation protocols offer greater accessibility.

The US Food and Drug Administration (FDA) has approved the H7 coil of deep transcranial magnetic stimulation (TMS) for treating OCD by stimulating the medial prefrontal cortex/anterior cingulate cortex. Following treatment, the response rate (defined as a 30% or greater reduction in symptoms) among 42 patients receiving active stimulation was 38%, rising to 45% at the one-month follow-up. Evidently, existing targets and treatment protocols for TMS in OCD remain suboptimal. The inferior frontal cortex (IFC) is closely associated with OCD's characteristic functions of response inhibition, conflict resolution, and uncertainty processing. Research indicates that cognitive behavioural therapy (CBT) can alter IFC volume. This study aims to explore the efficacy of repetitive transcranial magnetic stimulation (rTMS) using a novel, individualised IFC target combined with symptom-induction techniques.

II. Study Objectives

The primary objective is to validate the efficacy of 20Hz rTMS targeting the right inferior frontal cortex (rIFC) in alleviating OCD symptoms. Additionally, the study aims to investigate rTMS's effects on brain and cognitive functions, elucidating underlying neural mechanisms to provide evidence-based support for its clinical application in neurological and psychiatric disorders.

III. Research Process

1. How many individuals will participate in this study?

It is anticipated that 20 participants will be recruited for this study.

The study will recruit individuals aged 18–60 years with a primary diagnosis of obsessive-compulsive disorder who have not previously undergone any physical therapy. To ensure safety, the following individuals will be excluded: pregnant or breastfeeding women; those with a personal or family history of epilepsy; individuals with a history of or concomitant neurological disorders; those experiencing increased intracranial pressure, elevated intraocular pressure, or glaucoma; individuals with comorbid psychiatric disorders; and those exhibiting abnormal cognitive status.

2. Study Procedures

You will undergo baseline data collection, transcranial electrical stimulation intervention, and post-treatment assessment. During the baseline phase, you will

complete clinical symptom evaluations, cognitive function assessments, electroencephalogram (EEG) recordings, and magnetic resonance imaging (MRI) scans. Clinical symptom assessment comprises self-report questionnaires and clinician evaluations. Cognitive function assessments will be conducted on tablets and computers, requiring you to complete a series of tasks following verbal instructions. During MRI scanning, you must remove all metallic accessories, wear noise-cancelling earplugs, and lie on the MRI scanner bed for head imaging. Please keep your head as still as possible throughout the scan. Researchers will communicate with you via microphone for two-way voice interaction during the procedure. Should you require assistance or experience discomfort, please communicate with the researcher by pressing the alarm ball. During functional MRI, you will be asked to press buttons as instructed to complete a series of cognitive tasks.

Subsequently, you will undergo five consecutive days of transcranial magnetic stimulation (TMS) intervention. Prior to stimulation, the researcher will elicit your symptoms using visual stimuli. This process may cause discomfort; however, for the intervention's efficacy, we kindly request your patience. During the intervention, you will be required to remove all hair accessories and sit in the chair. The researcher will administer stimulation according to the predefined protocol. Please endeavour to keep your head still throughout the stimulation. Should you experience any discomfort during the stimulation, you may immediately inform the researcher. Transcranial magnetic stimulation must be conducted consecutively for five days, with six repetitions per day. Each stimulation session lasts three minutes, with intervals of at least one hour between sessions.

A rest area equipped with tables, chairs, and a television will be provided adjacent to the treatment room for your use during waiting periods.

Following the intervention, you will undergo clinical symptom assessment, cognitive function evaluation, electroencephalogram (EEG) recording, and magnetic resonance imaging (MRI) scans, mirroring the pre-intervention protocol. An online follow-up will be conducted at 2 weeks, with a further assessment of clinical symptoms and

cognitive function at 4 weeks. Additional online follow-ups will be scheduled at 3 and 6 months post-treatment completion.

3. Trial Duration

The overall study is planned to last three years. For your individual participation, the study comprises a baseline period, treatment intervention period, and post-treatment follow-up phase. During baseline data collection, clinical symptom assessment takes approximately 30 minutes, cognitive function assessment approximately 1 hour, and brain MRI scanning approximately 2 hours, totalling about 3.5 hours. The treatment intervention period requires five consecutive days, with six daily sessions. Each stimulation session lasts three minutes, with intervals of at least one hour between sessions, equating to approximately six hours per day. Post-treatment assessments comprise a one-hour cognitive function evaluation and a 70-minute MRI scan. The two-week follow-up will be conducted online, while the four-week follow-up mirrors the post-treatment assessment format.

IV. Risks and Benefits

1. What are the risks of participating in this study?

To date, among tens of thousands of participants worldwide who have undergone transcranial magnetic stimulation, no cases of permanent brain damage resulting from its use have been reported. However, a small proportion of subjects may experience mild headaches and fatigue during stimulation. A slight tingling sensation or mild itching may occur at the stimulation site. Depending on the location of stimulation, photopsia (flashes of light) or facial muscle twitching may also occur. These symptoms can be managed by adjusting stimulation parameters and are transient adverse reactions that resolve upon cessation of stimulation.

Beyond mild headaches, safety considerations for TMS include other factors documented in the literature. For instance, the risk of epileptic seizures typically arises in individuals with pre-existing brain disorders, those using medications that lower the seizure threshold, or those with a history of alcohol abuse. Therefore,

alongside screening criteria excluding neurological or psychiatric conditions and familial epilepsy history, this study will also exclude individuals at risk of seizure induction due to antiepileptic medication or alcohol use to minimise this possibility.

Our current TMS equipment allows full parameter adjustment, fully complying with the above specifications and representing a highly safe device. Throughout stimulation, professional medical personnel will be present at all times. Should any participant experience an epileptic seizure during transcranial magnetic stimulation, we will implement the following procedures:

1) Immediately disconnect the power supply to the transcranial magnetic stimulator and remove the stimulation coil from the participant's head.

2) Medical personnel will administer emergency treatment.

3) Notify family members.

4) Escort the subject to the nearest medical facility.

5) Study personnel will cover initial medical expenses, with the research team assuming full treatment costs.

6) Determine referral to another hospital based on clinical necessity.

2. What benefits does participation offer?

This study cannot guarantee direct, definitive medical benefits. While transcranial magnetic stimulation may alleviate symptoms, efficacy varies significantly between individuals.

Participation provides complimentary comprehensive brain MRI scans and cognitive function assessments. Study physicians will offer free consultations regarding your condition and clinical symptoms during follow-up visits.

This research investigates the underlying neurological mechanisms of the disease and potential treatment approaches. We hope insights gained from your participation may benefit you or others with similar conditions in the future.

V. Alternative Treatment Options

This study will not affect your existing treatment regimen.

VI. Use of Research Findings and Confidentiality of Personal Information

With your understanding and that of other participants, findings from this research project may be published in authoritative scientific journals. However, we shall maintain the confidentiality of your research records in accordance with legal requirements. Personal information of research participants will be strictly confidential and shall not be disclosed unless required by relevant legislation. Where necessary, government regulatory bodies, hospital ethics committees, and other relevant researchers may access your records as prescribed.

VII. Research Costs and Related Compensation

1. Medications/devices and associated examination fees

All costs incurred by this study will be covered. Routine treatments and examinations for any concurrent conditions will not be included in this complimentary provision.

2. Compensation for study participation

Reimbursement will be provided for travel expenses incurred due to study participation (receipts required).

VIII. Rights of Participants and Relevant Considerations

1. Your Rights

Your participation throughout this study is entirely voluntary. Should you decide not to participate, this will not affect other treatments you are entitled to receive. Should you choose to participate, you will be asked to sign this written informed consent form. You retain the right to withdraw from the trial at any stage without facing discrimination or unfair treatment, and your corresponding medical care and rights will remain unaffected.

2. Precautions

As a participant, you must provide truthful information regarding your medical history and current physical condition; inform the study physician of any discomfort experienced during the study period and any medications currently taken; individuals with a history of epilepsy, familial epilepsy, metallic implants, or claustrophobia are ineligible for this study and should inform the physician in advance.

IX. Contact Information for Accessing Study Information

Should any significant new information arise during the study that may affect your willingness to continue participation, your doctor will notify you promptly. If you wish to access your research data or learn about the study's findings after its conclusion, you may raise any questions regarding this research at any time and receive appropriate responses. Please contact Zhao Yijie at 021-68306699 ext. 1311.

This study has been reviewed and approved by the Ethics Committee. Should you have any concerns regarding your rights or interests, wish to report difficulties, dissatisfaction, or anxieties encountered during participation, or wish to provide feedback or suggestions concerning this study, please contact the Ethics Committee of Shanghai Pudong New Area Mental Health Centre via email: pdjw_ec@shspdjw.com.

You have ample time to consider whether to participate in the study and sign the informed consent form.

Each participant will be assigned a unique identification number and a file will be created. All your information will be used solely for this research. Your test content and personal details will be kept strictly confidential. Researchers are prohibited from discussing your test content or personal circumstances with anyone outside the study. Any research findings published will not disclose any of your personal information.

Informed Consent Form - Signature Page

I have read this informed consent form.

I have had the opportunity to ask questions and all questions have been answered.

I understand that participation in this study is voluntary.

I may choose not to participate in this study, or withdraw at any time by informing the researcher, without facing discrimination or reprisal, and my medical care and rights will not be affected as a result.

I will receive a signed copy of this informed consent form.

Name of Participant: _____

Signature of Participant: _____

Date: _____

I have accurately communicated this document to the respondent, who has accurately read this informed consent form. I confirm that the respondent had the opportunity to ask questions. I attest that his/her consent is voluntary.

Researcher's Name: _____

Researcher's Signature: _____

Date: _____