STUDY PROTOCOL

Study Official Title:

Effects of Transcranial Temporal Interference Stimulation Combined With Tai Chi Training on Cognitive Function, Dual-Task Performance, and Neuroimaging Mechanisms in Individuals With Mild Cognitive Impairment

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Sponsor:

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1. ABSTRACT

Background: Mild cognitive impairment (MCI) is a critical window for intervention before progression to dementia. Individuals with MCI commonly exhibit impairments in memory, executive control, and cognitive-motor dual-task performance. Transcranial temporal interference stimulation (tTIS) enables non-invasive modulation of deep brain regions such as the hippocampus, while Tai Chi provides repeated cognitive-motor practice that may support neuroplasticity.

Objective: To evaluate the effects of an 8-week program of individualized hippocampal tTIS combined with cognitively enhanced Tai Chi training on cognitive function and dual-task performance in individuals with MCI, and to investigate associated neuroimaging mechanisms and maintenance of selected effects at follow-up.

Design: Randomized, quadruple-blind, sham-controlled, parallel-group trial.

Population: Approximately 120 community-dwelling adults aged 60–80 years with MCI (MoCA < 26, CDR = 0.5, ADL < 26, no dementia).

Intervention: Active or sham individualized 5 Hz tTIS targeting the left hippocampus (2 mA, 2000/2005 Hz carrier frequencies), combined with standardized cognitively enhanced eight-form Tai Chi training, three sessions per week for 8 weeks. Each tTIS session lasts 20 minutes and each Tai Chi session approximately 60 minutes.

Outcomes: Primary outcomes include global cognition (MoCA and MMSE), working memory and executive control, episodic memory, cognitive dual-task performance, and MRI-assessed brain structure and function. Secondary outcomes include neuropsychiatric and sleep-related symptoms, functional status and health-related quality of life, task-evoked cerebral hemodynamic responses measured by fNIRS, blinding effectiveness, and adverse events/tolerability. Selected cognitive and clinical outcomes will be reassessed 16 weeks after completion of the intervention.

2. INTRODUCTION

2.1 Background and Rationale

MCI represents an important stage for delaying or preventing further cognitive decline. The hippocampus is among the earliest brain regions affected in Alzheimer's disease and plays a central role in episodic memory and cognitive-motor integration. Non-invasive brain stimulation techniques capable of modulating deep neural targets may therefore provide a promising approach for MCI. Temporal interference stimulation uses multiple high-frequency electric fields to generate a lower-frequency envelope in deeper tissue, allowing individualized targeting of the hippocampus without surgery. Preliminary data from our pilot study (n=14) showed that a single session of individualized hippocampal tTIS increased left hippocampal neural complexity ($p<0.001$) and improved face-name memory accuracy ($p=0.003$), with excellent tolerability. These findings support extending the intervention from an acute single-session paradigm to repeated stimulation designed to induce more durable neuroplastic effects.

Tai Chi is a multicomponent cognitive-motor exercise involving postural control, movement sequencing, attention, memory, and executive control. In the present study, an eight-form Tai Chi program is enhanced with cognitive dual-task exercises to increase interactive, reactive, verbal, and nonverbal cognitive demands. Combining repeated hippocampal tTIS with cognitively enhanced Tai Chi may provide complementary neural and behavioral stimulation and may strengthen the persistence of treatment effects.

2.2 Study Objectives

Primary Objective:

- To determine whether 8 weeks of active individualized 5 Hz hippocampal tTIS combined with cognitively enhanced eight-form Tai Chi, compared with sham tTIS combined with the same Tai Chi

program, improves global cognition, working memory and executive control, episodic memory, cognitive dual-task performance, and MRI-assessed brain structure and function in individuals with MCI.

Secondary Objectives:

- To determine whether selected cognitive and clinical improvements are maintained at the 16-week post-intervention follow-up.
- To evaluate neuropsychiatric and sleep-related symptoms, functional status, health-related quality of life, and task-evoked cerebral hemodynamic responses measured by functional near-infrared spectroscopy (fNIRS).
- To evaluate the safety, tolerability, adherence, and blinding effectiveness of repeated tTIS combined with Tai Chi training.
- To explore neuroplasticity mechanisms linking intervention-related changes in brain structure and function with changes in cognitive and dual-task outcomes.

3. STUDY DESIGN

3.1 Overall Design

This is a **randomized, quadruple-blind, sham-controlled, parallel-group trial**.

Approximately 120 participants will be randomly assigned in a 1:1 ratio to active individualized hippocampal tTIS plus cognitively enhanced Tai Chi or sham individualized hippocampal tTIS plus the same Tai Chi program. The intervention will be delivered three times per week for 8 weeks. Outcomes will be assessed at baseline and immediately after the 8-week intervention. Selected cognitive and clinical outcomes will also be assessed 16 weeks after the intervention (Week 24 from baseline).

Study Flow Diagram:

Visit	Activity
Screening (V0)	Informed consent, medical history, MoCA, CDR, ADL, GDS, eligibility review, MRI and stimulation safety checks.
Visit 1 (Baseline)	Randomization; T1-weighted MRI for individualized stimulation modeling; baseline cognitive, episodic memory, dual-task, MRI, fNIRS, and questionnaire assessments.
Weeks 1–8 (Intervention)	Active or sham individualized tTIS combined with cognitively enhanced eight-form Tai Chi training, three sessions per week (24 sessions total).
Visit 2 (Week 8)	Post-intervention cognitive, episodic memory, dual-task, MRI, fNIRS, questionnaire, safety, and blinding assessments.
Follow-up (Weeks 9–24)	No study stimulation. Participants continue usual activities and are contacted as needed for study follow-up.
Visit 3 (Week 24)	16-week post-intervention follow-up of prespecified global cognition, episodic memory, neuropsychiatric/sleep, functional status, quality-of-life, and safety outcomes.

3.2 Study Population

Inclusion Criteria:

- Age 60–80 years, community-dwelling
- Montreal Cognitive Assessment (MoCA) score < 26
- Clinical Dementia Rating (CDR) score = 0.5

- Activities of Daily Living (ADL) score < 26 (relatively intact daily function)
- Does not meet diagnostic criteria for dementia (based on DSM-5 or NIA-AA criteria)
- No contraindications for MRI examination (e.g., non-MRI-compatible metallic implants, severe claustrophobia)
- Able to provide written informed consent

Exclusion Criteria:

- Neurological conditions that may cause cognitive decline (e.g., cerebrovascular disease, encephalitis, Parkinson's disease, Huntington's disease)
- Severe visual, auditory, or language impairments preventing completion of neuropsychological assessments
- Severe depression (Geriatric Depression Scale > 10) or other major psychiatric disorders
- History of seizures or epilepsy
- Previous deep brain stimulation or electroconvulsive therapy within 6 months
- Alcohol or substance dependence
- Concurrent participation in another interventional clinical trial
- Contraindications for non-invasive brain stimulation, including electronic or ferromagnetic implants, non-MRI-compatible metal implants, history of seizures, or pregnancy

Vulnerable Population Protection:

Given that this study enrolls older adults with MCI, additional safeguards will be implemented. Cognitive status, psychological status, comorbidities, and social support will be reviewed before enrollment. Participants who are unable to understand the study procedures or provide valid informed consent will not be enrolled without appropriate legally authorized representative involvement.

Study staff will monitor participants' willingness to continue throughout the trial, and participation may be paused or discontinued if distress, reluctance, or safety concerns arise.

3.3 Randomization and Blinding

Randomization will be performed by an independent statistician using a computer-generated sequence with 1:1 allocation to the active tTIS + Tai Chi group or sham tTIS + Tai Chi group. Allocation concealment will be maintained using sequentially numbered opaque envelopes. Each envelope will contain only a coded stimulation assignment; the code-to-condition mapping will be retained by the independent statistician and will not be available to blinded study personnel until database lock, except when emergency unblinding is required for participant safety.

Blinding: Participants, care providers, investigators, and outcome assessors will be blinded to treatment allocation. The stimulation device will use pre-set coded programs corresponding to active or sham stimulation, such that the operator enters the assigned code without knowing the treatment condition. Active and sham stimulation will use the same electrode configuration, ramp-up/down procedures, session duration, and sensory experience. Tai Chi instructors will provide the same training program to both groups and will remain unaware of stimulation allocation.

4. INTERVENTIONS

4.1 Individualized tTIS (Active)

- **Target:** Left hippocampus, individualized based on each participant's T1-weighted MRI using finite element modeling.
- **Parameters:** 5 Hz target frequency, 2000 Hz and 2005 Hz carrier frequencies, 2 mA baseline-to-peak intensity.

- **Duration:** 20 minutes per session, with 30-second ramp-up and ramp-down; three sessions per week for 8 weeks (24 sessions total).
- **Electrode placement:** Determined by individualized finite element simulation (e.g., SimNIBS) to optimize electric field distribution to the left hippocampal target.

4.2 Sham Stimulation

- Same individualized electrode placement, session schedule, total duration, and ramp-up/down procedures as active stimulation.
- Active current is delivered only during the 30-second ramp-up and ramp-down periods; no effective current is delivered during the main 20-minute stimulation period.
- The sham protocol is designed to reproduce the sensory experience of active stimulation while minimizing effective neuromodulation.

4.3 Cognitively Enhanced Eight-Form Tai Chi Training

- **Program:** A standardized eight-form Tai Chi program provided identically to participants in both study arms.
- **Schedule:** Approximately 60 minutes per session, three sessions per week for 8 weeks.
- **Training structure:** Each session includes a warm-up phase, core Tai Chi training, cognitively enhanced dual-task training, and a relaxation/cool-down phase.
- **Cognitive enhancement:** The dual-task component incorporates interactive, reactive, verbal, and nonverbal cognitive exercises. Participants practice verbalizing movement sequences, responding to intended movement cues while inhibiting competing responses, recalling forms, associating form names with numbers, performing forms with reduced verbal or visual cues, switching sides or changing

form sequences when cued, and performing selected forms while completing verbal tasks such as word spelling.

- **Adherence:** Training attendance and completion will be recorded throughout the 8-week intervention period.

5. OUTCOME MEASURES

5.1 Primary Outcome Measures

#	Outcome	Description	Time Frame
1	Change in Montreal Cognitive Assessment (MoCA) Score	Global cognitive function assessed using the MoCA. Score range 0–30; higher scores indicate better cognitive function.	Baseline, Week 8, Week 24
2	Change in Mini-Mental State Examination (MMSE) Score	Global cognitive function assessed using the MMSE. Score range 0–30; higher scores indicate better cognitive function.	Baseline, Week 8, Week 24
3	Change in Working Memory and Executive Control Performance	Go/No-Go and n-back tasks assessed using accuracy and reaction time; Digit Span assessed using span-based scores. Higher accuracy and longer span indicate better performance, whereas shorter reaction time indicates faster task performance. Individual task outcomes will be analyzed separately.	Baseline, Week 8

4	Change in Episodic Memory Performance	Assessed using the Auditory Verbal Learning Test (AVLT), face-name matching task, and Mnemonic Similarity Task (MST). Recall/recognition, accuracy, and reaction-time measures will be analyzed separately.	Baseline, Week 8, Week 24
5	Change in Cognitive Dual-Task Performance	Single-task and dual-task Timed Up and Go (TUG) performance and spatiotemporal gait measures will be recorded. Metric-specific dual-task cost will be calculated as the percentage change from the corresponding single-task condition, with positive values reflecting deterioration during dual-tasking.	Baseline, Week 8
6	Change in Brain Structure and Function Assessed by Magnetic Resonance Imaging	Brain structural and functional changes will be assessed using multimodal MRI. Prespecified MRI-derived structural and functional measures will be used to characterize intervention-related brain changes.	Baseline, Week 8

5.2 Secondary Outcome Measures

#	Outcome	Description	Time Frame

1	Change in Neuropsychiatric and Sleep-Related Symptoms	Assessed using the Hamilton Anxiety Rating Scale (HAM-A), Hamilton Depression Rating Scale (HAM-D), Geriatric Depression Scale (GDS), Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ). Each instrument will be scored and analyzed separately.	Baseline, Week 8, Week 24
2	Change in Functional Status and Health-Related Quality of Life	Functional status assessed using the Functional Activities Questionnaire (FAQ) and health-related quality of life assessed using the 12-Item Short Form Health Survey (SF-12). The two measures will be analyzed separately.	Baseline, Week 8, Week 24
3	Change in Task-Evoked Cerebral Hemodynamic Responses Assessed by fNIRS	Task-evoked cerebral hemodynamic responses will be assessed using functional near-infrared spectroscopy (fNIRS) during the Go/No-Go, n-back, and Mnemonic Similarity Task. Prespecified oxygenated and deoxygenated hemoglobin	Baseline, Week 8

		measures will be quantified in predefined cortical regions.	
4	Blinding Effectiveness	Participants will indicate whether they believe they received active or sham tTIS. Treatment guesses will be used to evaluate the success of participant blinding.	During the 8-week intervention period
5	Incidence and Severity of Adverse Events and Tolerability	Occurrence, type, and severity of stimulation-related adverse events and discomfort will be recorded using structured questionnaires and participant reports.	Throughout the 8-week intervention period and at Week 24 follow-up

5.3 Safety Outcomes

- Adverse events recorded using a structured questionnaire during the intervention period and at follow-up.
- Tolerability ratings for stimulation-related symptoms (e.g., itching, tingling, burning, headache, dizziness, fatigue).
- Blinding effectiveness assessed using participant treatment-assignment guesses.

6. SAMPLE SIZE AND POWER

Sample size was estimated a priori using G*Power software (version 3.1.9.2, Germany) for a two-way mixed repeated-measures ANOVA (Group × Time). Because no published studies had reported effect sizes for global cognitive outcomes following individualized hippocampal tTIS combined with Tai Chi training in individuals with MCI, a conservative effect size (f = 0.13) was

assumed based on previous randomized controlled trials with comparable intervention designs evaluating cognitive function. Assuming an α level of 0.05 and a statistical power of 80%, a minimum total sample of 97 participants was required. To improve statistical robustness and account for approximately 20% potential participant attrition during the intervention and follow-up, the target sample size was set at **120 participants** (60 per group).

7. STATISTICAL ANALYSIS

7.1 Analysis Sets

- **Full Analysis Set (FAS):** All randomized participants who receive at least one assigned intervention session and have at least one post-baseline efficacy assessment. The FAS will be used for the primary efficacy analysis according to the intention-to-treat principle.
- **Per Protocol Set (PPS):** FAS participants who complete the assigned intervention with no major protocol deviations. The PPS will be used for sensitivity analyses.
- **Safety Set (SS):** All participants who receive any active or sham tTIS session. The SS will be used for safety and tolerability analyses.

7.2 Primary Analysis

Primary outcomes will be analyzed using a two-way mixed-design repeated-measures analysis of variance (ANOVA), with **Group** (active tTIS combined with Tai Chi vs sham tTIS combined with Tai Chi) as the between-subject factor and **Time** as the within-subject factor. The primary effect of interest will be the **Group × Time interaction**, indicating whether changes over time differ between the two intervention groups.

For outcomes assessed at baseline, Week 8, and Week 24, a **2 × 3 mixed-design repeated-measures ANOVA** will be performed. For outcomes

assessed only at baseline and Week 8, a **2 × 2 mixed-design repeated-measures ANOVA** will be used. When a significant interaction effect is identified, post hoc simple-effects and pairwise comparisons will be conducted with Bonferroni adjustment. Effect sizes will be reported as partial eta squared (ηp^2) with 95% confidence intervals where applicable.

For outcomes with three repeated measurements, sphericity will be assessed using Mauchly's test. If the assumption of sphericity is violated, the Greenhouse-Geisser correction will be applied.

7.3 Secondary Analysis

Continuous secondary outcomes will be analyzed using the same two-way mixed-design repeated-measures ANOVA framework according to their scheduled assessment time points. Categorical outcomes will be compared between groups using the chi-square test or Fisher's exact test, as appropriate.

Exploratory subgroup analyses may be conducted according to baseline characteristics such as age, sex, education level, and baseline cognitive function. These analyses will be considered hypothesis-generating.

7.4 Missing Data

Reasons for missing data and participant withdrawal will be documented. Missing primary outcome data will be handled using multiple imputation under the missing-at-random assumption when appropriate. Sensitivity analyses will include analyses based on the PPS and comparisons of results with and without multiple imputation.

Linear mixed-effects models including Group, Time, and the Group × Time interaction as fixed effects and participant as a random effect may additionally be used as sensitivity analyses to assess the robustness of findings in the presence of incomplete repeated measurements.

7.5 Neuroimaging and fNIRS Analysis

MRI and functional near-infrared spectroscopy (fNIRS) data will be preprocessed using established analysis pipelines. Prespecified structural and functional neuroimaging measures will be analyzed using the corresponding Group × Time repeated-measures framework. Appropriate correction for multiple comparisons, such as false discovery rate correction, will be applied where multiple imaging measures or regions are examined.

7.6 Mediation Analysis

Adverse events will be summarized as frequencies and percentages by intervention group and compared using the chi-square test or Fisher's exact test, as appropriate. Tolerability measures will be summarized descriptively and compared between groups using appropriate parametric or nonparametric tests. Blinding effectiveness will be assessed based on participants' guesses of treatment allocation.

7.7 Statistical Software

Statistical analyses will be performed using R (version ≥4.2) and IBM SPSS Statistics. All statistical tests will be two-sided, with $P < 0.05$ considered statistically significant unless otherwise specified.

8. DATA MANAGEMENT AND MONITORING

8.1 Data Collection and Storage

- Case report forms (CRFs) will be used for all clinical and behavioral assessments.
- Data will be entered into a secure electronic database that is password-protected and encrypted.
- Backup copies will be stored on a secure institutional server. Participant identifiers will be stored separately from coded research data.

8.2 Data Safety Monitoring Board (DSMB)

An independent DSMB comprising a neurologist, a biostatistician, and an ethicist will review safety data every 6 months and will have the authority to recommend continuation, modification, suspension, or termination of the study if important safety concerns arise.

8.3 Adverse Event Reporting

All adverse events will be recorded throughout the intervention period. Serious adverse events will be reported to the ethics committee and DSMB within 24 hours of the research team becoming aware of the event. Non-serious adverse events will be summarized and reviewed periodically.

8.4 Safety Monitoring for Older Adults with MCI

Pre-intervention preparation: Before each stimulation session, vital signs (blood pressure and heart rate) will be recorded and participants will be screened for acute illness, new medication changes, or discomfort that may affect participation.

Real-time monitoring: During stimulation, a trained researcher will remain with the participant, monitor for signs of distress, and inquire about subjective

sensations at regular intervals. If a participant reports intolerable discomfort or a clinically significant adverse event, stimulation will be stopped immediately.
Emergency preparedness: Appropriate emergency equipment and trained personnel will be available at the study site. A direct pathway for rapid transfer to a nearby hospital will be maintained in case of an unexpected serious medical event.
Fatigue prevention: Assessment sessions will include scheduled rest breaks. Participants may rest, pause, or postpone testing if they experience fatigue or discomfort.

9. ETHICS AND REGULATORY COMPLIANCE

9.1 Ethics Approval

The study protocol has been approved by the Shanghai University of Sport Research Ethics Committee (Approval No. 102772026RT012, date: April 15, 2026). Any substantial protocol amendment affecting participant safety, study procedures, or primary outcomes will be submitted for ethics review before implementation.

9.2 Informed Consent

All participants will provide written informed consent after a full explanation of the study purpose, procedures, potential risks, potential benefits, confidentiality protections, and the voluntary nature of participation. The informed consent form will be approved by the ethics committee before use.

9.3 Confidentiality

Participant data will be coded and stored separately from direct identifiers. Only the principal investigator and authorized study staff will have access to the re-identification key. Study results will be reported in aggregate form and will not identify individual participants.

9.4 Registration

The study is registered with ClinicalTrials.gov (NCT number not yet assigned at the time of Protocol Version 1.0). The registry record will be updated in accordance with ClinicalTrials.gov requirements.

9.5 Additional Safeguards for Cognitively Impaired Older Adults

Dual consent: Participants with MCI who retain decision-making capacity will provide their own written informed consent. When additional support is required, a legally authorized representative or family member may be involved in the consent discussion and co-sign in accordance with ethics requirements. Participants who lack sufficient decision-making capacity will not be enrolled unless consent by an authorized representative and participant assent are permitted by the approved protocol.

Simplified consent materials: Study information will be explained in clear language, with adequate time for questions and confirmation of understanding before consent is obtained.

Extended discussion period: Consent discussions will be conducted in a quiet setting by trained research personnel. Participants and accompanying family members will be encouraged to ask questions before signing.

Ongoing assent monitoring: Throughout the study, investigators will monitor participants' willingness to continue. If a participant shows distress, reluctance, or a meaningful decline in capacity, participation will be paused and reassessed.

10. PUBLICATION AND DATA SHARING

10.1 Publication Plan

Results will be submitted for publication in peer-reviewed journals regardless of the direction or statistical significance of the findings. Authorship will follow International Committee of Medical Journal Editors (ICMJE) recommendations.

Interim findings may be presented at scientific conferences and will be identified as preliminary when appropriate.

10.2 Data Sharing

De-identified individual participant data for primary and secondary outcome measures will be made available upon reasonable request to the corresponding author beginning 6 months after publication of the main results. Data will be shared with researchers who submit a methodologically sound research proposal and intend to use the data for non-commercial purposes. Approved requestors must sign a data access agreement. The study protocol, Statistical Analysis Plan, and Informed Consent Form may be posted on ClinicalTrials.gov in accordance with registry requirements.

11. DECLARATIONS

11.1 Integrity Statement

All investigators involved in this study commit to strictly adhering to the study protocol and relevant clinical trial regulations. All study data will be recorded truthfully, completely, and in a traceable manner. No fabrication, falsification, or manipulation of research data will occur. The study procedures, intervention protocols, and assessment standards will be followed rigorously to ensure the scientific validity and reliability of the research outcomes.

11.2 Conflict of Interest

All investigators declare no commercial or academic conflicts of interest related to this study. The study is supported by the Shanghai Eastern Talent Program - Top Talent Project (BJJY2024013) and the National Natural Science Foundation of China (Grants 12572370 and 12272238). Funds will be used for participant recruitment, intervention delivery, data collection,

participant compensation, and other direct research expenses. No improper financial relationships exist.

11.3 Intellectual Property

The data, results, manuscripts, and any intellectual property arising from this study will be managed by Shanghai University of Sport in accordance with institutional policies and applicable agreements. The principal investigator and major contributors will have authorship rights in accordance with ICMJE recommendations. Collaborating institutions, including Huashan Hospital where applicable, will be acknowledged according to their contributions.