Trials

STUDY PROTOCOL

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High-frequency magnetic paired associated stimulation promotes motor function recovery in ischemic stroke patients: a study protocol for single-center, sham stimulation randomized controlled trials (H2MPAS)

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Abstract

Background Numerous studies have validated the clinical effectiveness of electromagnetic pairing-associated stimulation. Building upon this foundation, we have developed a novel approach involving high-frequency magnetic paired-associated stimulation, aiming to enhance clinical applicability and potentially improve efficacy. However, the clinical effectiveness of this approach remains unclear. Our objective is to demonstrate the therapeutic efficacy of this novel approach by employing high-frequency pairing to intervene in patients experiencing motor dysfunction following a stroke.

Methods This is a single-center, single-blind, sham stimulation controlled clinical trial involving patients with upper limb motor dysfunction post-stroke. The intervention utilizes paired magnetic stimulation, combining peripheral and central magnetic stimulation, in patients with Brunnstrom stage III–V stroke lasting from 3 months to 1 year. Evaluation of patients' upper limb motor function occurred before the intervention and after 3 weeks of intervention. Follow-up visits will be conducted after 5 weeks and 3 months of intervention. The primary outcome measure is the Action Research Arm Test, with secondary measures including the Fugl-Meyer Assessment-upper, Modified Barthel Index, modified Tardieu scale, functional near-infrared spectroscopy, and neuroelectrophysiology.

Discussion The high-frequency magnetic paired associative stimulation used in this study combined high-frequency magnetic stimulation with paired stimulation, potentially facilitating both cortical excitation through high-frequency stimulation and specific circuit enhancement through paired stimulation. As dual-coil magnetic stimulation equipment becomes increasingly popular, magnetic-magnetic paired associated stimulation may offer patients improved clinical outcomes at reduced costs.

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Keywords Paired associated stimulation, Magnetic stimulation, Post-stroke, Randomized controlled trial

Administrative information

Title {1}	High-frequency magnetic-paired associated stimulation promotes motor function recovery in ischemic stroke patients: a study protocol for single-center, sham stimulation randomized controlled trials (H2MPAS)
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Name and contact information for the trial sponsor {5b}	Dongsheng Xu Email:dxu0927@shutcm.edu.cn
Role of sponsor {5c}	GYZ,HS and DSX devised the study question and design. GYZ and SPW is the main writer of the manuscript. Others provided support in clinical study execution details and ethical review materials

Introduction

Background and rationale {6a}

Stroke is currently one of the most prevalent major diseases in clinical practice. With the aging of society, the incidence of stroke in China has been steadily increasing over the years. According to national surveys, the age-standardized prevalence, incidence rate, and mortality of stroke among Chinese individuals aged 18 years and above are 1.1%, 246.8/10 thousand person-years, and 114.8/10 thousand person-years, respectively [1]. This high incidence and disability rate not only significantly reduces the quality of life for patients but also imposes a substantial economic burden on society. More than 80% of stroke patients experience contralateral upper limb hemiplegia, with over 40% facing residual motor dysfunction [2]. Common manifestations of upper limb movement disorders include muscle weakness or spasticity, changes in muscle tone, joint laxity, and impaired motor control. These challenges profoundly affect the fine motor function of the patient's upper limbs, hindering tasks such as reaching, picking up objects, and grasping objects to complete basic daily activities [3].

Neurological damage caused by stroke leads to the impairment of sensorimotor integration networks. Studies have shown that 62% of acute stroke patients exhibit deficits in hand and arm positioning in space [4]. Sensory information affects the initiation, modification, and control of motor tasks through various mechanisms. Sensorimotor integration orchestrates voluntary movements through complex neural activities to complete specific tasks. It represents a dynamic interplay between sensory input and intentional motor responses [5]. Precise control of fine and targeted contractions of the small hand muscles necessitates incoming sensory information. Fine voluntary movement control comprises three main components: brainstem, subcortical, and cortical control. Among these, the cerebral cortex serves as the third layer of sensorimotor integration and diverse sensory stimuli and integrate and process different sensations to form comprehensive task-related information, which is then transmitted to motor-related cortex regions to guide voluntary movement. The severity of motor function deficits in stroke patients correlates with impairments in the sensorimotor integration process: reduced integration ability in damaged areas and enhanced function through functional remodeling in undamaged areas [5, 6]. This aligns closely with the adverse compensation theory in rehabilitation. The direct projection from S1 to M1 is crucial for somatosensory and motor information integration [7]. S1-M1 connections establish the foundation for complex information integration and may play an important role in motor control and learning [8]. In summary, closed-loop rehabilitation of sensory-motor circuits holds significant clinical value and scientific importance in studying fine motor recovery and its underlying mechanisms post-stroke.

Non-invasive brain stimulation (NIBS) represents a significant breakthrough in stroke motor function rehabilitation in recent years. Transcranial magnetic

stimulation (TMS), a prominent example of NIBS, is recommended as level A in the latest authoritative international guidelines for treating stroke motor dysfunction [9]. However, TMS primarily enhances patient function by increasing the excitability of motor pathways, ignoring the importance of sensory regulation. In the 2019 international guidelines, all treatment options involve single-target stimulation, neglecting circuit-based multitarget regulation technology. Previous studies using magnetic stimulation for stroke motor rehabilitation have predominantly focused on improving upper limb motor functions, with limited exploration of its impact on fine hand functions. Paired associative stimulation (PAS) emerges as an innovative technique combining peripheral and central magnetic stimulation. It involves time-locked paired stimulation of peripheral electrical stimulation and central magnetic stimulation, which can selectively enhance specific targets and circuits [10]. PAS induces synaptic strengthening of specific targets within the target circuit through Hebbian theory. According to Hebbian theory, the connection between co-excited neurons is strengthened, whereby presynaptic membrane excitation preceding postsynaptic membrane excitation leads to enhanced functional connectivity between the neurons across the synapse [11]. The classic PAS technology is based on this principle. Following peripheral electrical stimulation transmission to the motor cortex through sensory pathways (time is about 25 ms), magnetic stimulation is applied to the central region, creating a sequential excitation pattern of the motor cortex and its upstream neurons. This, in turn, enhances sensorimotor circuit function via Hebbian plasticity [12]. Unlike classic magnetic stimulation mode, PAS fully considers the importance of sensory-motor loop functional regulation by mimicking natural nerve conduction pathways. It activates the entire sensory upstream and motor downstream through combined peripheral electrical stimulation and central magnetic stimulation, aligning more closely with biological processes. More importantly, PAS is site-selective. Current research demonstrates that PAS significantly enhances neuromuscular function corresponding to peripheral electrical stimulation while minimally affecting adjacent neuromuscular functions [13]. This specific enhancement may have important implications for fine motor rehabilitation. In isolated movement training, it is essential to suppress the activity of muscles unrelated to the movement, consistent with the classic mechanism of forced exercise therapy. As mentioned previously, increased sensorimotor integration in nonlesioned brain areas may inhibit integration in the injured area [14, 15]. PAS technology can selectively improve the circuit excitability of target nerves corresponding to specific muscles. Leveraging this, isolated function training may prove effective in enhancing the recovery of fine motor functions after stroke [16]. While PAS offers numerous benefits, its clinical application remains limited, primarily due to challenges in accessing equipment for magnetoelectric correlation stimulation. Currently, magnetoelectric correlation stimulation equipment used in scientific research requires the serial connection of electromyography and magnetic stimulation equipment through wires to achieve paired stimulation [17, 18]. However, this requires both electromyography and magnetic stimulation equipment, which is not suitable for clinical use. To address this limitation, we proposed magnetic paired associated stimulation, wherein peripheral magnetic stimulation replaces peripheral electrical stimulation in classic PAS. By integrating this approach with the dual-beat magnetic stimulation equipment widely used in China, we aim to overcome barriers to technology adoption. Furthermore, we have upgraded traditional low-frequency paired stimulation to high-frequency paired stimulation. Research has demonstrated that high-frequency paired stimulation has better efficacy and may incorporate the benefits of high-frequency magnetic stimulation lacking in traditional magnetic stimulation, potentially improving the efficacy of paired stimulation.

Objectives {7}

We aim to demonstrate the clinical efficacy of high-frequency magnetic paired associative stimulation compared to traditional high-frequency magnetic stimulation, particularly in hand function recovery. Additionally, we seek to explore the effects of high-frequency magnetic paired stimulation on sensorimotor cortex excitability and network connectivity using functional near-infrared spectroscopy (fNIRS).

Trial design {8}

H2MPAS is designed as a single-center, blinded patient, parallel-arm design, sham stimulation controlled clinical trial. The randomized trials is the two arm, exploratory trial with 1:1 allocation ratio.

Methods: participants, interventions and outcomes

Study setting {9}

Participant recruitment will take place at the outpatient clinics and wards of Tongji Hospital, Tongji University, located in Shanghai, China.

Eligibility criteria {10}

The inclusion criteria are as follows: (a) patients diagnosed with stroke through clinical assessment and comprehensive imaging examination [19]; (b) first cerebral infarction with a disease duration of 3 to 12 months; (c) aged between 45 and 80 years, both male and female; (d)

Brunnstrom stage III–V [20]; (e) normal cognitive function (simple mental status examination is normal) [21].

The exclusion criteria are as follows: (a) severe systemic diseases such as cardiopulmonary conditions that preclude rehabilitation treatment; (b) confirmed mental illness, severe depression, epilepsy, or related family history; (c) severe systemic diseases including diabetes and uremia; (d) contraindications to magnetic stimulation and functional magnetic resonance examination, according to safety guidelines, such as metal foreign bodies or implanted electronic devices, etc.; (e) use of medication altering cortical excitability within 1 month (e.g., antiepileptic, anti-anxiety, and depression drugs, etc.); (f) during drug or alcohol withdrawal [22].

Who will take informed consent? {26a}

Informed consent will be obtained by the recruiting physician, who will provide detailed information regarding the trial's intervention methods, patients' post-trial requirements, and potential risks and benefits associated with participation. Subsequently, the physician will present the informed consent form to the patient and their authorized representative, addressing any queries they may have. The patient or their authorized representative will sign the written informed consent form if both parties agree to participate in the trial.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

N/A. This study does not involve the collection of human samples.

Interventions

Explanation for the choice of comparators {6b}

This study used a positive control: high-frequency stimulation intervention targeting the affected side's M1. This method has been validated by numerous studies for its efficacy in promoting motor function recovery during the subacute stage of stroke. Stimulation parameters align with commonly used clinical high-frequency magnetic stimulation protocols, with peripheral magnetic stimulation added to ensure effective intervention in both groups.

Intervention description {11a}

Patients will be randomly assigned to either a single-target group or a paired stimulation group (PAS group). All patients will undergo resting motor threshold testing before treatment. In cases where motor-evoked potentials cannot be measured on the affected side, thresholds from the unaffected side will be used as replacements.

Magnetic stimulation intervention program

This study used a dual-coil magnetic stimulation device (NS3000, Wuhan Yiruide Medical Equipment New Technology Co., Ltd., China). This device is equipped with two "8"-shaped coils, allowing for flexible adjustment of the stimulation interval with millisecond accuracy. The intervention plan for the PAS group is as follows: pairing frequency: 10 Hz, stimulation duration: 2 s, rest duration: 5 s; co-stimulation pulses: 1200; pairing interval: 25 ms; peripheral stimulation target: median nerve of the affected limb; stimulation intensity: the minimum intensity inducing wrist movement; central stimulation target: affected side brain M1; stimulation intensity: 100% rMT. The intervention plan for the single-target group is identical to the PAS group, except the peripheral stimulation intensity is set to 0 (Fig. 1).

Regular rehabilitation program

To ensure all patients receive basic rehabilitation training tailored to their functional status, we designed a targeted

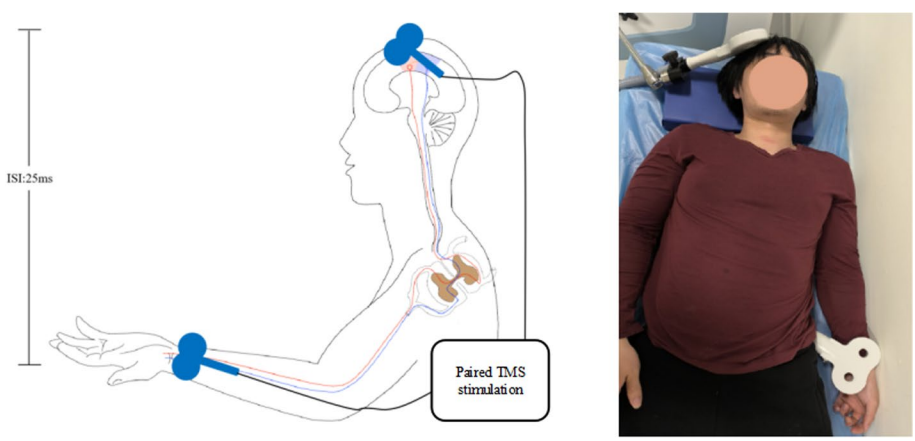

Fig. 1 Magnetic-magnetic paired associative stimulation intervention model diagram

rehabilitation program based on the Brunnstrom stage of each patient (see attachment). Each patient will undergo approximately 2 h of daily rehabilitation training, including anti-spasticity exercises, muscle strength training, activities of daily living training, and programmed upper limb and hand function rehabilitation robot training guided by rehabilitation therapists.

Criteria for discontinuing or modifying allocated interventions {11b}

N/A. This study did not encountered any circumstances that would require modification of the intervention.

Strategies to improve adherence to interventions {11c}

Patients need to come to the hospital for each treatment and evaluation throughout the study with the help of doctors and therapists. Compliance with the treatment plan can be guaranteed, and the therapist will record it after each patient treatment.

Relevant concomitant care permitted or prohibited during the trial {11d}

Subjects must not have been treated with other neuromodulation techniques within 1 month before the start of the trial. In order to ensure the stability of the patient's functional status, patients must not modify their routine care and drug therapy plans after the start of the experiment. If modifications are necessary, they need to inform the physician and record them in the CRF form. The routine rehabilitation programs of the two groups will be formulated by the same therapist under the same guidelines and assigned to different therapists for implementation. This can ensure that the routine treatment programs obtained by the two groups of patients are highly consistent.

Provisions for post-trial care {30}

Provisions for post-trial care is shown in Fig. 2.

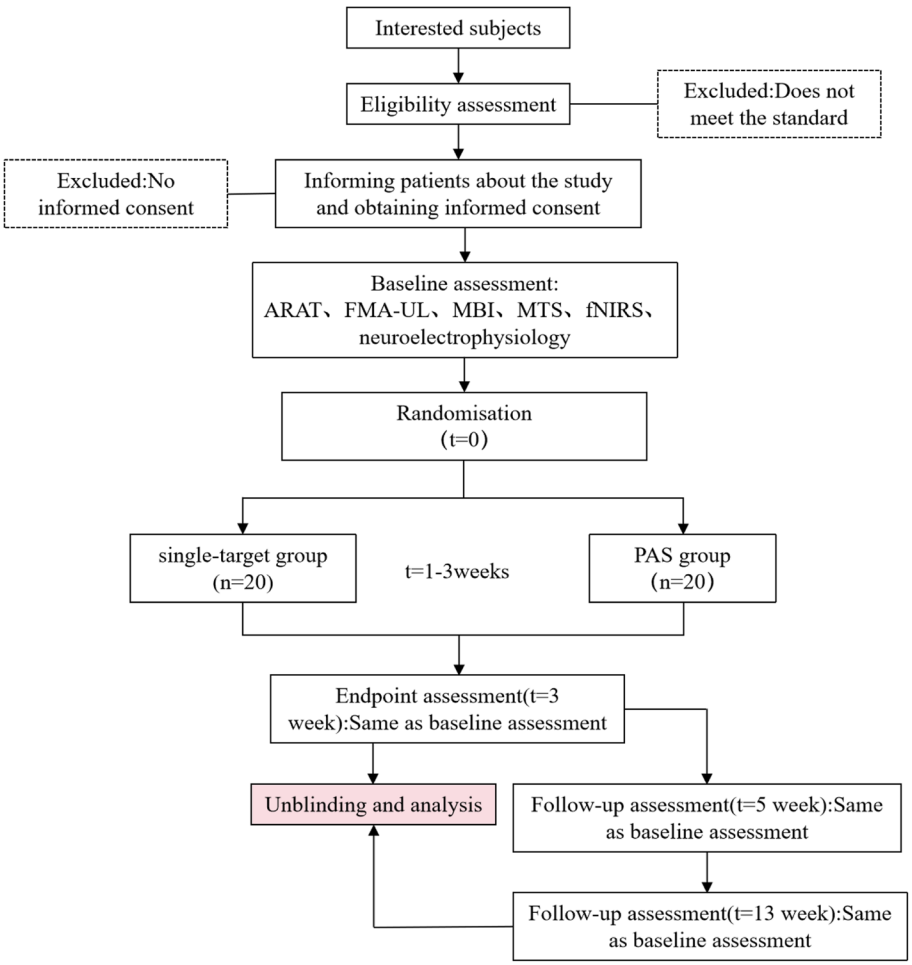

Fig. 2 Flow of participants. The study end-point will be set at the third week post-intervention, with all subsequent assessments conducted during follow-up

Outcomes {12}

Primary outcome

The primary outcome measure in this study is the Action Research Arm Test (ARAT) which will be used to assess upper limb function before the start of the trial and at 3, 5, and 13 weeks after the start of the trial. ARAT is an internationally recognized assessment tool for upper limb function, including fine function tests such as grasping, holding, and pinching. It is currently a commonly used hand-function assessment tool in post-stroke clinical trials [23].

Secondary outcome

The rehabilitation scale, electrophysiology, and fNIRS, like the primary indicators, will be assessed before the start of the trial and once at 3, 5, and 13 weeks after the start of the trial. Secondary outcomes include the following: functional scales (Fugl-Meyer assessment-upper limbs (FMA-UL), modified Barthel Index (MBI), modified Tardieu scale (MTS)), functional near-infrared spectroscopy (fNIRS), neuro electrophysiology (motor evoked potential (MEP), somatosensory evoked potential (SEP), cortical resting period (CSP) [24, 25]. FMA_UL evaluates overall upper limb function, MTS assesses spasticity of the affected limb, MBI measures activities of daily living ability, fNIRS examines cortical functional remodeling, and electrophysiology assesses sensorimotor circuit conduction function [23, 26–28].

fNIRS data acquisition

The fNIRS equipment used in this study is the BrainScope-5000 (Wuhan Zilian Hongkang Technology Co., Ltd., China). fNIRS data collection comprised both resting and task state measurements. Patients will be instructed to recline on the treatment bed, focus their eyes straight ahead, and maintain a stable body position. A skilled therapist fitted the fNIRS headgear on the patient, ensuring that the Cz point on the headgear aligned with the root of the nose and 1/2 of the posterior occipital protuberance. Signal quality is adjusted to ensure optimal signal quality in the region of interest. Initially, resting state data will be collected, with patients informed of a 10-mi collection time and instructed to keep their eyes looking straight ahead. Data collection commenced once the patient achieved a suitable posture. Subsequently, task state data collection occurred, during which patients will be informed of an 8-min collection period and instructed to perform a finger-tapping task in response to sound prompts (20 s tapping, 40 s resting, repeated 8 times). Upon completion of data collection, the patient removed the headgear and rose slowly before departing. Data will be promptly saved with appropriate naming to avoid confusion.

Participant timeline {13}

The participant timeline is shown in Fig. 3.

Sample size {14}

The primary efficacy evaluation index for the trial is the change in upper limb ARAT motor function score. Based on previous research and preliminary experimental data, patients in the M1 stimulation group will be expected to show an 8-point improvement in ARAT, while those in the PAS stimulation group will be expected to improve by 12 points, with a common standard deviation of 3.5 points. Assuming an 80% test efficiency and a bilateral type I error probability of 5%, with a 1:1 distribution ratio between the two groups, the required sample size is determined to be 34 cases. Considering a dropout rate of less than 20%, the trial will enroll 40 cases (20 per group). The calculation formula used is as follows:

$$n_1 = n_2 = \frac{2(z_{a/2} + z_{\beta/2}) * \sigma^2}{(\mu_1 + \mu_2)^2}$$

Recruitment {15}

Recruitment will primarily occur through physician recommendations and recruitment advertisements. Advertisements will be placed in outpatient clinics and wards of the Department of Rehabilitation Medicine and Neurology as well as on social media and online platforms. Preliminary screening via online communication will precede patient arrivals to improve recruitment quality. Additionally, recruitment advertisements will be circulated among previous co-researchers, to identify suitable patients in nearby hospitals. Patients meeting the criteria after preliminary screening will be directed to Shanghai Tongji Hospital to participate in the study.

Assignment of interventions: allocation

Sequence generation {16a}, concealment mechanism {16b} and implementation {16c}

Patients meeting the inclusion criteria and baseline assessment will be randomly assigned to either the single-target group or the PAS group at a 1:1 ratio. Simple randomization will be used, with random numbers generated using SAS by an uninvolved individual. The random assignment outcomes will be concealed within 40 opaque envelopes. Only the third party responsible for randomization will be aware of the randomization results, with involvement in the trial. Randomization outcomes will be archived and provided to data analysts upon trial completion.

	STUDY PERIOD						
	Enrolment	Allocation	Post-allocation				Close-out
TIMEPOINT	*-Day 1*	0	*Week1*	*Week2*	*Week3*	*Week5*	*Week13*
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
MMSE	X						
Allocation		X					
INTERVENTIONS:							
single-target Group			—	—	—		
PAS Group			—	—	—		
ASSESSMENTS:							
ARAT	X				X	X	X
FMA-UL	X				X	X	X
MTS	X				X	X	X
MBI	X				X	X	X
fNIRS	X				X	X	X
Neuroelectrophysiology	X				X	X	X
Adverse	X				X	X	X

Fig. 3 The schedule of enrolment, interventions and assessments

Assignment of interventions: blinding

Who will be blinded {17a}

Physicians responsible for patient recruitment, therapists conducting assessments, therapists administering routine rehabilitation, and patients will be unaware of the group assignment of the patient they are dealing with. The randomizer and the therapist administering the intervention will know the group assignment but will remain independent of the aforementioned physicians and therapists. They are required to maintain strict confidentiality and refrain from disclosing the group status to blinded individuals. The data analysis team will be independent of both the assessment and intervention teams and will only access blinded data after the study is completed.

Procedure for unblinding if needed {17b}

In the event of a patient emergency requiring disclosure of their group assignment, the recruiting physician will request permission from the principal investigator. Upon approval, the treating therapist will reveal the blinded status to the principal investigator, who will then inform the recruiting physician. Additionally, recruiting physicians must provide written justification for the unblinding within 24 h.

Data collection and management

Plans for assessment and collection of outcomes {18a}

In addition to the standardized CRF form, we have developed an additional assessment rubric. This detailed guide provides clear instructions and scoring criteria for all assessment items. Moreover, a seasoned occupational

therapist with extensive clinical experience will systematically train the study's evaluators. The assessment processes will be recorded via camera for subsequent review.

For the primary indicator, this study used the Chinese version of ARAT, which is one of the commonly used hand function assessment tools in clinical practice and has been proven to be able to well reflect the status of the participants' upper limb function and hand function [27]. The scales in the secondary indicators include FMA-UL, MBI, and MTS, of which FMA-UL and MBI are the most commonly used assessment scales in clinical practice and can be used proficiently by every therapist. The MTS is also frequently used in clinical practice, and its Chinese version has been shown to have high reliability and validity [29]. Even though therapists have clinical experience in both, we still developed a set of standard assessment rules and provided centralized training to those responsible for assessment to ensure that their assessment results are highly consistent.

Plans to promote participant retention and complete follow-up {18b}

Patients who complete the standard 3-week treatment and assessment protocol will be considered to have completed the trial, and subsequent assessments will be conducted during follow-up. To minimize patient dropout, we aim to accommodate inpatient treatment needs and cover travel expenses for outpatient participants. Throughout the trial, the recruiting physician will maintain communication with patients via WeChat to address any problems they may encounter.

Data management {19}

Data collection includes paper CRF forms and an ACCESS-based database. The assessing therapist will evaluate and videotape the patient's function as required, with evaluation forms securely stored in a designated cabinet. Two data entry clerks will perform double data entry weekly, followed by joint consistency checks of the two data sets. Data backups will be conducted after each entry, with backup dates noted for reference.

Confidentiality {27}

Patient personal information is strictly confidential and accessible only to those essential for study participation. CRF forms will separate personal information from evaluations. Apart from the recruiting physician who fills in personal information, other study personnel can only access patient identification numbers. The database is installed on a specific computer and password protection, limiting access to the principal investigator and data entry personnel.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

N/A. This study does not involve the collection of human samples.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

The main indicator in this study is ARAT, with secondary indicators including FMA-UL, MBI, and MST. Previous studies have shown that these indicators follow a normal distribution; thus, they are expressed as mean ± standard deviation, and the independent sample *t*-test is used to compare their differences.

The case distribution analysis is as follows: describe drop-out and excluded cases. Compare the differences in dropout rate and rejection rate between the two groups to see if there is any statistical significance. All scales will be tested for normality first to determine whether they conform to the normal distribution; for data that conforms to the normal distribution, it is expressed as the mean ± standard deviation; for binary data that does not conform to the normal distribution, it is expressed as a percentage; for multi-categorical data and other data that do not conform to the normal distribution, use the median (quartile) representation. The comparability analysis is as follows: first compare the initial situations of the two groups to ensure that the two groups are comparable. For data that conforms to normal distribution and homogeneity of variances, two independent samples *t*-test will be used to compare whether there are differences between the two groups. For data that do not conform to the normal distribution or homogeneity of variances, such as gender and other two-category data, the chi-square test or the exact probability method is used; for multi-category data and other data, the Wilcoxon rank sum test is used to compare the differences between the two groups. If a comparison of a variable at baseline between the two groups was statistically significant and clinically significant, that variable was included in the analysis as a covariate. The efficacy analysis is as follows: for data that conform to normal distribution and homogeneity of variances in the primary and secondary indicators, *t*-test is used to compare whether the difference between the two groups before and after treatment is statistically significant. For hierarchical data with non-normal distribution or uneven variance, the Wilcoxon rank sum test was used for analysis. The safety analysis is as follows: chi-square test or exact probability method was used to compare the incidence of adverse events and adverse reactions between the two groups.

fNIRS data preprocessing and analysis

After data collection, the FC-NIRS software is used for data quality control. Data exhibiting unprocessable abnormal fluctuations or with a signal-to-noise ratio lower than 20 dB will be removed [30]. For resting state data, FC-NIRS is used for data preprocessing (including data conversion, head motion correction, and bandpass filtering) and correlation analysis. For task state data, the NIRS_SPM toolbox based on Matlab is used for activation analysis, the Homer2 toolbox is used for data preprocessing and block averaging, and then the self-written code is used to calculate the eigenvalues [31]. Statistical analysis is performed using self-written code and SPSS, and data visualization is performed using the Origin software and the Matlab-based BrainNet toolbox [32, 33].

Interim analyses {21b}

No interim analyses are planned for this study.

Methods for additional analyses (e.g., subgroup analyses) {20b}

No subgroup analyses are planned for this study.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Missing values for the scale assessment at 3 weeks of treatment will be filled using the mean of the before and after values. Missing values for scale assessments after 3 weeks will not be included in the data analysis directly. The missing values of the channels in fNIRS will be filled using the mean value of the surrounding channels, and the missing data of a single time will be directly eliminated.

Plans to give access to the full protocol, participant-level data and statistical code {31c}

All data will be shared on the Chinese clinical trial registration website within 3 years after the trial ends.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The qualified chief physician and deputy chief physician will coordinate the entire trial, including the patient's routine treatment and clinical trial procedures, and address any arising issues. The principal investigator is responsible for overseeing the overall conduct of the trial. Tongji Hospital Affiliated with Tongji University has a professional clinical trial data analysis team independent of the research team. They will provide and execute a statistical analysis plan before the end of the study.

Composition of the data monitoring committee, its role and reporting structure {21a}

Due to the study's simplicity, a data monitoring committee is not required. The data analysis team and ethics committee of Tongji Hospital Affiliated with Tongji University will evaluate the data collection status of the trial every year.

Adverse event reporting and harms {22}

Adverse events will be monitored throughout the trial. Recruiting physicians are primarily responsible for adverse events. When evaluators, therapists, or other personnel discover an adverse event in a patient, they will first perform necessary emergency treatment and notify the recruiting physician. Physicians will then report adverse events to the principal investigator and the ethics committee. The principal investigator needs to report specific adverse events and circumstances to the ethics committee, and recruiting physicians must accurately record adverse events in the CRF form.

Frequency and plans for auditing trial conduct {23}

The Clinical Research Center of Tongji Hospital Affiliated with Tongji University will require the research team to submit a research progress report at the end of each year. The report needs to describe in detail the progress of the current research (excluding specific data), adherence to the research plan, and any necessary plan adjustments.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

The principal investigator will evaluate the trial's progress and submit protocol revision applications, if necessary, to the ethics committee. The revised plan can only be implemented after review by the ethics committee. When there are major changes to the protocol, all researchers need to re-verify the details.

Dissemination plans {31a}

The protocol of this study will be registered with the China Clinical Trial Registry and will be accessible to everyone. The main results will be published in peer-reviewed academic journals and shared with the academic community through conferences and seminars. Each subsequent paper will need to be reviewed by the researchers before publication to determine its authenticity and scientificity. In addition, we plan to write an easy-to-understand summary and share it with all participants so that they can better understand the findings

and significance of the study. We will organize seminars to invite patients and relevant interest groups to participate in discussing the significance and application of the research results. All data will be uploaded to the National Medical Research Registration and Filing Information System (www.medicalresearch.org.cn) in accordance with the policy, and other researchers can apply for data sharing by email to the project leader. The fNIRS data collected in this study will be released in a public data set for everyone to use after removing private information.

Discussion

The construction of circuits and networks in the injured brain is an important way to promote functional recovery. With the development of non-invasive neuromodulation technology, especially TMS technology, targeted stimulation of focused targets in circuits and networks has attracted increasing attention [34]. Use neuroimaging and electrophysiological techniques to calculate the conduction time from the upstream and downstream targets to the target. On this basis, we sequentially intervene in the upstream and downstream targets to form paired stimulation of electrical activity in the target area, thereby improving circuit function. It is a frontier method of non-invasive neuromodulation. The increase and reorganization of sensorimotor circuit function is a potential method to promote the rehabilitation of upper limb motor function after stroke [35]. Combining magnetic stimulation at both central and peripheral areas is being explored as an exploratory treatment, showing promising results. Yan Jingjing et al. conducted a controlled clinical trial on peripheral sham stimulation and compared the clinical efficacy of central magnetic stimulation alone (20 Hz) and peripheral magnetic stimulation (8 Hz) combined with central magnetic stimulation [36]. It was observed that central repetitive magnetic stimulation and central combined with peripheral repetitive magnetic stimulation improved the motor function of stroke patients' limbs and their ability to perform activities of daily living. In another study, the treatment model of central combined with peripheral repetitive magnetic stimulation was more effective in treating post-stroke motor dysfunction. Similar results have been identified in multiple studies [37–39]. For instance, Xu et al. demonstrated that unpaired peripheral combined central magnetic stimulation can better promote neurological recovery. In terms of animal research, multiple studies have confirmed that magnetic stimulation of non-injured areas can inhibit inflammation in the injured area, promote synaptic functional remodeling in the injured area, and thereby improve motor function [40–43]. While this finding is based on an animal model of spinal cord injury, it suggests that peripheral nerve stimulation may also benefit stroke recovery. This stimulation, applied through nerve pathways, could potentially improve the damaged tissue environment in the stroke area by promoting regeneration and remodeling. Provide evidence support for touch remodeling. On this basis, the high-frequency magnetic-magnetic paired associated stimulation mode formed by combining unpaired peripheral combined central magnetic stimulation and the classic PAS mode may have the advantages of both.

As described in the classic rehabilitation treatment technique "forced movement therapy," the rehabilitation of a specific motor function must suppress the excitability of other muscles that may affect the execution of this movement. Fine motor rehabilitation related to hand function follows the same principle. Traditional central magnetic stimulation aimed at improving motor function broadly activates the entire primary motor cortex. While this can help, it lacks the precision to specifically target the smaller muscles crucial for hand function. The magneto-magnetic PAS mode stimulates the wrist nerve and forms a Hebbian connection with the primary motor cortex corresponding to the nerve, which can only enhance the circuit function of controlling the small muscles of the hand without enhancing the circuit function of other muscles of the upper limb. This may be an effective approach of fine motor rehabilitation. On this basis, task-oriented hand function training is utilized to strengthen task-related circuit functions thereby obtain high selective circuit enhancement.

In summary, the recovery of fine hand movements in stroke motor rehabilitation is currently a clinical focus and challenge. Although TMS can promote the recovery of motor functions, it does not sufficiently recover fine functions. This may be because the TMS technology currently used in clinical applications mainly focuses on improving the down-transmission function of movement, while ignoring the importance of sensory up-loading. The integrated function of the sensorimotor circuit is an important basis for fine motor recovery. High-frequency magnetic-magnetic PAS technology shows potential for enhancing fine motor rehabilitation in stroke patients. By merging sensory and motor stimulation, it facilitates the recovery of the sensorimotor loop while harnessing the excitability-enhancing effects of high-frequency TMS. Nonetheless, further research is warranted to comprehensively elucidate its efficacy and the underlying mechanisms involved.

Trial status

Protocol version number and date: February 20, 2024,Version 1.0.This study will begin recruiting subjects on May 1, 2024, and is expected to complete recruitment on May 1, 2025.

Abbreviations

PAS	Paired associated stimulation
FMA-UL	Fugl-Meyer assessment-upper limbs
MBI	Modified Barthel Index
MTS	Modified Tardieu scale
fNIRS	Functional near-infrared spectroscopy
MEP	Motor evoked potential
SEP	Somatosensory evoked potential
CSP	Cortical resting period

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Not applicable.

Authors' contributions {31b}
GYZ, HS, and DSX devised the study question and design. GYZ and SPW are the main writers of the manuscript. YHC provided support in the clinical study execution details and ethical review materials. GDZ provides experience in rehabilitation patient management. Others are responsible for assessment and treatment. All authors read and approved the final manuscript.

Authors' information
Previous research by DSX's team mainly focused on the clinical efficacy and basic mechanisms of peripheral magnetic stimulation and unpaired peripheral combined central magnetic stimulation and has good clinical trial foundation and theoretical knowledge. GYZ and DSX wrote the "*Expert Consensus on Peripheral Combined Central Dual Target Magnetic Stimulation to Promote Rehabilitation of Motor Dysfunction in Stroke.*"

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Availability of data and materials {29}
After the trial is completed and the article is published, the data can be obtained from the Chinese Clinical Trial Registration Platform or from the author.

Declarations

Ethics approval and consent to participate {24}
The research protocol, informed consent form, participant qualifications, etc., of this study have been reviewed by the Ethics Committee of Tongji Hospital Affiliated to Tongji University ((Tong) Ethical Review No. 2024–031), and the implementation of the trial was approved. All of the enrolled participate had signed a written informed consent form.

Consent for publication {32}
Personal photos used in this article were obtained with permission. At the same time, we added mosaic to the face to avoid the leakage of personal information. The participant information materials and informed consent form are available from the corresponding author on request.

Competing interests {28}
The authors declare that they have no competing interests.

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