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Does the alternating timing of rTMS combined with soft-hand rehabilitation robot affect the recovery of hand function in patients after stroke? A study protocol for a multicentre randomised controlled trial

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ABSTRACT

Introduction Combining repetitive transcranial magnetic stimulation (rTMS) with robotic training could result in more significant improvements in motor function than either treatment alone. The efficacy of this combination may depend on the sequencing of the interventions. However, few studies have explored the possibility of interleaving or alternating between the two treatment modalities within a single session or over a shorter time frame. The objective of this study is to evaluate the efficacy of alternating rTMS and soft-hand rehabilitation robot therapy to enhance upper limb and hand function in patients with ischaemic stroke.

Methods and analysis This multicentre study will be conducted as a single-blind, controlled, randomised trial, enrolling 132 post-stroke patients with a disease duration ranging from 1 week to 3 months. The study participants will be randomly assigned to group A (n=44), group B (n=44) and group C (n=44). All participants will undergo a 4-week neurological rehabilitation programme, which includes standardised physical and occupational therapy administered by experienced therapists. Group A will receive 10 Hz high-frequency rTMS (HF-rTMS) over the ipsilesional primary motor cortex (iM1) for 20 min, followed by 20 min of soft-hand rehabilitation robot training. Group B will receive 5 min of 10 Hz HF-rTMS over the iM1 followed by 5 min of soft-hand rehabilitation robot training, repeated four times. Group C will receive sham rTMS with other parameters identical to those of group A. The above treatments will be administered once daily, 5 days a week, for 4 weeks. The primary outcome measurement is the Fugl-Meyer assessment of upper extremity (FMA-UE). The secondary outcome measurements include the Hong Kong edition of Functional Test for the Hemiplegic Upper Extremity (FTHUE-HK), the Modified Ashworth Scale (MAS), and the International Classification of Functioning, Disability and Health upper extremity entries (ICF-Upper Extremity Entries). Assessments will be conducted at baseline and after 4 weeks of treatment.

Ethics and dissemination This study has been approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (2024-SR-515). The findings of this study will be spread through networks of scientists, professionals and the general public, as well as peer-reviewed scientific papers and presentations at pertinent conferences.

Trial registration number ChiCTR2400089583.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This will be a multicentre, single-blind, controlled, randomised clinical study to identify optimal strategies for integrating repetitive transcranial magnetic stimulation (rTMS) and robotic interventions in neurorehabilitation.
⇒ We will use stratified block randomisation, stratifying by centre and then applying block randomisation within each centre.
⇒ Additionally, various outcome assessments will be included to compare the effectiveness of alternating treatments combining rTMS with soft robotic glove (SRG) to conventional therapy involving rTMS and SRG in enhancing hand function recovery among post-stroke patients.
⇒ Due to the nature of TMS intervention, blinding the operator is not feasible.

INTRODUCTION

Stroke is the second-leading cause of death globally,[1] and statistics from 1990 to 2019 reveal that the absolute number of stroke incidents worldwide has surged by 70%, while disability-adjusted life years attributed to stroke have increased by 32%.[2] Ischaemic stroke accounts for 87% of all stroke cases, with its incidence continuing to rise annually.[3] Moreover, over 80% of stroke survivors

experience upper limb motor dysfunction,[4] and the decline in hand function is particularly significant. Approximately 67% of patients who had a stroke with complications remain unable to use their hands even 4 years after the stroke onset,[5] greatly affecting their daily activities and quality of life. Therefore, rehabilitation of hand function remains a central challenge in poststroke motor recovery. Currently, conventional clinical interventions for enhancing upper limb hand function poststroke encompass constraint-induced movement therapy, non-invasive brain stimulation techniques, neuromuscular electrical stimulation, upper limb robotics and virtual reality therapy.[6] In practical healthcare settings, to optimise treatment outcomes, comprehensive rehabilitation strategies are frequently employed. These strategies may involve combining exercise therapy with neuromuscular electrical stimulation or integrating upper limb robotic-assisted therapy with non-invasive brain stimulation. Non-invasive brain stimulation techniques combined with hand function training have been found to improve motor recovery in patients who had a stroke.[7] This combination enhances neuroplasticity and functional outcomes, making it a promising approach for rehabilitation.[8]

Repetitive transcranial magnetic stimulation (rTMS) is a widely used non-invasive brain stimulation technique. In the brain, induced currents generated by a magnetic field activate neurons in the cortical and subcortical regions, leading to neuronal depolarisation.[9] Previous studies have shown that applying high-frequency rTMS (HF-rTMS) to the ipsilesional primary motor cortex (iM1) has positive effects on improving motor function in the affected hand and upper limb after stroke.[10] rTMS can significantly enhance the connectivity between brain networks, reduce the intensity of the island area,[11] decrease infarct volume and apoptosis[12] and effectively regulate the local neuroplasticity of the stimulated region. It can also play a crucial regulatory role in targeting both local and distant brain regions, as part of a tightly connected cortical and subcortical network.[13]

Additionally, hand function training is crucial for patients who had a stroke. Modulating the excitatory inputs of neurons within the body's neuroreflex loop can accelerate the reorganisation and plasticity of brain function, thereby promoting motor function recovery.[14] Soft robotic glove (SRG) enhances brain sensorimotor function by providing various environmental stimuli, including sensory, motor and postural cues, along with repetitive skill learning.[15] This approach effectively enhances the sensorimotor plasticity and interhemispheric inhibition between the cerebral sensorimotor cortex, allowing the brain to undergo functional adaptive changes after focal injury.[16] A meta-analysis confirmed the benefits of SRG in stroke rehabilitation. Compared with traditional rehabilitation methods, SRG-based rehabilitation has both immediate and long-term effectiveness in promoting limb function in poststroke hemiparesis patients.[17] Nasrallah *et al*[18] used task-based and resting-state functional MRI to explore changes in brain networks in patients who had a stroke with hemiplegic upper limb after SRG therapy. Their findings indicate that continuous passive motion exercise in bimanual exercise can activate the primary motor area and supplementary motor area (SMA) in the poststroke brain and increase the connectivity of the supramarginal gyrus and SMA within the somatosensory network and salience network, which can significantly improve the stroke survivors' motor control ability, thereby promoting motor function recovery.

Taken together, both rTMS and exercise training promote neural plasticity and contribute to brain network remodelling. Therefore, combining rTMS with exercise training could have a synergistic effect, enhancing their individual therapeutic benefits.[19] In recent years, the rehabilitation concept of 'central-peripheral-central' has gained popularity in stroke treatment. Jia[20] introduced the closed-loop theory, which integrates central and peripheral interventions to form a positive feedback loop, promoting motor function recovery in patients who had a stroke. Yang *et al*[8] demonstrated the significant advantages of HF-rTMS combined with grip training in improving hand function and upper limb motor function in patients who had a stroke. Most evidence indicates that rTMS combined with physical exercise is the optimal strategy for regulating cortical plasticity and improving motor function in patients after stroke.[19] However, the efficacy of this combination may depend on the timing, intensity and sequencing of the interventions.

Most research on the sequencing of rTMS and robotic intervention has primarily focused on the alternating application, encompassing either rTMS followed by robotic therapy or vice versa, as well as simultaneous implementation of these treatments.[21] This approach aims to determine the most effective order of treatments for enhancing motor recovery. However, few studies explore the possibility of interleaving or alternating between the two treatment modalities within a single session or over shorter time frames. There is one study to date that has explored an alternating treatment strategy combining rTMS intervention with upper limb motor function training by Chang *et al*.[22] They conducted a study involving 21 patients who had a stroke randomly divided into two groups. Both groups received 10 Hz HF-rTMS or sham rTMS for 5 s, followed by sequential finger training for 50 s with a 5 s rest period. The results indicated that this alternating treatment strategy may induce modulatory effects in the motor network by increasing activation of cortico-basal ganglio-thalamocortical circuits, thereby enhancing motor performance. Despite the promising results of these combined intervention protocols, further investigation is needed to determine the optimal time window for their implementation.

Interleaving rTMS and robotic interventions could potentially offer several advantages. However, few clinical trials have investigated the combination timing of rTMS and physical exercise, and there is a particular lack of large-sample and multicentre randomised controlled clinical trials (RCT), which could provide a

deeper understanding of the potential synergistic effects. Hence, this multicentre RCT aims to compare the effectiveness of alternating treatment combining rTMS with SRG to conventional therapy involving rTMS and SRG in enhancing hand function recovery among poststroke patients, to explore these combined approaches and identify optimal strategies for integrating rTMS and robotic interventions in neurorehabilitation. We hypothesise that the alternating treatment combining rTMS with SRG can promote the recovery of hand function after stroke, and the alternating treatment combining rTMS with SRG is superior to the conventional therapy involving rTMS and SRG in enhancing hand function recovery among poststroke patients.

METHODS AND ANALYSIS

This study is a multicentre, single-blind, controlled, randomised clinical trial with three groups (A, B and C).

Study setting

Recruitment for this study will begin on 1 October 2024 and is expected to be completed by 4 March 2026. The study itself will start on 1 October 2024 and is anticipated to conclude by 1 June 2026. Participants will be recruited from the First Affiliated Hospital of Nanjing Medical University, Zhongda Hospital Southeast University, the Affiliated Huaian Hospital of Xuzhou Medical University, the First People's Hospital of Lianyugang and Jiangsu Shengze Hospital. All of these centres are hospitals that provide inpatient services and are well-equipped with the necessary medical and rehabilitation facilities to support the treatment of participants.

Patient and public involvement

Patient and public involvement (PPI) groups will be engaged in both the design and management of this study. During the study design phase, PPI representatives will help refine the research question and ensure that the study's aims are relevant to the patient population. They will also contribute to the development of the study protocol, offering insights on inclusion criteria, patient recruitment strategies and participant burden.

Recruitment

Participants will be identified from the patient records of the five subcentres. Eligible patients will be identified through admission records, based on predefined inclusion and exclusion criteria. The hospital staff, including physicians and research coordinators, will screen patient records to identify potential participants who meet the eligibility requirements for this trial. Before the trial, detailed information about the research project will be provided to potential participants. After patients voluntarily sign the informed consent form, they will be enrolled in the trial. The improvement of adherence relies on adequate communication before enrolment, ensuring that participants fully understand the significance and responsibilities of this study and volunteer to participate. In addition, participants will receive reminders about treatment schedules, and research staff will address any barriers to participation. Adherence will be tracked using a checklist, and any missed sessions will be followed up to ensure continued participation. All eligible participants will be randomly assigned (1:1:1) to group A (n=44), group B (n=44) or group C (n=44).

Participants

Inclusion criteria

The inclusion criteria are as follows: (1) ischaemic stroke confirmed by CT and/or MRI, meeting the diagnostic criteria for cerebral infarction in the cerebrovascular disease; (2) primary or unilateral onset, or previous onset without residual neurological dysfunction; (3) stable vital signs and clear consciousness; (4) age between 40 and 70 years; (5) disease duration ranging from 1 week to 3 months; (6) Brunnstrom stage of hemiplegic upper limb and hand between I and III; (7) absence of cognitive dysfunction; (8) the selected candidate or their relatives sign the informed consent form.

Exclusion criteria

The exclusion criteria are as follows: (1) history of epilepsy, family history of epilepsy or taking medications that cause seizures; (2) severe deficits in cognition and communication that impede patient participation during evaluation and therapy; (3) posterior circulation infarction; (4) presence of a pacemaker or intracranial metal implants; (5) severe cervical spondylosis, including severe cervical stenosis and cervical spinal instability; (6) complete occlusion of the internal carotid artery; (7) direct injuries or skull defects in the stimulation area; (8) women during pregnancy.

Sample size

The sample size was estimated using PASS V.15.0 software to evaluate the impact of alternating treatment combining rTMS with SRG on functional motor performance of the upper extremities, with Fugl-Meyer assessment of upper extremity (FMA-UE) as the primary outcome. Based on previous studies that reported a minimal clinically important difference for upper extremity motor recovery in patients who had a stroke, a margin of superiority of 13 points in the FMA-UE score was considered to represent a clinically meaningful improvement.[23] Within 4 weeks, the sample size is expected to reach a statistical power of 80% at the significance level of 0.05 (two-sided test). Considering a 20% loss to follow-up rate, the sample size was calculated to be 132 participants (44 participants in each group).[8]

Randomisation and blinding

After the inclusion/exclusion criteria are checked, patients will be allocated to one of the three intervention groups (Group A, Group B or Group C) by using a computer-generated randomisation sequence with random-sized permuted blocks of either 6 or 12, which

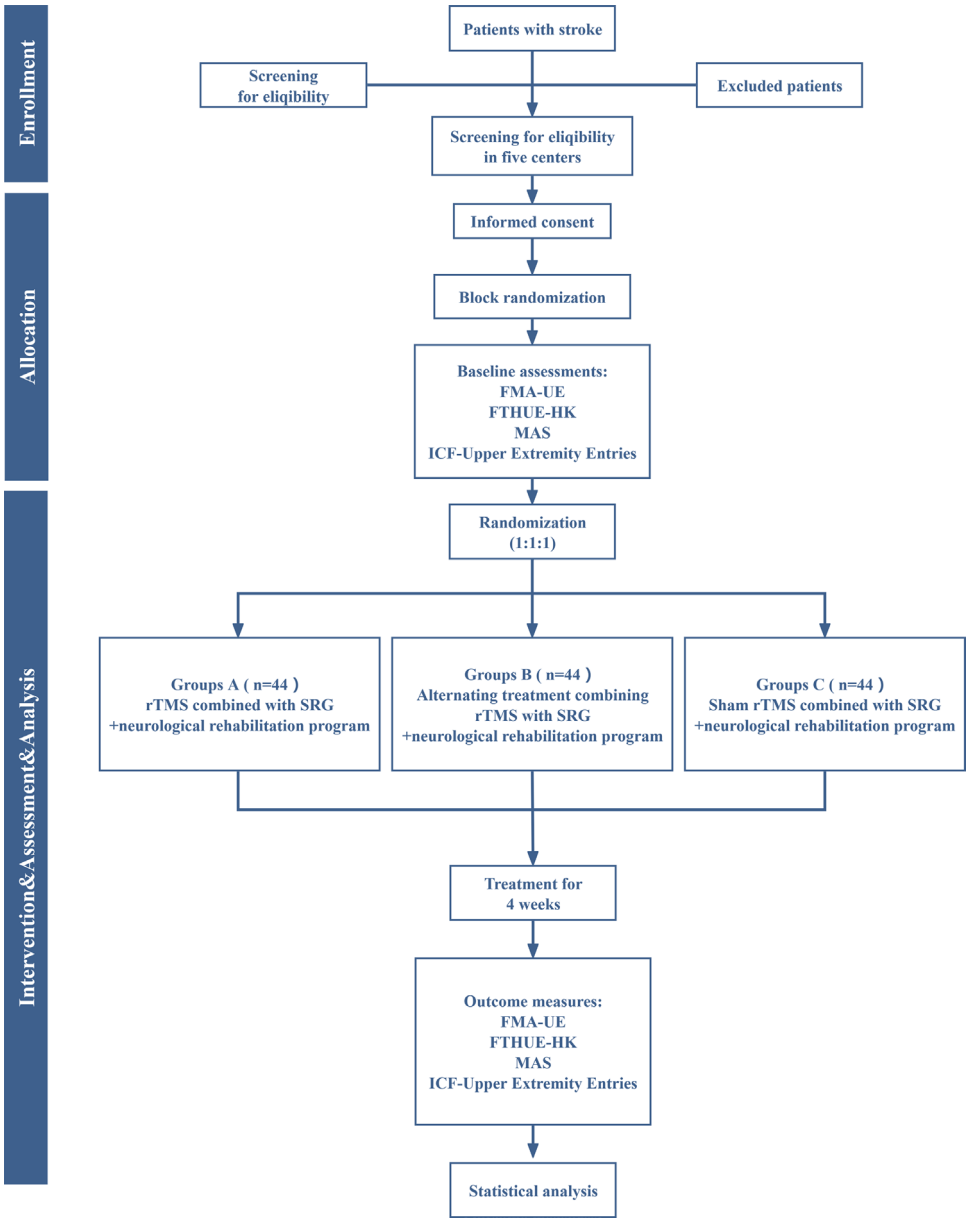

Figure 1 Experiment flowchart. FMA-UE, Fugl-Meyer assessment of upper extremity; FTHUE-HK, Hong Kong edition of Functional Test for the Hemiplegic Upper Extremity; ICF-Upper Extremity Entries, International Classification of Functioning, Disability and Health upper extremity entries; MAS, Modified Ashworth Scale.

remains unknown to the investigators and with stratification for site. Randomisation will be supervised by a researcher to ensure protocol adherence. Throughout the trial, subjects will be identified by codes instead of real names. Due to the nature of the intervention, neither patients nor clinical investigators can be blinded to the treatment allocation. Assessors and statisticians will remain blinded, conducting independent assessments and data analyses (figure 1).

Intervention

In addition to the treatment components specific to this study, all participants will undergo a 4-week neurological rehabilitation programme, which includes standardised physical and occupational therapy administered by experienced therapists, including stretching, joint range-of-motion exercises, neuromuscular electrical stimulation and activities of daily living training. Treatments will be administered once daily, 5 days a week, over a period of 4 weeks, totalling 20 sessions.

The relevant period segments of the experiment are shown in figure 2.

Determination of the resting motor threshold

Each patient will sit comfortably in a recliner with their hands resting relaxed on a pillow. rTMS will be applied with the MTS F10R magnetic stimulator (Reseader Medical Technology Co., Ltd., China, peak magnetic field=7T). The centre of the figure-of-eight-shaped coil will be positioned tangentially over the contralesional primary motor cortex, with the handle positioned at 45° from the sagittal plane. Surface electromyography data

	Study Period					
	Enrollment	Allocation	Post-allocation			
TIME POINT	W-1	0	W1	W2	W3	W4
ENROLLMENT:						
Eligibility screen	×					
Informed consent	×					
Randomization	×					
Allocation		×				
INTERVENTIONS:						
Group A: HF-rTMS over iM1 20min+SRG training 20min			←	—	—	→
Group B: HF-rTMS over iM1 5min+SRG training 5min , repeat 4 times			←	—	—	→
Group C: sham HF-rTMS over iM1 20min+SRG training 20min			←	—	—	→
ASSESSMENTS:						
FMA-UE	×					×
FTHUE-HK	×					×
MAS	×					×
ICF-Upper Extremity Entries	×					×

Figure 2 Schedule of participant enrolment, interventions and assessments. FMA-UE, Fugl-Meyer assessment of upper extremity; FTHUE-HK, Hong Kong edition of Functional Test for the hemiplegic upper extremity; HF-rTMS, high-frequency repetitive transcranial magnetic stimulation; ICF-Upper Extremity Entries, International Classification of Functioning, Disability and Health upper extremity entries; iM1, ipsilesional primary motor cortex; MAS, Modified Ashworth Scale.

from the abductor pollicis brevis on the uninjured side will be collected, and the potential difference between the highest peak and lowest peaks will be measured as the motor-evoked potential (MEP). The resting motor threshold (RMT) is defined as the minimal intensity required to elicit at least 5 out of 10 MEPs in a relaxed target muscle with amplitudes>50 µV.[24 25]

rTMS application and SRG training

The intervention will use the multi-modal intelligent hand rehabilitation robot controlled by central-peripheral closed loop (Reseader Medical Technology Co., Ltd., China). The device is an integrated machine, which can realise the alternating or interleaving treatment of rTMS combined with SRG.

rTMS treatment will be administered using the MTS F10R magnetic stimulator (Reseader Medical Technology Co., Ltd., China, peak magnetic field=7T). According to the latest safety recommendations,[26] the stimulation frequency will be 10 Hz and the stimulation intensity will be 90% of the RMT during the treatment. The centre of the figure-of-eight coil will be positioned over the iM1, and each stimulation will last for 1 s, with 5 s intervals. A total of 2000 pulses will be delivered during the 40 min treatment session.

SRG training will be conducted using the RSD R10P Reshow Hand Trainer (Reseader Medical Technology Co., Ltd., China). The SRG is powered by pneumatic pressure to drive hand movement. The entire device consists of pneumatic gloves and a control interface, connected by pneumatic cables to ensure smooth and accurate operation. During the treatment process, the system will guide the subject to perform passive grasping exercises of the affected hand according to the preset parameters. The duration of each grasp will be 15 s, followed by a 5 s rest. Subjects will complete 60 cycles of grasping exercises during the 40 min treatment session.

Combining rTMS and SRG training

For Group A, 2000 pulses of 10 Hz HF-rTMS at 90% RMT will be applied over the iM1 for 20 min. After preconditioning with rTMS, the patients will perform SRG training for 20 min.

For Group B, 500 pulses of 10 Hz HF-rTMS at 90% RMT will be applied over the iM1. This train will be repeated four times with a 5-min intertrain interval, delivering a total of 2000 pulses during the 40-min session. During each intertrain interval, patients will perform SRG training for 5 min. A total of 20 min will be devoted to SRG training during the 40 min session.

Group C will receive rTMS with the sham coil, using the same parameters as Group A. All patients will receive routine rehabilitation training.

Outcome assessment

Outcome measures will be assessed at baseline (prior to the intervention) and post-treatment (after the 4 week intervention), including both primary and secondary measures.

Primary outcome

FMA-UE[27] assesses the performance-based motor function of the affected upper extremity. It comprises 9 main items and 33 subitems. Each item is scored on a scale of 0–3, with a total score of 0 (no activity) to 66 (normal active activity). Higher scores indicate lower motor impairment.

Secondary outcome

FTHUE-HK[28] consists of 12 test items with seven functional levels to assess the overall upper extremity function. Higher levels indicate better motor function of the upper extremity and a stronger ability to use the upper limbs in daily activities.

MAS[29] is one of the most commonly used clinical tools for assessing increased muscle tone after central nervous system lesions, expressed by measuring the resistance of muscles to passive movement when the full range of joint motion is completed in 1 s. There are five grades: 0, 1, 1+, 2, 3 and 4. Grade 0 indicates no increase in muscle tone and grade 4 indicates stiffness.

ICF upper extremity entries[30] include 56 items such as d4400 picking up, d4401 grasping and d4451 pushing. Each item is assessed based on the presence or absence of impairment, and the degree of impairment is rated on a scale of 0, 1, 2, 3, 4, 8 and 9. Scores of 0, 1, 2, 3 and 4 represent no, mild, moderate, severe and complete impairment, respectively. A score of 8 indicates insufficient information to quantify the severity of the problem, while a score of 9 represents not applicable.

Statistical analysis

The primary analysis will follow an intention-to-treat approach, which includes all participants who were randomised, regardless of whether they completed the study or adhered to the treatment protocol. This approach preserves the randomisation process and provides an unbiased estimate of the treatment effect. In addition, a per-protocol analysis will be conducted, which will include only those participants who strictly adhered to the study protocol, completed the intervention as assigned, and did not experience any major protocol violations. This analysis will help assess the effect of the treatment under ideal conditions, when participants fully comply with the intervention.

Subgroup analyses will be conducted based on baseline characteristics, such as age, gender or severity. The decision to conduct these subgroup analyses will be made after reviewing the baseline data.

Statistical analyses will be conducted using R V.4.3.1. The normality of data distribution will be assessed with the Shapiro-Wilk test. Continuous variables will be reported as mean±SD for normal distributions and as median with IQR for non-normal distributions. Categorical variables will be summarised as frequencies and percentages. The χ^2 test will be used to evaluate differences in motor function indices before and after treatment for categorical variables. For continuous variables, analysis of variance will assess treatment effects between groups if normally distributed, while the Kruskal-Wallis test will be used for non-normally distributed variables. A p value of <0.05 will be considered statistically significant. The absence of primary outcome data will be addressed by using baseline data as a reference point and conducting additional sensitivity analyses.

DATA COLLECTION, MANAGEMENT AND MONITORING

Data collection will be carried out by senior attending physicians and therapists, who are independent of the grouping and treatment procedures. They will immediately input the collected data into the designated case report form (CRF). Subsequently, a designated individual will digitise all data, ensuring the use of unique identifiers to protect patient privacy and data security. Pseudonymisation will be applied during data processing to further protect patient identity, ensuring that the data cannot be traced back to individual participants without a separate key.

After digitisation, paper copies will be securely stored in locked filing cabinets at the research site for 5 years as per institutional regulations. Once this period has expired, paper copies will be securely destroyed to ensure patient confidentiality. The electronic database used for data storage will be password-protected and accessible only to authorised personnel. Data access will be granted only to researchers involved in the analysis and oversight of the trial, with access levels assigned based on their role and need to know. All electronic data will be stored in compliance with applicable data protection laws, and encryption will be used to protect sensitive information. Regular backups of the electronic data will be performed to ensure data integrity and security.

The Data Monitoring Committee (DMC) will verify that the clinical trial is conducted, generated, documented and reported in accordance with the protocol's regulatory requirements, the monitoring plan and written standard operating procedures. They will check the consistency, logic and validity of the data by regularly reviewing the collected data, including verifying data entry and storage against predefined criteria and guidelines. They will compare the input data with the source data to confirm its accuracy and consistency. If any anomalies or potential issues are identified, the DMC will investigate and correct them immediately. They may communicate with data collectors, researchers or other interested parties to clarify and resolve issues, ensuring the validity and

reliability of the data. The goal of data monitoring is to minimise data errors and biases and ensure data quality to support accurate data analysis and reliable research conclusions.

HARMS

The intensity, frequency and other parameter settings of the rTMS will adhere to the safety guidelines issued by the International Association for Transcranial Magnetism in 2021.[26] To reduce the likelihood of adverse events, participants will be rigorously screened according to the exclusion and inclusion criteria. Adverse effects and events will be closely monitored during the clinical trial, and if they occur, they will be recorded in the CRF. Certain events will prompt monitoring and discontinuation of treatment if deemed inappropriate, such as exacerbations, serious adverse events, loss of follow-up due to poor compliance or the development of a new serious illness that affects the course of this protocol. This study is being conducted under the supervision of the Hospital Research Ethics Committee. Research progress and any existing issues are reported semiannually, with adjustments made promptly to overcome them.

ETHICS AND DISSEMINATION

Research ethics approval

This study has received approval from the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (2024-SR-515).

Protocol amendments

Protocol amendments will be decided through thorough discussions by the Hospital Research Ethics Committee. On approval by the Chinese Clinical Trial Registry, the modified protocol (V.1.2, dated 2024-07-04) will be implemented.

Consent or assent

Effective adherence improvement requires adequate pre-enrolment communication so participants fully comprehend the study's significance and responsibilities before volunteering. Researchers will provide comprehensive information to all eligible participants, including details on the study's purpose, associated risks, potential benefits and any possible adverse effects. This ensures that participants have a clear understanding of the information. At the same time, participants will be informed of the randomisation process and the possibility of receiving a 'sham' treatment will be explained clearly. The researchers will emphasise that participation in the trial is entirely voluntary, and patients are free to withdraw at any point without affecting their medical care. If a participant chooses to withdraw from the study, they will be informed of the procedure to do so and the potential consequences. Participants are asked to sign an informed consent form only after confirming their full understanding and demonstrating their voluntary participation.

Access to data

Principal investigators and the study statistician will have access to the final dataset. Data distributed to project team members will be anonymised to ensure confidentiality.

Dissemination policy

The findings of this study will be disseminated through scientific networks, peer-reviewed papers and presentations at relevant conferences to scientists, professionals and the general public.

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Contributors YS and HW conceived and designed the study. XW, XL and FL performed the study and collected materials. TZ, QS and JX analysed the results. XW, XC and KC wrote the manuscript. WD, CG and XW helped coordinate the study and reviewed the manuscript. Guarantor is YS. All authors contributed to the article and approved the submitted version.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Consent obtained from parent(s)/guardian(s).

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