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Personalised functional imaging-guided multitarget continuous theta burst stimulation for post-stroke aphasia: study protocol for a randomised controlled trial

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ABSTRACT

Introduction Continuous theta burst stimulation (cTBS), a form of repetitive transcranial magnetic stimulation (rTMS), targeting the language network in the right hemisphere of post-stroke aphasia (PSA) patients shows promising results in clinical trials. However, existing PSA studies have focused on single-target rTMS, leaving unexplored the potential benefits of multitarget brain stimulation. Consequently, there is a need for a randomised clinical trial aimed to evaluate the efficacy and safety of cTBS targeting on multiple critical nodes in the language network for PSA.

Methods and analysis This is a prospective, multicentre, double-blind, two-arm parallel-group, sham-controlled randomised trial. The study will include a total of 60 participants who will be randomly assigned in a 1:1 ratio to either the active cTBS group or the sham cTBS group. Using precision resting-state functional MRI for each participant, we will map personalised language networks and design personalised targets in the inferior frontal gyrus, superior temporal gyrus and superior frontal gyrus. Participants will undergo a 3-week cTBS intervention targeting the three personalised targets, coupled with speech and language therapy. The primary outcome is the change in the Western Aphasia Battery-Revised aphasia quotient score among participants after a 3-week treatment. Secondary outcomes include Boston Diagnostic Aphasia Examination severity ratings, Token Test and the Chinese-version of the Stroke and Aphasia Quality of Life Scale 39-generic version.

Ethics and dissemination The study has been approved by the ethics committees of Affiliated Hospital of Hebei University, Hebei General Hospital and Affiliated Hospital of Chengde Medical University. The findings of this study will be reported in peer-reviewed scientific journals.

Trial registration number The study has been registered on ClinicalTrials.gov (NCT05957445).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This will be the first randomised controlled trial to evaluate the efficacy and safety of continuous theta burst stimulation (cTBS) targeting multiple targets in the language network in patient with post-stroke aphasia.
⇒ The stimulation targets are individually tailored for each participant using precision resting-state functional MRI-based mapping of their personalised language network.
⇒ In addition to participants, research physicians, assessors and statisticians, this study will also strictly blind the transcranial magnetic stimulation operators.
⇒ The outcome measures include not only language functions but also the quality of life.
⇒ The follow-up assessments are limited to 3 weeks and 90 days after the initiation of cTBS treatment, without evaluation at longer time intervals.

INTRODUCTION

Post-stroke aphasia (PSA) is a prevalent condition affecting approximately 30% of stroke survivors, resulting in persistent language impairment or chronic aphasia.[1] PSA significantly impedes a patient's ability to engage independently in daily activities and hinders rehabilitation, placing substantial burdens on patients, families and society. While the speech and language therapy (SLT) currently stands as the primary rehabilitation approach for PSA, the inherent indirectness of behavioural therapies in addressing neurological disorders underscores the pressing need for a more direct and targeted therapeutic strategy to facilitate language recovery post-stroke.

Recent research has spotlit the therapeutic potential of repetitive transcranial magnetic stimulation (rTMS), a non-invasive neurostimulation technique, in PSA patients.[2–4] A specific rTMS form, continuous theta burst stimulation (cTBS), has demonstrated the ability to effectively induce inhibitory effects.[5] Notably, clinical studies have shown promising

results with cTBS targeting the language network in the right hemisphere of PSA patients.[6–9] Furthermore, cTBS has exhibited treatment efficacy comparable to or surpassing that of conventional rTMS, and it has the added benefit of a shorter treatment duration, making it a particularly promising therapeutic paradigm.[10]

The identification of appropriate stimulation targets is a critical determinant of rTMS efficacy in neuromodulation therapy for aphasia. The language network involves critical regions, notably the inferior frontal gyrus (IFG), superior temporal gyrus (STG) and superior frontal gyrus (SFG).[11 12] IFG and STG are commonly chosen for brain stimulation due to their well-established roles in speech production and language comprehension, respectively.[2 3 13–15] The efficacy of targeting either IFG or STG for aphasia treatment has been demonstrated in several studies.[9 16–18] The SFG is crucial in the language network, showing increased task-induced activation during recovery, correlating with language improvements in PSA patients.[19 20] Moreover, SFG was anatomically linked to the IFG via the frontal aslant tract,[21 22] and their functional connectivity also increases during recovery, aligning with enhanced language function.[23] A recent clinical trial by Ren *et al*[11] also demonstrated substantial language improvement in PSA patients following SFG stimulation.

While single-target rTMS has been the focus of existing PSA studies, the potential of multitarget neuromodulation therapy remains relatively unexplored in the PSA, despite its success in addressing other neurological disorders.[24–26] Hence, we propose a multitarget neuromodulation therapy that combines IFG, STG and SFG stimulation to potentially achieve a comprehensive therapeutic effect and enhance language function recovery in PSA patients.

Furthermore, traditional methods of identifying stimulation targets often rely on rules of thumb or anatomical landmarks, which may overlook individual differences in functional organisations and limit the precision of neuromodulation. To address this limitation, we introduce a personalised brain functional sector (pBFS) approach based on precision resting-state functional MRI (fMRI) (rs-fMRI) to map personalised language network for each patient.[27] This approach enables the identification of precise rTMS targets within the personalised language network, taking into account individual functional idiosyncrasies. By integrating the personalised targeting approach with real-time neuronavigation for coil placement guidance, we aim to enhance the neuromodulatory effect on the specific language network of interest.

In summary, the efficacy and safety of the multitarget neuromodulation protocol for patients with PSA is worthy to be evaluated through a randomised clinical trial (RCT).

OBJECTIVES

Accordingly, the primary objective of the clinical trial is to evaluate the efficacy and safety of the personalised functional imaging-guided cTBS targeting the IFG, STG and SFG for enhancing language rehabilitation in PSA patients after 3-week treatment. The secondary objectives of the study are: (1) to evaluate efficacy in language improvements from different aspects at different time points; (2) to evaluate the changes in quality of life at different time points.

METHODS

The trial protocol has been prepared according to the Standard Protocol Items: Recommendations for Interventional Trials statement.[28]

Trial design

This study employs a prospective, multicentre, double-blind, two-arm, parallel-group, sham-controlled RCT in China. Subjects will be allocated randomly in a 1:1 ratio to either the active cTBS group or the sham cTBS group. The flow chart of the study is as follows in figure 1. The overview of the study timeline of enrolment, interventions and assessments is shown in table 1. Recruitment procedures are conducted at three medical centres: The Affiliated Hospital of Hebei University, Hebei General Hospital and the Affiliated Hospital of Chengde Medical University. The Changping Laboratory serves as the trial sponsor and establishes an autonomous data coordinating centre to oversee comprehensive data management.

Participants and recruitment

Participants will be recruited from the inpatient or outpatient departments of the three hospitals mentioned above. Participants must meet all the following inclusion criteria: (1) aged between 35 and 75 years; (2) have a diagnosis of left-hemisphere ischaemic or haemorrhagic stroke,[29 30] with a duration spanning 15 days or more but not exceeding 6 months; (3) first-ever stroke; (4) with aphasia quotient (AQ) of the Chinese version of the Western Aphasia Battery-Revised (WAB-R) less than 93.8; (5) with normal language function before the onset of stroke, with Mandarin Chinese as the native language and a minimum educational level of primary school; (6) able to give informed written consent.

Participants who meet any of the following criteria will be excluded: (1) presence of severe dysarthria (National Institute of Health Stroke Scale (NIHSS) item 10: Dysarthria ≥2 points); (2) aphasia resulting from brain tumours, traumatic brain injury, Parkinson's disease, motor neuron diseases or other conditions; (3) presence of a cardiac pacemaker, cochlear implant or any other implanted electronic device, or contraindications to MRI scans such as claustrophobia or contraindications to TMS; (4) history of epilepsy; (5) presence of severe cardiological, pulmonary, hepatic, renal or other systemic diseases which cannot be managed with conventional medications; (6) presence of a disorder of consciousness (NIHSS item 1(a) ≥1 point); (7) malignant hypertension; (8) severe organic diseases, such as malignant tumours, with an expected survival time

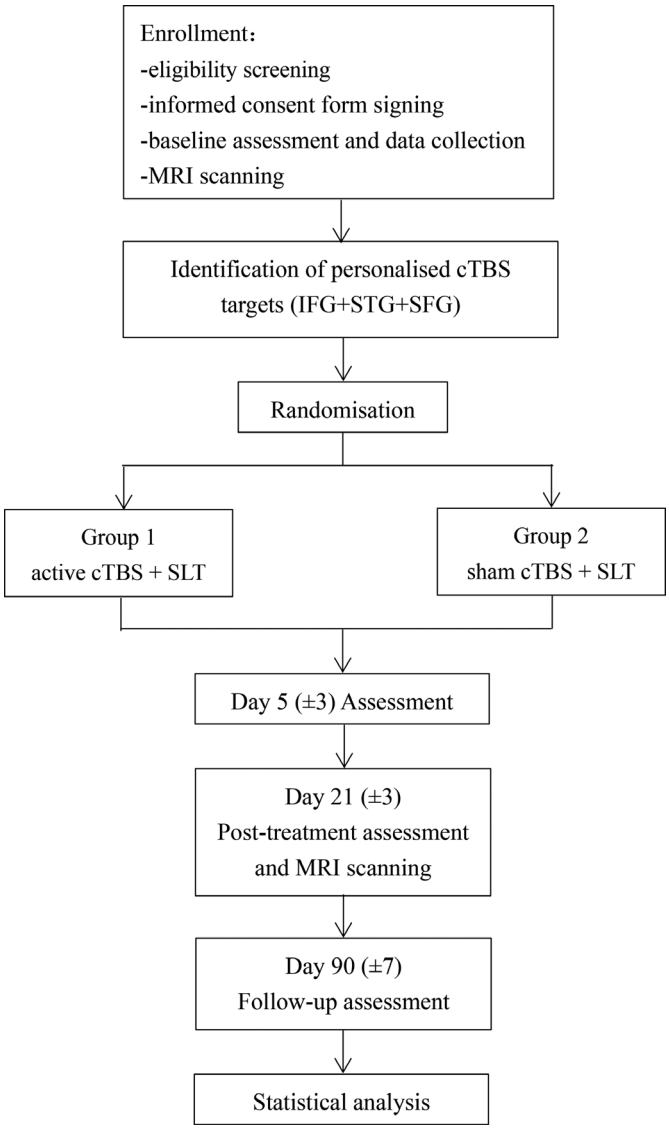

Figure 1 Trial flow chart. cTBS, continuous theta burst stimulation; IFG, inferior frontal gyrus; SFG, superior frontal gyrus; SLT, speech and language therapy; STG, superior temporal gyrus.

of less than 1 year; (9) severe auditory, visual, or cognitive impairments hindering the ability to cooperate with the trial; (10) severe depression, anxiety or other mental disorders potentially hindering trial completion. (11) Receipt of TMS, transcranial electric stimulation or other neuromodulation therapy within 3 months prior to enrolment; (12) history of alcohol abuse, drug abuse or substance misuse; (13) presence of other conditions rendering the individual ineligible for participation, as determined by the investigator; (14) inability to complete follow-up due to geographical or other reasons; (15) women of childbearing age who are pregnant, breast feeding, intending to become pregnant during the trial or at risk of pregnancy; (16) current participation in other clinical trials.

Sample size estimation

In this trial, participants in the treatment group will undergo active cTBS, while those in the control group will receive sham stimulation. The primary outcome for assessment is the difference between the pretreatment and post-treatment WAB-R AQ. Based on prior studies,[31 32] we have conservatively estimated that the treatment group would produce an effect size of 0.9 compared with the control group after a 3-week intervention. To ensure a statistical power of 0.85 with an alpha risk of 0.05 (two-sided), sample size calculations conducted using PASS 21 software have indicated a sample size of 24 participants for each group. Accounting for an estimated dropout rate of approximately 20%, both the treatment and control groups will be expanded to include 30 participants for each, aggregating to a total of 60 participants.

Randomisation

This study will employ a stratified block randomisation with variable block sizes, stratified based on the medical centres. Participants will be assigned in a 1:1 ratio to either the active cTBS group or the sham cTBS group. The randomisation plan will be devised by an independent statistician (WX), using SAS, V.9.4. To uphold the concealment of group allocation, the allocation for each participant will be encased in sequentially numbered opaque envelopes. These envelopes will be preserved by personnel with no involvement in this trial, ensuring the prevention of unauthorised access. At each medical centre, an independent non-blinded researcher will be designated to unseal the envelope corresponding to the serial number on it before the initiation of the treatment. This procedure will be carried out to confirm the random number and the allocated group for each participant.

Blinding

This trial adheres to a double-blind design, ensuring that both participants and essential individuals involved in the trial remain unaware of the treatment conditions. Blinding encompasses a broad spectrum of individuals, including participants, their family members, caregivers, recruiters, research physicians, TMS operators, clinical healthcare professionals, assessors and data analysts.

To ensure the integrity of blinding throughout the trial, blinding requirements have been documented in the informed consent. Moreover, researchers have planned appropriate treatment sessions and follow-up visits to minimise the possibility of participant interactions or communication. Furthermore, a figure-of-eight coil with both active and sham sides has been employed for the cTBS. This coil design ensures that one side administers active stimulation while the other side delivers sham stimulation, with no discernible differences in appearance. In order to choose the correct stimulus side during treatment, unblinded personnel will label each side of the coil with letters ‘A’ or ‘B’. Only unblinded personnel will know which letters correspond to the active or sham stimuli side. Each participant is required to undergo baseline assessment and MRI scanning before randomisation. Blinded imaging data analysts will process the MRI data without knowing the group information. Once the

Table 1 Schedule of enrolment, interventions and assessments

	Study period				
	Screening and allocation	Post-randomisation			Follow-up
Time Point	Day −7~0	Day 1	Day 5 (± 3 day)	Day 21 (±3 day)	Day 90 (±7 day)
Enrolment					
Eligibility screening	×				
Informed consent	×				
MRI scanning	×				
Randomisation	×				
Intervention					
Group1: active cTBS (IFG+STG+SFG)+SLT		←	—	→	
Group2: sham cTBS (IFG+STG+SFG)+SLT		←	—	→	
Assessment					
EHI	×				
NIHSS	×				
WAB-R	×		×	×	×
BDAE severity ratings	×			×	×
Token test	×			×	×
SAQOL-39g	×			×	×
MRI scanning				×	
AEs/SAEs		×	×	×	×

AEs, adverse events; BDAE, Boston Diagnostic Aphasia Examination; cTBS, continuous theta burst stimulation; EHI, Edinburgh Handedness Inventory; IFG, inferior frontal gyrus; NIHSS, National Institute of Health Stroke Scale; SAEs, serious adverse events; SAQOL-39g, the Chinese-version of the Stroke and Aphasia Quality of Life Scale 39-generic version; SFG, superior frontal gyrus; SLT, speech and language therapy; STG, superior temporal gyrus; WAB-R, Western Aphasia Battery-Revised.

individualised cTBS targets for each participant is identified, unblinded personnel will randomise the participants to get the random numbers and groupings corresponding to letters 'A' or 'B'. Then, the unblinded personnel only need to inform the TMS operator whether to use the side 'A' or 'B' of the coil for treatment. Additionally, because only the unblinded personnel know which side of the coil represents the real stimulus, they will measure the participant's resting motor threshold (RMT) using the real stimulus coil side. Unblinding shall be restricted, permissible only in situations where knowledge of the allocation is indispensable for a participant care, such as suspected unexpected serious adverse events (SAE).

MRI scanning

All participants will undergo MRI scanning both before and at the end of the 3-week treatment. Before scanning, investigators will perform a safety check to ensure that participants do not have any contraindications to MRI scanning. Each clinical centre involved in this study uses a 3.0T MRI scanner. To maintain consistency in the acquired image data, all images from the same centre are required to be obtained using the same 3.0T MRI scanner. The scanning sequences include structural images (three-dimensional (3D) T1-weighted (T1w) imaging, 3D T2-weighted (T2w) imaging) and rs-fMRI. For the structural images, the voxel size is 1×1×1 mm and each sequence lasts approximately 6–8 min. For the rs-fMRI, the voxel size is 3×3×3 mm, with a repetition time of 3 s, covering the whole brain, lasting for 6 min per run and five runs, equivalent to 30 min in total. During the scan, the participant will be instructed to keep their eyes closed and maintain a rest state. To minimise the head motion artefacts during the relatively long scanning time, the participants' head will be secured using padding within the head coil. If significant head motion occurs during the scan, the participant should be reminded to stay still and adjustments should be made. If head movement compromises the quality of the data, a rescan should be conducted. Furthermore, to ensure the comfort of the subjects during the scan, noise-reducing earplugs, blankets, small pillows or foam for leg support are available.

MRI data processing

Rs-fMRI data will be processed using pBFS Cloud V.1.0.7 (Neural Galaxy, Beijing). The preprocessing pipeline was developed according to our previously described pipeline[33–35] and has been used in our previous study.[11] The pipeline includes (1) slice timing correction using stc_sess from the FreeSurfer V.6.0.0 software package

(http://surfer.nmr.mgh.harvard.edu), (2) rigid body correction for head motion using mc_sess from FreeSurfer (https://surfer.nmr.mgh.harvard.edu/fswiki/mcsess), (3) normalisation for global mean signal intensity across runs, (4) linear detrending and bandpass filtering (0.01–0.08 Hz) and (5) regression of nuisance variables, including six motion parameters, white-matter signal, ventricular signal, global signal and their first temporal derivatives. Moreover, structural data will be processed using FreeSurfer V.6.0. Surface mesh representations of the cortex from each subject's structural images will be reconstructed and registered to a common spherical coordinate system.[36] The structural and functional images will be aligned using boundary-based registration[37] from the FsFast software package (http://surfer.nmr.mgh.harvard.edu/fswiki/FsFast). Furthermore, the preprocessed rs-fMRI data will be aligned to the common spherical coordinate system via sampling from the middle of the cortical ribbon in a single interpolation step.[38] The rs-fMRI data of each patient will be registered to the FreeSurfer cortical surface template (fsaverage6) that consists of 40 962 vertices in each hemisphere. A 6 mm full-width half-maximum smoothing kernel was then applied to the fMRI data in the surface space. Additionally, the stroke lesion masks will be delineated by experienced radiologists according to both T1w and T2w images.

pBFS mapping

The pBFS will be mapped for each patient, as previously described.[27 39 40] Briefly, the whole cerebral cortex will be parcellated into 213 individualised, fine-grained functional sectors using a population-level functional atlas as the initialisation. To yield individualised functionally homologous pBFS, we will apply a previously reported iterative parcellation strategy based on precision rs-fMRI for each patient.[27] Moreover, a confidence value will be calculated for each vertex to indicate the confidence of assigning the vertex to a specific functional sector relative to other sectors, using the method previously reported.[27]

Personalised stimulation target localisation

Three personalised stimulation targets in the personalised language network will be identified according to the following steps before treatment commencement (figure 2), following a similar procedure previously described.[11] First, the personalised language homologous sectors in the IFG, SFG and STG will be determined in each patient's right hemisphere, according to the pBFS mapping. Second, taking TMS accessibility into account, we fine-tuned the target regions in SFG through anatomical restriction, by using sulcal masking and medial surface masking, to form a candidate area for the optimised target. Finally, the optimised personalised targets were determined through comprehensively considering the functional confidence value and TMS accessibility.

Treatment

All enrolled participants will undergo comprehensive medical and rehabilitation therapies in accordance with well-established clinical guidelines.[29 30 41] These basic treatments will be tailored to the individual conditions and symptoms of each participant. The personalised treatment plans will encompass a comprehensive spectrum of strategies, including neuroprotective measures, management of risk factors, targeted rehabilitation training and specialised nursing care. Each treatment will be recorded, ensuring documentation within the case report form (CRF).

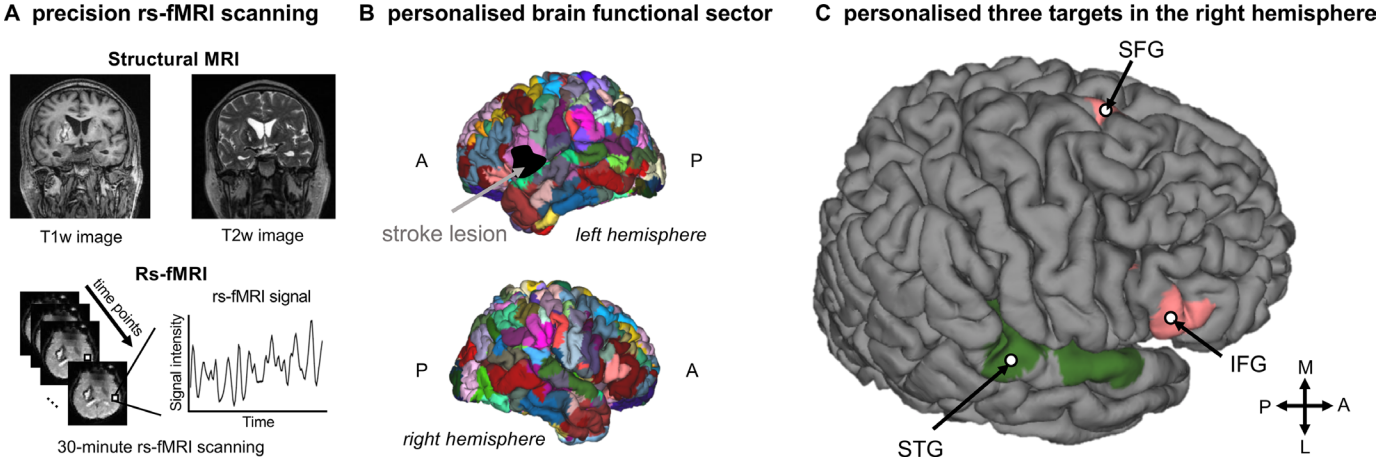

Figure 2 Schematique of personalised TMS targets localisation for language rehabilitation. This figure illustrates the process of localising personalised TMS targets for language rehabilitation, using brain images from a randomly-selected participant with post-stroke aphasia. (A) Participants undergo MRI scanning, which includes both T1-weighted and T2-weighted structural MRI scans and a 30 min resting-state functional MRI (rs-fMRI) scan. (B) The personalised brain functional sector (pBFS) is mapped using precision rs-fMRI. A colour-encoded representation of the pBFS for the representative participant is displayed on lateral views of reconstructed cortical surfaces. The stroke lesion is shown in black on the left-hemisphere cortical surfaces. (C) The language-related functional sectors and their corresponding three personalised targets in the right-hemisphere IFG, STG and SFG are presented on the lateral view of the right cortical surface. A, anterior; IFG, inferior frontal gyrus; L, lateral; M, medial; P, posterior; SFG, superior frontal gyrus; STG, superior temporal gyrus; TMS, transcranial magnetic stimulation.

The cTBS will be delivered using MT20A magnetic stimulator with a neuronavigation system (Neural Galaxy, Beijing), equipped with a figure-of-eight coil integrating both active and sham stimulation. RMT will be determined for each participant by identifying the minimum stimulation intensity over hot spots to evoke a motor-evoked potential larger than 50 µV in 5 of 10 trials over the contralesional first dorsal interosseous muscle. Participants will receive cTBS stimulation pattern (triplet 50 Hz bursts, repeated at 5 Hz; 40 s) at 90% of the right-hemisphere RMT using either the active stimulation in the treatment group or the sham stimulation in the control group. The daily treatment initiates with 600 pulses targeting the personalised target in the right IFG, followed by another 600 pulses targeting the right STG, then the final session concludes with 600 pulses aimed at the right SFG. Then the treatment sequence will be repeated once more 15 min later. Consequently, a total of 3600 pulses will be administered per treatment day. This treatment protocol will be conducted five times per week for 3 weeks, resulting in a total of 15 treatments for each participant. All TMS operators at the medical centres will undergo standardised training and assessment before their participation in the trial. Ensuring a uniform and reliable approach, each participant will consistently receive cTBS intervention from the same designated TMS operator throughout the trial. Following the cTBS treatment, a 30 min session of SLT will be performed by a certified speech-language therapist for each participant.

Outcome measurements

Primary outcome

The primary outcome measure in this study is the change in the WAB-R AQ score among participants before and after a 3-week treatment. The evaluation will be conducted using a Chinese version of the WAB-R. Specifically, the evaluation will focus on the first four subsets of the WAB-R: Spontaneous speech, auditory verbal comprehension, repetition and naming and word finding, which will be aggregated to calculate an AQ, ranging from 0 to 100, with lower 93.8 indicating aphasia. Lower AQ signifies more pronounced language impairments.

Secondary outcomes

In addition to the changes in post-treatment WAB AQ, we will also measure the WAB-AQ in both 5 days and 90 days after the initiation of cTBS treatment as one of the secondary outcomes. Moreover, the assessment of Boston Diagnostic Aphasia Examination (BDAE) severity ratings will be performed 3 weeks and 90 days after the commencement of cTBS treatment. BDAE severity ratings serve as a clinical tool for evaluating aphasia severity. This assessment encompasses four domains: communication abilities, language content, speech sound production and response abilities. Scores range from level 0 to level 5, with lower scores denoting more severe aphasia. Furthermore, the assessment of Token test will be performed 3 weeks and 90 days after the commencement of cTBS treatment. The Token test assesses an individual's comprehension of spoken language and ability to follow instructions. Points are awarded based on task complexity, with the total score ranging from 0 to 36. Higher scores signify superior language abilities. Additionally, an assessment of the Chinese-version of the Stroke and Aphasia Quality of Life Scale 39-generic version (SAQOL-39g) will be performed 3 weeks and 90 days after the commencement of cTBS treatment. SAQOL-39g is a quality-of-life assessment tool that explores the impact of stroke and aphasia on a patient's well-being. This questionnaire comprises 39 items covering domains like communication, physical functioning, mood and social support. Higher scores indicate a higher quality of life, providing valuable insights into the broader impacts of the intervention on participants' overall well-being.

Adverse events and safety

Adverse events (AEs) encompass undesirable medical incidents experienced by participants during a clinical study, irrespective of their connection to the investigated treatment. SAEs include incidents leading to life-threatening conditions, permanent or severe disability, hospitalisation or extended hospital stays. In order to minimise or prevent AEs, SAEs and associated risks related to TMS treatment to the greatest extent possible, we will strictly adhere to the inclusion and exclusion criteria when recruiting participants. Additionally, the TMS operators will strictly follow the standard treatment procedures and the latest safety recommendations outlined in the guidelines.[2 42] Throughout the study, investigators will document all observed, non-leading questions obtained or participant-reported AEs, irrespective of study group affiliation or treatment association. In the event of AEs or SAEs during the trial, investigators will actively conduct scientific and medical judgement, ensuring participant safety through appropriate medical measures. The management of these AEs and SAEs adhere to the guidelines outlined in Good Clinical Practice (GCP), ensuring the ethical conduct and integrity of the clinical study.

Data collection and management

In this study, all data will be collected by professional neurologists and rehabilitation physicians who have been trained in GCP. All data obtained will be documented in the CRFs, along with other study-related documents, will be preserved and managed by designated personnel to ensure their integrity, accuracy and confidentiality. The sponsor, Changping Laboratory, has established an independent data management centre to supervise the data collection process.

Highly trained and qualified investigators will uniformly record clinical data, encompassing demographic information, laboratory test results, MRI images, assessments and AEs/SAEs. In particular, MRI images will be managed following established protocols for collection, de-identification, quality control and backups. Clinical research

associates and data managers will conduct data verification and quality control throughout the trial period.

Participants discontinuing the study will be replaced to maintain a final count of 60 completing the study. Participants' discontinuation after randomisation constitutes dropout, while termination before randomisation is a screening failure. Data collected until withdrawal will remain coded for analysis. Moreover, all participating hospitals and sponsor will be responsible to retain all original study-related records for at least 10 years.

Statistical analysis

Statistical analyses for this study will be executed by independent statisticians employing SAS V.9.4 statistical software. Two-sided tests or a 95% CI will be used, with a significance level of $p<0.05$ indicating statistical significance. The primary analysis will employ the modified intention-to-treat analysis. This approach excludes individuals who (1) did not receive any treatment post-randomisation and (2) were deemed ineligible after randomisation.

Furthermore, to assess treatment efficacy, the study will employ per-protocol (PP) analysis as a sensitivity analysis. PP analysis further excludes participants classified as non-compliance, specifically those with treatment disruptions lasting consecutive 3 days or those unable to complete the treatment within 26 days. These rigorous analytical methods ensure a robust evaluation of the trial's outcomes, aligning with the highest standards of statistical rigour and scientific integrity.

Analysis of baseline characteristics

In this study, participants' demographic and clinical characteristics before treatment will be comprehensively presented through descriptive analysis. Between-group comparisons of baseline indicators will be performed employing specific statistical methods: (1) between-group comparisons for continuous variables will be carried out using either a t-test or Wilcoxon rank-sum test; (2) between-group comparisons for categorical variables will employ a χ^2 test or Fisher's exact test.

Efficacy analysis

As the primary and secondary outcomes used in this trial are repeatedly measured continuous variables, we will adopt linear mixed models to evaluate the efficacy of the intervention.[43] The model incorporates three variables: the groups (0=control group; 1=treatment group), the time variable (with four time points: 0=baseline, 1=5 days of treatment, 2=3 weeks of treatment and 3=90 days after the commencement of treatment), and the interaction term group×time representing the interaction between group and time. The regression coefficient of this interaction term represents the change in language function from day 0 to day 90 for each group, with the control group as the reference. The model can provide the differences in changes of the primary and secondary outcomes between the treatment group and the control group over 5 days, 3 weeks and 90 days, respectively. One of the advantages of this analysis method is its direct inclusion of baseline values when analysing efficacy, eliminating the need for baseline value corrections. Additionally, linear mixed models have the capability to handle missing data.

Safety evaluation

AEs and SAEs will be systematically documented and summarised for analysis. Either a χ^2 test or Fisher's exact test will be conducted to determine if there are any statistically significant differences in the occurrence of AEs and SAEs between the groups.

Compliance analysis

We will record the participants' adherence to treatment compliance rates, which will be divided into two categories: below 80% and 80%–100%. The between-group comparison in compliance will be conducted using χ^2 test.

Current status

The first participant was enrolled on 23 August 2023.

ETHICS AND DISSEMINATION

This study adheres to the principles outlined in the Helsinki declaration, the guidelines of GCP, and has been approved by the ethics committees of the Affiliated Hospital of Hebei University, Hebei General Hospital and Affiliated Hospital of Chengde Medical University. Signed informed consent will be obtained from all participants. The confidentiality rules of participants' information will adhere to the GCP. The research has been registered on ClinicalTrials.gov. JH is responsible for communicating important protocol modifications to relevant parties. The results of this study will be reported through publication in peer-reviewed scientific journals.

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Contributors JH, JR and HL conceived the original idea for the trial, developed the trial design and wrote the manuscript. JH and JR contributed equally to this work. HL is responsible for the overall content as guarantor. WX wrote the statistical analysis plan and revised the manuscript. RP performed technical review. NX has been part of the trial design. All authors read and approved the manuscript.

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Competing interests HL is the chief scientist of Neural Galaxy. Neural Galaxy is not a sponsor of this study. The remaining authors declare no conflict of interest regarding the publication of this work.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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