BMJ Open

# Effects of the intermittent theta burst stimulation on gait, balance and lower limbs motor function in stroke: study protocol for a double-blind randomised controlled trial with multimodal neuroimaging assessments

Guilan Huang ,[1] Hewei Wang,[2] WeiWei Zhao,[1] Yao Qian,[1] Yu Yao,[1] Li Zhang,[1] Yating Chen,[1] Lianxin Song,[1] Jinyu Yang,[1] Zhichao Liu,[2] Bin Su,[1] Limin Sun [2]

**To cite:** Huang G, Wang H, Zhao W, *et al*. Effects of the intermittent theta burst stimulation on gait, balance and lower limbs motor function in stroke: study protocol for a double-blind randomised controlled trial with multimodal neuroimaging assessments. *BMJ Open* 2024;**14**:e082019. doi:10.1136/bmjopen-2023-082019

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2023-082019).

GH, HW and WZ contributed equally.

Received 13 November 2023
Accepted 03 June 2024



For numbered affiliations see end of article.

**Correspondence to**
Professor Bin Su; 13951585359@163.com and Dr Limin Sun; tracy611@sina.com

## ABSTRACT

**Introduction** Approximately, 50% of stroke survivors experience impaired walking ability 6 months after conventional rehabilitation and standard care. However, compared with upper limb motor function, research on lower limbs rehabilitation through non-invasive neuromodulation like repetitive transcranial magnetic stimulation (rTMS) has received less attention. Limited evidence exists regarding the effectiveness of intermittent theta-burst stimulation (iTBS), an optimised rTMS modality, on lower limbs rehabilitation after stroke. This study aims to evaluate the effects of iTBS on gait, balance and lower limbs motor function in stroke recovery while also exploring the underlying neural mechanisms using longitudinal analysis of multimodal neuroimaging data.

**Methods and analysis** In this double-blinded randomised controlled trial, a total of 46 patients who had a stroke will be randomly assigned in a 1:1 ratio to receive either 15 sessions of leg motor area iTBS consisting of 600 pulses or sham stimulation over the course of 3 weeks. Additionally, conventional rehabilitation therapy will be administered following the (sham) iTBS intervention. The primary outcome measure will be the 10 m walking test. Secondary outcomes include the Fugl-Meyer assessment of the lower extremity, Timed Up and Go Test, Functional Ambulation Category Scale, Berg Balance Scale, modified Barthel Index, Mini-Mental State Examination, montreal cognitive assessment, tecnobody balance assessment encompassing both static and dynamic stability evaluations, surface electromyography recording muscle activation of the lower limbs, three-dimensional gait analysis focusing on temporal and spatial parameters as well as ground reaction force measurements, corticomotor excitability tests including resting motor threshold, motor evoked potential and recruitment curves and multimodal functional MRI scanning. Outcome measures will be collected prior to and after the intervention period with follow-up at 3 weeks.

**Ethics and dissemination** The study has received approval from the Medical Research Ethics Committee of Wuxi Mental Health Center/Wuxi Central Rehabilitation Hospital (no. WXMHCCIRB2023LLky078). Results will be disseminated through peer-reviewed journals and scientific conferences.

**Trial registration number** ChiCTR2300077431.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The trial strictly adheres to the principles of randomisation and concealed allocation when grouping patients, thereby minimising confounding factors and selection bias.
⇒ Methodologically, this trial ensures adequate blinding for both participants and assessors, enhancing the authenticity and credibility of the results.
⇒ The outcomes encompass a comprehensive assessment of gait, balance and lower limbs motor function in patients who had a stroke through both qualitative and quantitative measurements.
⇒ The limitations of this trial include its single-centre design and the absence of a direct comparison of the clinical efficacy between intermittent theta-burst stimulation and repetitive transcranial magnetic stimulation.

## INTRODUCTION

Stroke is a prevalent cause of adult disability,[1 2] ranking third among the leading global causes of mortality.[3] Notably, stroke survivors face challenges in regaining independent walking ability, significantly impacting their quality of life and daily functioning. Actually, some studies reported that the integrity of corticospinal tract (CST) is the most important predictor of motor recovery.[4] Early motor recovery highly relies on how much CST is preserved (this process is spontaneous recovery)[5] but neuroplasticity for later recovery.[6] In addition to spontaneous recovery, neuroplastic changes involve the

reorganisation of the central nervous system's structure, function and connectivity to compensate for damage in regions affected by the stroke, which has been found in training responders.

In recent years, repetitive transcranial magnetic stimulation (rTMS) has emerged as a novel neurological rehabilitation therapy. Previous research has demonstrated its efficacy in alleviating motor dysfunction following cerebral stroke by regulating brain excitability.[7] Intermittent theta-burst stimulation (iTBS), an optimised rTMS modality, has the characteristics of short time (approximately 3 min). Pilot studies indicate that iTBS can significantly lead to long-term potentiation (LTP) and promote the excitability of the posterior parietal cortex to improve balance and gait function in patients who had a chronic stroke.[8 9] According to the Clinical Application Guidelines for rTMS,[10] iTBS targeting the contralateral primary motor cortex's leg area for managing lower limbs spasticity in multiple sclerosis is supported by level B evidence. However, the application of iTBS in poststroke lower extremity rehabilitation has not been explored yet. Therefore, further exploration of the application of iTBS in lower limbs stroke rehabilitation and expansion of existing research are warranted.

The effectiveness of iTBS is highly dependent on the depth of coil stimulation. Although previous studies commonly used the eight-figure coil for iTBS,[8 9] it presents challenges in stimulating deep-seated leg motor areas as it is primarily suitable for surface brain stimulation. Recently, the double cone coil has emerged as a promising alternative for deep brain region stimulation due to its significantly slower magnetic field decay rate over distance compared with the figure-of-eight coil. This enables effective magnetic field generation at depth without excessively increasing the electrical field intensity in superficial cortical regions. Stokić *et al* successfully elicited motor evoked potentials (MEPs) in leg muscles of healthy males using the double cone coil[11] while Terao *et al* employed this coil to stimulate leg motor cortical areas and analyse MEPs' D-wave and I-wave components from these regions.[12] Moreover, our prior research validated the reliability and efficacy of the double cone coil, particularly for measuring the anterior tibial muscle of lower limbs.[13] Therefore, in this study, we applied iTBS—an optimised rTMS modality—over the lower limb primary motor cortex (M1) using the double cone coil to induce simultaneous stimulation of affected leg motor areas.

Neuroimaging is extensively used to investigate neural plasticity, which serves as the intrinsic foundation for stroke rehabilitation. Both task-based functional MRI (fMRI), focusing on a spontaneous brain activity and resting-state fMRI, targeting baseline brain activity during rest to explore functional connectivity between regions of interest, can serve as valuable tools for investigating brain reorganisation during stroke recovery. Up to now, various neuroimaging methodologies have been used in the examination of the neural mechanisms underpinning walking impairment in individuals recovering from stroke. Several studies have used task-based fMRI to investigate brain activation patterns related to walking function during stroke recovery. Enzinger *et al* reported that enhanced walking function was associated with increased brain activation in the bilateral primary motor area, cingulate motor areas, caudate nuclei and the thalamus of the affected hemisphere, as revealed by ankle-dorsiflexion paradigm in fMRI.[14] Another fMRI study indicated that different brain regions, including cortical layers, subcortical layers and the brainstem, may contribute differently to gait control.[15] Furthermore, superior walking performance was linked to reduced contralateral sensorimotor cortex activation in the brainstem; whereas stronger engagement of ipsilateral sensorimotor and bilateral somatosensory cortices was observed in patients with subcortical and cortical stroke respectively. Based on the aforementioned research findings, it is evident that neural network plasticity may adapt to facilitate recovery of walking function, potentially achieved within or across damaged hemispheres and manifested as increased cortical excitability or enhanced functional connectivity in key brain regions. However, the brain network reorganisation mechanism of iTBS in the recovery of lower limb motor function after stroke is not yet clear.

Recently, resting-state fMRI has gained increasing popularity for assessing the effects of rTMS. This technique analyses low-frequency components of blood oxygenation level-dependent signals during the resting state, providing insights into spontaneous neural activity in the brain.[16] Unlike task-based fMRI, resting-state fMRI does not require participants to perform complex tasks, thus eliminating the confounding influence of different action paradigms on brain activity levels. Consequently, resting-state fMRI is well suited for patients who had a stroke with moderate to severe limb motor dysfunctions. Previous resting-state fMRI studies have revealed a potential association between motor function deficits following a stroke and abnormalities in motor network connectivity.[17] As motor function gradually recovers, there is evidence to suggest that this functional connectivity also progressively restores itself.[18] Additionally, it has been reported that the recovery of motor deficits is often linked to a stable increase in resting-state connectivity, particularly between the ipsilesional M1 and contralateral regions.[19 20] Li *et al* recruited 12 patients who had experienced subcortical stroke within 5 days of onset and conducted resting-state fMRI scans before and after rTMS intervention. The results indicated that rTMS, while promoting upper limb motor recovery in patients who had a stroke, significantly enhanced interhemispheric functional connectivity (FC) and reduced FC within the damaged hemisphere.[17] Taking into consideration the findings from the aforementioned studies, it can be concluded that rTMS intervention elicits notable neural network remodelling in patients who had a stroke. This remodelling can occur within the damaged hemisphere or extend across interhemispheric regions, manifesting as increased cortical excitability or enhanced FC within critical brain areas.

Diffusion tensor imaging (DTI), an MRI technique that measures the random movement of water molecules in brain tissue, provides unique anatomical information about brain connectivity and pathology not available through other imaging methods. In patients who had a stroke, fractional anisotropy (FA) measurements of the CST were found to be correlated with motor functional recovery.[21] FA values decreased rapidly at an early stage after cerebral infarction, reflecting cone bundle Wallerian degeneration, and furthermore, changes in FA values in the ipsilateral cone bundles were negatively correlated with National Institute of Health stroke scale (NIHSS) scale scores, but positively correlated with motor indices, Barthel index.[22] Thomalla *et al* examined DTI in patients with subacute supratentorial ischaemic stroke and found that the FA value of the affected cerebral peduncle was decreased, and there was a negative correlation between the ratio of FA of the affected cerebral peduncle to that of the contralateral peduncle and the NIHSS, and the lower the FA, the greater the degree of degeneration, and the worse the recovery of neurological motor function.[23] A diffusion-weighted MRI demonstrates that lower limbs motor function improves with greater anatomical connection between the ipsilesional M1 and the red nucleus, thalamus and cerebral peduncle.[24]

This prospective, single-centre, randomised controlled clinical trial aims to investigate the efficacy of iTBS delivered by a double cone coil for facilitating lower limbs functional rehabilitation in patients who had a stroke. The study outcomes will encompass a comprehensive assessment of gait, balance and lower limbs motor function in patients who had a stroke using both qualitative and quantitative methods. This study represents a longitudinal trial investigating the underlying neural mechanisms of iTBS for lower limbs rehabilitation. Multimodal fMRI scanning will be conducted to elucidate the effects of iTBS on brain reorganisation in patients who had a stroke. Specifically, resting-state fMRI will be employed to analyse preintervention and postintervention functional connections between key brain regions while DTI will be to used quantitatively evaluate the structural integrity of CST. We hypothesise that patients with lower extremity dysfunction who receive 15 sessions of iTBS will demonstrate greater improvements in walking ability compared with those receiving sham stimulation. These clinical effects may be attributed to specific remodelling patterns involving structural, functional or effective connectivity between key motor-related cortical and subcortical areas at both hemispheres as revealed through multimodal neural imaging analysis.

## MATERIALS AND METHODS

### Study design

The study has received approval from ethics committees and has been registered on www.chictr.org.cn. The study protocol will adhere to the principles of the Declaration of Helsinki and follow Good Clinical Practice guidelines, with reporting based on the Standard Protocol Items: Recommendations for Interventional Trials 2013 Checklist. The checklist of this protocol is provided in online additional file 1.

This prospective, randomised, controlled trial will be conducted at Wuxi Central Rehabilitation Hospital in Wuxi, China from May 2024 to November 2025. Eligible patients will be randomly assigned to either receive 15 sessions of iTBS (600 pulses) or sham stimulation. Outcome measures of gait, balance and lower limbs motor function will be assessed immediately on enrolment (T0), as well as immediately and 3 weeks after the last iTBS intervention (T1 and T2). Multimodal fMRI scanning will be performed at baseline and at the end of the iTBS intervention (T0 and T1). A detailed flow diagram of the trial is presented in figure 1 and the trial schedule is shown in table 1.

### Patient recruitment

The patient recruitment process will consist of four steps:

Step 1: Promotional efforts for inpatient recruitment will be conducted through the hospital's social media website (WeChat subscription), as well as posters, flyers, outpatient clinics and surrounding community service centres.

Step 2: A clinical research assistant will assess potential participants' eligibility for the trial based on strict inclusion and exclusion criteria.

Step 3: The study coordinator responsible for recruitment will arrange a conversation with eligible individuals to provide detailed information about the study's purpose, procedures and potential risks and benefits.

Step 4: Patients will voluntarily agree to participate and provide informed consent by signing a consent form only after fully understanding these aspects.

### Inclusion and exclusion criteria

Screen subjects according to the inclusion and exclusion criteria are in table 2. The inclusion criteria include individuals who had experienced their first unilateral stroke; hemiparesis due to left or right subcortical lesion confirmed by brain CT or MRI; age between 40 and 80; stable condition with a duration of 3–12 months since stroke onset; ability to independently walk over 10 m with or without orthosis; Brunnstrom lower limb stages III–V; capable of communicating in a simple manner sufficient for trial intervention and assessment completion; informed consent signed by the patients. The exclusion criteria for this study include the following: standard contraindications to iTBS or fMRI, such as the presence of irremovable metal objects in and around the body (eg, cardiac pacemaker, implanted medication pump) and pregnancy; obvious impairments in speech, attention, hearing, vision,[25] intellect, mental state or cognition (Mini-Mental State Examination (MMSE) < 24); pre-existing lower limbs motor dysfunction prior to stroke; significant physical pain (Visual analogue scale>4); the presence of other severe medical conditions that can

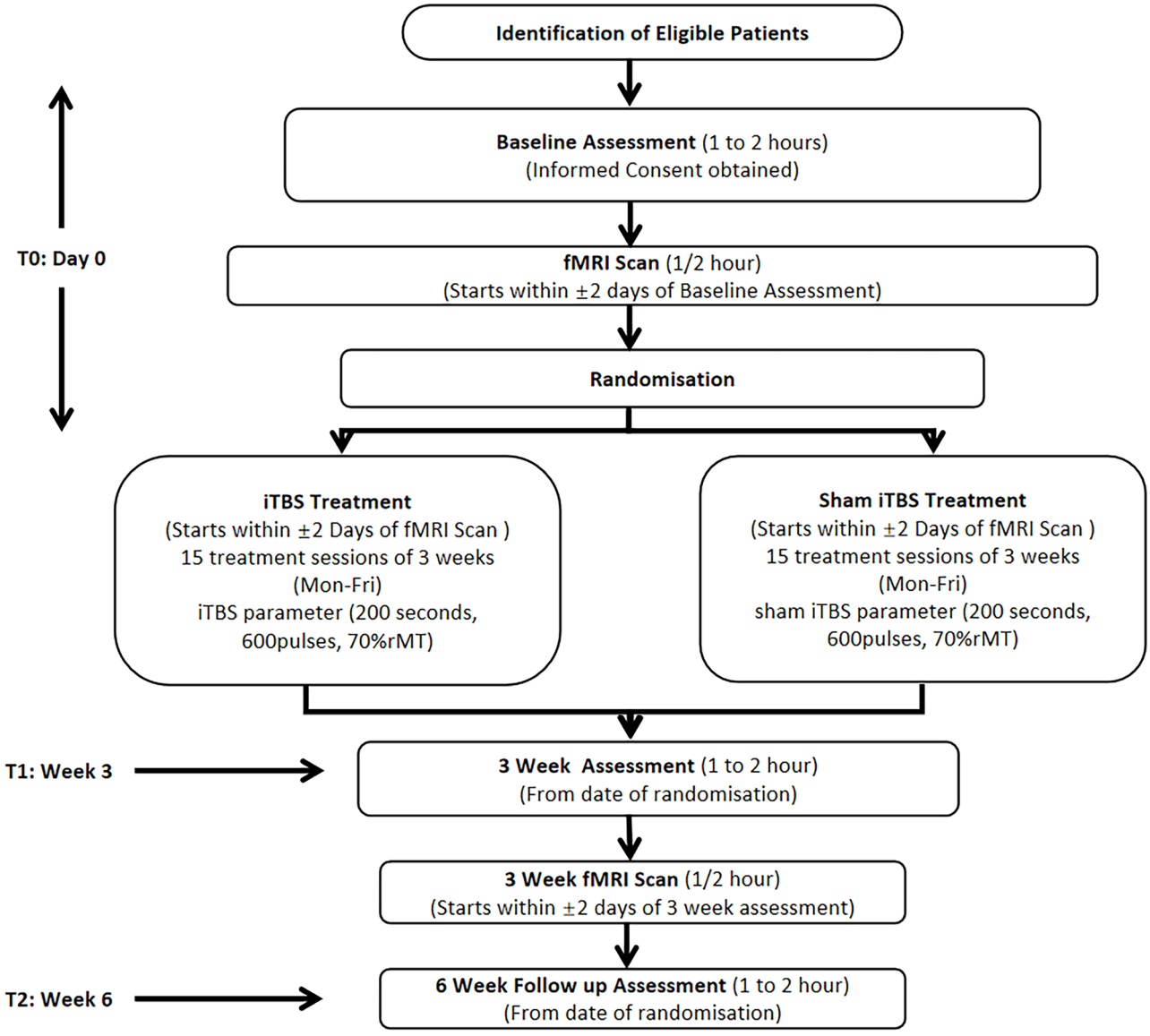


**Figure 1** Flow chart of study procedure. fMRI, functional MRI; iTBS, intermittent Theta Burst Stimulation; rMT, resting Motor Threshold.

affect outcome assessment results including cardiovascular disease, endocrine disorders, hepatic dysfunction; currently enrolled in other clinical trials; poor compliance with treatment regimens; other situations deemed unsuitable for inclusion by the researcher.

### Randomisation procedure

Subject numbers will be sequentially assigned to participants on their entry into the study, and randomisation procedure will occur immediately prior to the first treatment session. Participants will be randomised to receive either iTBS or sham iTBS treatments using a random-deterministic minimisation algorithm. To ensure balanced treatment groups, the algorithm will randomly allocate the first 10% of participants without minimisation in order to prevent predictability. Subsequently, the minimisation algorithm will be applied with an allocation ratio that is not fully deterministic, favouring an 80% bias towards allocations that minimise imbalance. The randomisation algorithm will consider three baseline prognostic variables: sex (male or female), time of onset (<6 months or ≥6 months) and types of cerebrovascular disease (cerebral infarction and cerebral haemorrhage).

### Blind

The investigator, physical therapists and participants were blinded to the treatment allocation. A laboratory technician, not involved in the study, handled the random allocation of participants to either the sham or real rTMS group. Additionally, the outcome assessor remained blinded to the allocation. Participants were instructed not to disclose their treatment assignment to the treatment technicians or fellow participants.

**Table 1** Participant timeline and schedule of assessments

| Time point | Study setup | Screening | Baseline assessment (T0) | Randomisation /allocation | Intervention | Follow-up assessment (T1) | Follow-up assessment (T2) |
|---|---|---|---|---|---|---|---|
| Preregistration checklist | | × | | | | | |
| Consent | | × | | | | | |
| Eligibility | | × | | | | | |
| Sociodemographics | | | × | | | | |
| Multimodal neuroimaging | | | × | | | × | |
| 10 MWT | | | × | | | × | × |
| FMA | | | × | | | × | × |
| TUG | | | × | | | × | × |
| FAC | | | × | | | × | × |
| BBS | | | × | | | × | × |
| BI | | | × | | | × | × |
| MMSE | | | × | | | × | × |
| MOCA | | | × | | | × | × |
| Pro-kin System Assessment | | | × | | | × | × |
| Surface electromyography recordings | | | × | | | × | × |
| 3D gait analysis | | | × | | | × | × |
| Corticomotor excitability test | | | × | | | × | × |
| Training healthcare staff | × | | | | | | |
| Randomisation and allocation | | | | × | | | |
| iTBS or sham iTBS | | | | | × | | |
| Clinical and technical support | | | | | × | | |
| Fidelity to the intervention | | | | | × | | |

BBS, Berg Balance Scale; BI, Barthel Index; 3D, three-dimensional; FAC, Functional Ambulation Category Scale; FMA, Fugl-Meyer assessment; MMSE, Mini-Mental State Examination; MOCA, Montreal Cognitive Assessment; 10 MWT, 10 m walking test ; TUG, Timed Up and Go Test .

Table 2 Method of ascertainment and justification for inclusion and exclusion criteria

| Inclusion criterion | Method of ascertainment | Justification |
|---|---|---|
| Individuals with first unilateral stroke | Medical record; imaging (CT or MRI) | Target population of the trial |
| Hemiparesis due to left or right subcortical lesion | Imaging (CT or MRI) | High variability of cortical injury on patient functioning and fMRI analysis |
| Age:40–80 years | Medical records | The stroke population is mainly concentrated in this age group |
| Stable condition with a duration of 3–12 months since stroke onset | Medical records; physical health screening and examination of neurological reports | Target population of the trial |
| Ability to independently walk over 10 metres with or without orthosis; Brunnstrom lower limb stages III-V | Pre-intervention screening measures; The 10 m walking test and Brunnstrom scale | Functions required to complete subsequent evaluations |
| Capable of communicating in a simple manner sufficient for trial intervention and assessment completion | Preintervention screening measures; MMSE scores ≥24 | Sufficient for completion of the trial intervention and assessment |
| Informed consent signed by the patients | Meeting with principal investigator to discuss study and sign consent form | Required |
| **Exclusion criteria** | **Method of ascertainment** | **Justification** |
| Standard contraindications to iTBS or fMRI, such as the presence of irremovable metal objects in and around the body (eg, cardiac pacemaker, implanted medication pump) and pregnancy | Medical records, interview with participant or guardian and use of a checklist | Safety |
| Obvious impairments in speech, attention, hearing, vision, intellect, mental state or cognition (MMSE <24) | Medical records, preintervention screening measures | Participant needs to understand study assent and instructions related to the testing and intervention |
| Pre-existing lower limb motor dysfunction prior to stroke | Medical records, interview with participant and guardian | May confound ability to drive changes in lower limb motor function |
| Significant physical pain | Visual analogue scale>4 | Pain may confound assessment results of the lower limbs in one way, and it may also cause the patient to move excessively while having the MRI taken. |
| Presence of other severe medical conditions that can affect outcome assessment results including cardiovascular disease, endocrine disorders, hepatic dysfunction, renal diseases and cognitive disorders | Medical records,interview with participant and guardian | Severe medical conditions are not suitable for participating in the experiment, which may exacerbate the progression of the condition |
| Currently enrolled in other clinical trials | Medical records, interview with participant and guardian | May confound the study results |
| Poor compliance with treatment regimens | Interview with participant | May affect study schedule, data collection |
| Other situations deemed unsuitable for inclusion by the researcher | Communication with an expert, principal investigator or clinician | Exclusion of any further contraindications that might emerge throughout the study but have not been considered |

fMRI, functional MRI; iTBS, intermittent Theta-Burst Stimulation; MMSE, Mini-Mental State Examination.

### Conventional rehabilitation and iTBS protocol

Each patient will be scheduled to participate in 40 min of targeted mobility exercises aimed at enhancing lower extremity function in a conventional physical therapy training room. All interventions will be performed by skilled and experienced physical therapists. Physical therapy includes lower extremity strength exercises, active-assisted mobilisations, progressive neuromuscular facilitation training, balance exercises, gait training, trunk control exercises and specific postural and transfer training protocols. Specific measures will be customised to each patient's functional ability. Patients will be

encouraged to work as hard as possible on each task and will be given verbal feedback and coaching to improve their performance.

Prior to each daily conventional physical therapy session, the Magneuro (Vishee Medical Technology., Nanjing, China) will be employed with a 110 mm double-cone coil positioned over the M1's representation of the affected tibialis anterior (TA) for administering the iTBS intervention. The TA M1 area will initially be estimated to be located at the hot spot approximately 1.5–2 cm laterally from vertex,[26] with the long axis of the two-wing intersection pointing anteroposteriorly and inducing a posterior–anterior current direction in the cortex.[27] The 'hot spot', namely the location evoking the greatest TA MEPs, will then be found by slightly adjusting the position. This approach activates M1 foot area cells at the lowest threshold, thereby inducing MEP in the contralateral ankle muscles.[28] The stimulation intensity will be determined based on the active motor threshold (aMT), which is defined as the minimum intensity capable of eliciting at least 5 out of 10 MEP with an amplitude greater than 200 µV peak to peak in the TA muscle. The iTBS protocol comprises a total of 600 pulses delivered over a duration of 200 s at an intensity equivalent to 80% of each individual's aMT. In cases where MEPs cannot be evoked, we will identify the motor hot spot by using the mirror site from the unaffected hemisphere.[29 30] Sham iTBS procedures will be conducted using a customised sham coil placed at identical locations and frequencies with matching intensities, ensuring that all participants experience similar clicking noises. Consequently, this protocol effectively ensures maintenance of participant blinding towards the intervention (figure 2).

## Study outcomes

### Primary outcome

The 10 m walking test (10 MWT) is a validated and reliable measure of ambulatory capacity in individuals who have experienced a stroke.[31] This assessment evaluates the time taken by subjects to walk a distance of 10 m at their maximum speed, with or without the assistance of a gait aid.

### Secondary outcomes

#### *Clinical assessment*

The motor performance of the lower extremity will be evaluated using the Fugl-Meyer assessment (FMA).[32] The FMA has been widely recognised for its excellent reliability and validity.[33 34] The FMA items comprehensively evaluate reflexes, synergies and coordination, with a maximum score of 34 for the lower extremity. Each item is rated on a 3-point ordinal scale: a score of 2 indicates 'no impairment', a score of 1 indicates 'partial impairment' and a score of 0 indicates 'severe impairment'. The Timed Up and Go Test is commonly used for the evaluation of mobility and fundamental functional abilities in poststroke individuals. Remarkable reliability has been reported among patients who had a chronic stroke.[35] The assessment necessitates a chair equipped with armrests, a measuring tape, a strap and a stopwatch. Patients will be instructed to independently rise from a seated position, ambulate forward for 3 m (with or without assistive devices if necessary), execute a turn, return to the chair and subsequently sit down again. A chronometer will be employed to record the total duration of the entire procedure.

The Functional Ambulation Category Scale (FAC) is a rapid and cost-effective visual assessment tool for

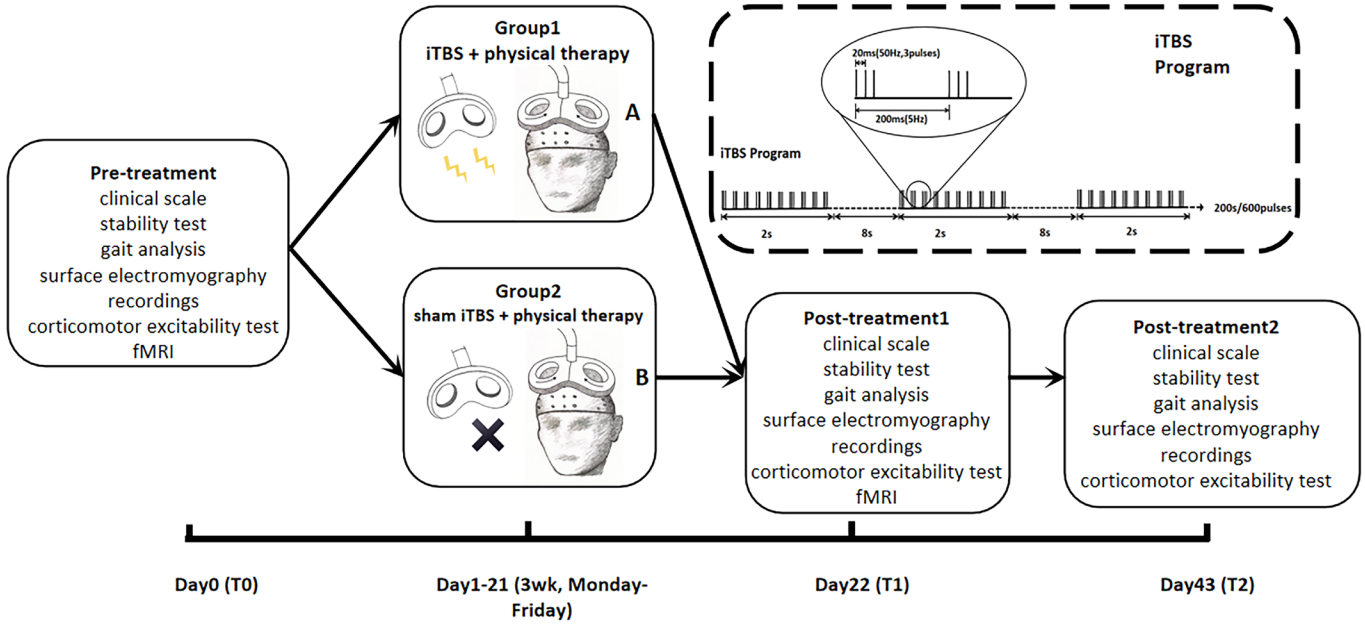


**Figure 2** An illustrative depiction of the (sham) iTBS implementation throughout the trial. fMRI; functional MRI; iTBS, intermittent Theta-Burst Stimulation.

measuring walking ability,[36] which has demonstrated excellent reliability, predictive validity and responsiveness in patients who had a stroke.[37]

The Berg Balance Scale (BBS), a highly validated scale used for evaluating balance in individuals with neurological conditions, exhibits robust reliability and internal validity. It achieves an intraclass correlation coefficient of 0.97 for intermeasure reliability and 0.98 for intrameasure reliability.[38 39] The BBS consists of 14 items, each rated on a scale ranging from 0 (indicating poor balance) to 4 (indicating excellent balance), resulting in a total score of 56.

The modified Barthel Index (MBI) serves as a crucial assessment tool for evaluating patients' functional capacity in performing activities of daily living. Consisting of 10 items, the MBI provides a maximum score of 100 points, where higher scores indicate increased independence in the patient's everyday life.

The MMSE is a comprehensive cognitive assessment tool covering multiple domains, including orientation, memory, attention, computation, language and visual ability. Scores on the MMSE range from 0 to 30, with higher scores indicating better cognitive function. Studies have demonstrated the good sensitivity (0.924) and specificity (0.806) of the MMSE in assessing cognitive impairment.[40]

The Montreal Cognitive Assessment scale evaluates multiple cognitive domains, including attention, memory, language, visuospatial skills, executive functions and orientation, with a maximum score of 30 points.

### Evaluation of static and dynamic stability

This study will use a Pro-Kin254P balancing instrument (TecnoBody Company, Italy) to evaluate balance function, including both static and dynamic stability. The assessment is based on the instantaneous data of postural sway using a force platform that measured movements of the centre of pressure.[41] Centre of pressure represents the weighted average of all pressures exerted on the ground surface area in contact. This device is considered valid and reliable for measuring static and dynamic balance function.[42] Participants will be positioned comfortably in a standardised stance on the platform, with their arms at their sides and eyes focused straight ahead on a stationary target displayed on a screen surface. Static testing involves two 30 s standing tests: one with eyes open and one with eyes closed. Perimeter measurements (in mm), as well as ellipse area measurements (in $mm^2$), will be recorded under each condition, resulting in four different outcome variables. Each test will be performed twice, and the mean score will be documented. Dynamic stability will be assessed through limits of stability (LOS) and overall balance index (OBI). During LOS testing, participants will be instructed to shift their weight to eight quadrants in order to reach corresponding target objects while maintaining this position for a specific duration.[43] This test aims to evaluate an individual's effective weight shifting ability and voluntary LOS towards different directional targets, where lower LOS scores indicate increased fall risk. OBI is calculated by measuring total variance in displacement from the centre of the platform using established calculations; it reflects an individual's capacity to control dynamic balance, with larger OBI values indicating greater fluctuations and poorer postural control, see table 3 for details.[44]

### Surface electromyography recordings

Using the FREEEMG 300 wireless surface EMG device (BTS Bioengineering, Milan, Italy), the root mean square values of rectus femoris, biceps femoris, anterior tibialis and gastrocnemius during flexion and extension (maximum isometric contractions) were recorded thrice and averaged.[45]

### Three-dimensional gait analysis

The three-dimensional movement data will be collected using a gold standard Qualisys motion capture system,

**Table 3** The descriptions and clinical implications of platform measures

| Posturographic measure | Definition | Clinical implication |
|---|---|---|
| The postural parameters in static stability | | |
| Centre of pressure | The point of application of forces exchanged between feet and ground | Reflecting the capacity for active body control |
| Total sway area ($mm^2$) | The area ellipse containing 90% of the sampled positions of the centre of pressure | Larger values indicate poorer postural stability and greater body sway |
| Total sway perimeter (mm) | The layout of a line connecting the different positions of the centre of pressure | |
| The postural parameters in dynamic stability | | |
| LOS (%) | An individual's weight-shifting ability and voluntary limits of stability to eight directional targets | Reflecting the interlimb coordination based on different task requirements in different directions |
| OBI (°) | The total variance in displacement from the centre of the platform | Reflecting the ability of neuromuscular control |

LOS, Limits of Stability; OBI, Overall Balance Index.

**Figure 3** Three-dimensional gait analysis using a gold standard Qualisys motion capture system.

comprising 8×Miqus M3 Cameras, 1×Miqus Video Camera and 32 Super Spherical Markers for static measurements (28 for dynamic measurements) with Ø14 mm.[46] This system is equipped with the Qualisys Track Manager 3D Software and Visual 3D Gait Analysis Software. Prior to the test, detailed instructions regarding the required time and purpose of the procedure will be provided to the patients. Subsequently, both the force platform and camera will undergo calibration. Retroreflective markers will be applied to specific anatomical landmarks on the lower limbs of the patients. These include bilateral anterior superior iliac spine, posterior superior iliac spine, greater trochanter of femur, medial and lateral femoral epicondyles, medial and lateral malleoli, first, third and fifth metatarsals as well as heel. Additionally, four points on mid-thighs and mid-calves each will also have markers applied. In total, there will be 28 markers used for static data collection (see figure 3). During the process of dynamic data collection, a total of 10 markers will be excluded, including the bilateral greater trochanters of the femur as well as the medial and lateral femoral epicondyles and malleoli.

Patients will be instructed to walk back and forth in a 10 m walkway at their usual walking speed, completing a total of 4–6 rounds. Based on factors such as uniform speed and correct foot placement on the force platform, four segments of gait data will be selected. The gait analysis software will capture the moment when the patient's heel touches the ground to the moment when the ipsilateral toe leaves the ground, representing one gait cycle. The software will obtain data on gait temporal parameters, spatial parameters, joint range of motion angles and ground reaction force. Specifically, the gait temporal parameters will include gait speed, step frequency, step width and step length. The spatial parameters will include the percentage of stance phase on the affected limb, the ratio of stance phase between the unaffected and affected limbs, and the percentage of double stance phase. Joint range of motion angles will include the maximum hip, knee and ankle flexion-extension angles. Ground reaction force will include the vertical and anterior peak ground reaction forces as a percentage of body weight.

### Corticomotor excitability

We will record the changes in rMT, MEP and recruitment curves (RCs). The MEP will be noted at 130% of rMT, 20 trials collect with intertrial intervals of 5 s and averaged.[47] The MEP changes over a range of stimulus intensities are quantified using RCs. This curve was created by graphing the average peak-to-peak MEP amplitude of five successive TMS stimuli versus the corresponding TMS output intensities, which will be applied in 10% increments and range from 100% to 150% of rMT. It has been proposed that RCs represent the neurophysiological potency of corticospinal and intracortical connections.[48]

### fMRI scan

All participants will undergo multimodal MRI scanning at T0 and T1 on a 3.0 Tesla MRI scanner (GE SIGNA Architect, America) in Wuxi Ninth People's Hospital. The scans will assess various parameters, including T1-weighted images, T2-weighted images, resting-state fMRI and diffusion-weighted images. All patients will lay supine with their heads fixed by foam pads with a standard birdcage head coil to minimise head movement. Participants will be instructed to remain as still as possible, open their eyes, remain awake and not think of anything.

High-resolution T1-weighted images will be acquired by 3D magnetisation-prepared rapid gradient-echo (MPRAGE) sequence (repetition time (TR)=7.7 ms; echo time (TE)=3.1 ms; flip angle (FA)=12°; matrix=256×256; field of view (FOV)=240×240 mm$^2$; slice thickness/gap=1/1 mm; 176 slices covered the whole brain) for image registration and functional localisation.

Transverse turbo-spin-echo T2-weighted images will be scanned for lesions identification (TR=5472 ms, TE=119.4 ms, FOV=240×240 mm$^2$, FA=111°, matrix=416×416, 22 axial slices, thickness=5 mm, gap=6.5 mm).

The resting-state fMRI will be collected with a gradient-recalled echo-planar imaging pulse sequence (TR=2500 ms; TE=30 ms; FA=90°; matrix=80×80, FOV=240×240 mm$^2$; thickness/gap=3/0 mm; slice numbers=62). A total of 200 volumes will be obtained in this acquisition sequence and each functional resting-state session will last approximately 500 s.

Diffusion-weighted images will be performed using a diffusion-weighted single-shot echo-planar imaging sequence (TR=10 090 ms, TE=103.2 ms, single average (NEX=1), FOV=240×240 mm$^2$, matrix=120×120, 72 axial slices, thickness=2.3 mm, gap=2.3 mm, FA=90°, 30 gradient encoded directions, b value=1000 s/mm$^2$).

## STATISTICAL ANALYSIS

### Sample size

The sample size is determined prior to the commencement of the study, employing a previously documented approach.[49 50] It is predicated on the assumption that there would be an 11 m/min disparity in mean performance between the two groups during the 10 MWT, with a shared SD of 12 m/min across both cohorts. Additionally, we anticipate a drop-out rate of 10% and maintain an equal distribution ratio of participants between the iTBS group and sham group at 1:1. Consequently, after setting a power threshold of 80% and significance level at 0.05, our ultimate target sample size was established as comprising 46 individuals, consisting of 23 subjects.

### Analysis of clinical data

Data analysis will be performed by an independent statistician using SPSS software (V.24.0). To ensure homogeneity between the two groups at baseline, statistical tests including Student's t-test, $\chi 2$ test and Mann-Whitney U test will be employed. Longitudinal data will be analysed using a two-way repeated measures analysis of variance with time (preintervention and postintervention, and at 3 weeks follow-up) as the within-subject factor and treatment condition (iTBS and sham iTBS) as the between-subject factor. The normality of data distribution will be assessed using the Kolmogorov-Smirnov statistic. In case of violation of the assumption of Mauchly's test of sphericity, probability values for multiple df will be adjusted using the Greenhouse-Geisser correction factor. All analyses will adhere to the intention-to-treat principle. The missing data will be imputed by carrying forward the last observed value, or if no previous value is available, by using the next recorded value. The results will be presented as the mean and 95% CIs, with statistical significance defined as $\alpha$=0.05 for a two-sided probability.

### Analysis of multimodal neuroimaging data

#### Resting-state fMRI

The resting-state fMRI data will be preprocessed using DPARSF, which provides a pipeline workspace based on Statistical Parametric Mapping (SPM, Wellcome Trust Centre for Neuroimaging, London). Images of the patients with left-sided lesions will be flipped along the midsagittal plane to ensure that all the patients have 'virtual' right hemisphere lesions. Slicing timing, realignment, normalisation and smoothing will be performed on the BLOD fMRI data. First, slice timing will be performed to correct the delay in slice acquisition. Second, the head motion will be realigned using a six-parameter rigid body spatial transformation. Excessive motion is defined as more than 2.5 mm of translation or greater than a 2.5° rotation in any direction. Third, structural images of each patient will be coregistered to the mean functional image, then segmented into grey matter, white matter and cerebrospinal fluid with a unified segmentation algorithm. The realigned images will be spatially normalised to the Montreal Neurological Institute standard space and then resampled to a 3 mm isotropic voxel with the parameters estimated during unified segmentation. Fourth, the normalised images will be smoothed with a 4 mm full-width half-maximum isotropic Gaussian kernel to increase the signal-to-noise ratio. Finally, the linear trends from the time courses will be removed, and the temporal band-pass filtering (0.01–0.08 Hz) will be performed to remove the effects of low-frequency drift and high-frequency noise, such as respiratory and heart rhythms.

A set of 90 network nodes will be established based on the Anatomical Automatic Labelling atlas. Subsequently, Pearson correlation analyses will be conducted on the preprocessed RS fMRI data, yielding a 90×90 correlation matrix that signifies the functional connectivity between each pair of network nodes. This matrix will be binarised using a specified threshold, with correlation coefficients surpassing the threshold assigned a value of 1 while those below it assigned a value of 0. Topology attributes, such as global network efficiency, local network efficiency, network betweenness, characteristic path length and clustering coefficient, will be computed for each patient using the correlation matrix.

#### Diffusion tensor imaging

DTI data will be preprocessed using FMRIB software (FMRIB Centre, Department of Clinical Neurology, University of Oxford, Oxford, UK) following visual inspection of all diffusion-weighted images. An affine transformation will be applied to register the diffusion-weighted images to the corresponding b=0 images in order to correct for eddy current distortions. FA, mean diffusivity, radial diffusivity and axial diffusivity images

will be generated by fitting a diffusion tensor model. These images will then be spatially normalised using parameters estimated from the coregistered T1-weighted images through SPM12 software. The FA maps for all participants will be non-linearly transformed based on the DARTEL template created from the T1-weighted images. For patients with left hemisphere lesions, their FA maps will be flipped left-to-right so that we can use the mask on the lesioned side for voxel-based statistical analyses. A Gaussian kernel with a half maximum width of 4 mm will be used to smooth the FA maps. Additionally, VOI-based analysis will be conducted on significant clusters identified by voxel-wise analysis and the VOI values will be averaged across all voxels within each VOI region.

### Safety

Adverse events observed in this trial will encompass seizures and other potential complications or side effects, including hearing issues, syncope, local pain, muscle twitching, cognitive changes and acute psychiatric changes.[51] Seizures represent the most severe acute adverse effect of rTMS, with high-frequency stimulation carrying a higher risk as indicated by the FDA.[52] Vagal reactions such as vasodepressor syncope may occur more frequently than seizures.[53] Other side effects are infrequent and transient; generally subsiding after a brief period of rest. However, strict adherence to screening for indications and contraindications significantly reduces the occurrence of rTMS-induced seizures. Our team is well prepared to manage any adverse events that may arise during the study with an equipped emergency area within our laboratory. Immediate measures will be promptly implemented if any adverse events occur and meticulously documented throughout the 3-week treatment duration.

## PATIENT AND PUBLIC INVOLVEMENT

The study design, recruitment, implementation and reporting will not involve patients and the general public. Nevertheless, the findings of the study will be disseminated to the public through academic publications and conference presentations.

### Ethics and dissemination

The study will be conducted in accordance with the principles outlined in the Declaration of Helsinki and relevant ethical guidelines. Approval for the entire project has been obtained from the ethics committees of Wuxi Mental Health Center/Wuxi Central Rehabilitation Hospital (ID: WXMHCIRB2023LLky078). Prior to their inclusion in the study, patients have the right to be informed about its purpose, content, process and considerations. They may exercise their discretion or engage in discussions with their relatives before signing an informed consent form. Furthermore, it is essential for investigators to clarify that participants can withdraw from the study at any time.

### Data management

Data will be diligently recorded on case report forms in a timely, comprehensive and precise manner. Two investigators will independently input the data into the EpiData software (V.3.1, the EpiData Association, JM Lauritsen) followed by a built-in double-checking process within this software. Access to all study-related electronic files will be restricted solely to authorised personnel while computer systems will be safeguarded through password protection measures. To ensure consistency across study-related documentation, each subject will receive a unique identifier on enrolment. Furthermore, physical copies of paper case report forms and study files shall be securely maintained within a locked cabinet under the supervision of the study coordinator in a designated secure office space. The investigators will strictly adhere to the study protocol in order to meticulously examine, gather, document and safeguard the data promptly with the aim of minimising any potential occurrence of missing data. If missing data occur in a small percentage of patients, we will handle it with multiple imputations. We will perform source data verification by comparing them with authentic medical records to assess the accuracy, completeness and representativeness of registry data.

## DISCUSSION

This is the inaugural study investigating the clinical effectiveness, feasibility and safety of iTBS administered via a double cone coil for the purpose of restoring lower limbs motor function poststroke. We anticipate that iTBS has the potential to facilitate recovery in this domain. This hypothesis is grounded on compelling evidence.

First, neural plasticity plays a critical role in rehabilitating lower limbs motor functions. Studies have demonstrated that facilitatory rTMS can augment synaptic responses by inducing LTP, which represents a crucial model for investigating the mechanisms of persistent alteration in synaptic efficiency within the central nervous system.[54] In fact, numerous studies have demonstrated that facilitatory rTMS applied over the ipsilesional M1 can effectively enhance corticomotor excitability, thereby promoting motor function recovery in patients who had a stroke.[55 56] Augmenting excitability of the motor cortex is a fundamental prerequisite for neural plasticity, facilitating surviving neurons to reorganise in response to therapeutic interventions.

In addition, animal studies have also demonstrated that iTBS, an optimised rTMS modality, exhibits potential in promoting stroke recovery through vascular protection and neovascularisation. Furthermore, it has been observed to downregulate the expression of specific genes and proteins which are closely associated with the reduction in inhibitory neuron activity.[57] These alterations can consequently induce corresponding modifications in synaptic connections within the brain, potentially expediting the restoration of relevant brain functions.

Moreover, the model of interhemispheric competition inhibition is also considered a crucial factor in motor recovery after stroke.[58 59] Within this framework, it is postulated that the unaffected motor cortex experiences disinhibition due to reduced transcallosal inhibition from the affected motor cortex. Consequently, this phenomenon leads to enhanced interhemispheric inhibition of the affected motor cortex by the disinhibited unaffected motor cortex, thereby negatively impacting functional motor recovery. Building on this theoretical foundation, our study employed iTBS targeting the affected lower limb's motor cortex as a means to directly modulate corticospinal excitability and potentially engage an interhemispheric reciprocal process whereby increased excitability in the affected hemisphere may influence its disinhibited counterpart via transcallosal pathways.

In addition to its potential clinical implications, this study aims to investigate the underlying mechanism of brain reorganisation through longitudinal analysis of multimodal neuroimaging before and after the intervention. Following the model proposed by Ameli *et al* known as the 'network shaping effect', it is hypothesised that rTMS can extend its effects beyond the targeted motor area and influence other nodes within the motor network.[60] Notably, previous research has demonstrated that focal stimulation of M1 not only produces local effects but also exerts remote effects on various motor areas in both hemispheres.[61] The fMRI studies have revealed that the premotor cortex (PMC) and supplementary motor area (SMA), which exhibit preactivation prior to walking initiation, play a pivotal role in the preparation and initiation of human locomotion.[62] Furthermore, these investigations have demonstrated the involvement of SMA and PMC in posture adjustment during ambulation. For instance, they facilitate proactive body posture adjustments to counteract potential disturbances and enhance walking stability.[63] When navigating unfamiliar environments or overcoming obstacles, brain regions responsible for integrating multisensory information, such as the junction of temporal parietal lobe and occipital cortex, are fully engaged to regulate gait. Additionally, it has been established that subcortical structures including basal ganglia, cerebellum and brainstem significantly contribute to the generation and maintenance of rhythmic walking patterns.[14 15] Based on the aforementioned research findings, we postulate that the restoration of lower limb ambulatory capacity in patients who had a stroke is not solely linked to the conventional sensorimotor cortex but also encompasses a broad spectrum of cortical functions encompassing visual, auditory and proprioceptive sensations. Furthermore, various subcortical structures may play a role in motor network reorganisation during recuperation of walking function. Consequently, employing resting-state fMRI in this study will furnish valuable insights into alterations within brain networks subsequent to iTBS intervention while DTI will offer profound understanding regarding motor pathway remodelling. Collectively, these outcomes will enhance our comprehension of neural impacts associated with diverse protocols of iTBS therapy for gait rehabilitation following stroke.

In conclusion, the iTBS is a highly promising non-invasive brain stimulation technology that offers several advantages including short stimulation time, easy implementation and wide applicability. Our aim is to investigate the efficacy of iTBS using a double cone coil in enhancing the walking ability of patients who had a stroke while exploring its potential underlying intervention mechanisms. We firmly believe that our research findings will provide valuable insights for the development of an innovative rehabilitation approach targeting poststroke walking ability.

**Author affiliations**
[1]Department of Rehabilitation, Wuxi Central Rehabilitation Hospital, The Affiliated Mental Health Center of Jiangnan University, Wuxi, China
[2]Department of Rehabilitation, Huashan Hospital Fudan University, Shanghai, China

**Contributors** GH, HW, YQ, YY, LZ, YC, JY, ZL, LS, WZ, LS and BS are involved in the conception, design and critical revision of this study protocol. YQ, YY, GH, YC, LS, WZ and LZ are responsible for recruiting subjects and assessment. BS, GH, LS and HW sought funding and ethical approval and helped with its implementation. LS and HW are responsible for revising the manuscript.

**Funding** This project is being supported by the Scientific and Technological Development Fund from Wuxi Science and Technology Bureau (Y20212008), Top Talent Support Program for young and middle-aged people of Wuxi Health Committee (HB2023085), Wuxi Municipal Health Commission Scientific Project (T202144), Shanghai Sailing Program(21YF1404600), National Natural Science Foundation of China (82102665, 81974356), Shanghai Health SystemKey Supporting Discipline Construction Project (2023ZDFC0304), Shanghai Natural Science Foundation (23ZR1408500).

**Competing interests** None declared.

**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.

**Provenance and peer review** Not commissioned; externally peer reviewed.



**ORCID iDs**
Guilan Huang http://orcid.org/0000-0001-9384-607X
Limin Sun http://orcid.org/0000-0002-7010-680X

## REFERENCES

1 Abo M, Kakuda W, Momosaki R, *et al*. Randomized, multicenter, comparative study of NEURO versus CIMT in poststroke patients with upper limb hemiparesis: the NEURO-VERIFY Study. *Int J Stroke* 2014;9:607–12.

2 Barros Galvão SC, Borba Costa dos Santos R, Borba dos Santos P, *et al*. Efficacy of coupling repetitive transcranial magnetic stimulation and physical therapy to reduce upper-limb spasticity in patients with stroke: a randomized controlled trial. *Arch Phys Med Rehabil* 2014;95:222–9.
3 GS Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the global burden of disease study 2019. *Lancet Neurol* 2021;20:795–820.
4 Siegel JS, Ramsey LE, Snyder AZ, *et al*. Disruptions of network connectivity predict impairment in multiple behavioral domains after stroke. *Proc Natl Acad Sci U S A* 2016;113:E4367–76.
5 Stinear CM, Barber PA, Petoe M, *et al*. The PREP algorithm predicts potential for upper limb recovery after stroke. *Brain (Bacau)* 2012;135:2527–35.
6 Honaga K, Fujiwara T, Tsuji T, *et al*. State of intracortical inhibitory interneuron activity in patients with chronic stroke. *Clin Neurophysiol* 2013;124:364–70.
7 Du J, Yang F, Hu J, *et al*. Effects of high- and low-frequency repetitive transcranial magnetic stimulation on motor recovery in early stroke patients: Evidence from a randomized controlled trial with clinical, neurophysiological and functional imaging assessments. *Neuroimage Clin* 2019;21:101620.
8 Koch G, Bonnì S, Casula EP, *et al*. Effect of cerebellar stimulation on gait and balance recovery in patients with hemiparetic stroke: a randomized clinical trial. *JAMA Neurol* 2019;76:170–8.
9 Liao L-Y, Xie Y-J, Chen Y, *et al*. Cerebellar theta-burst stimulation combined with physiotherapy in subacute and chronic stroke patients: a pilot randomized controlled trial. *Neurorehabil Neural Repair* 2021;35:23–32.
10 Lefaucheur J-P, Aleman A, Baeken C, *et al*. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014-2018). *Clin Neurophysiol* 2020;131:474–528.
11 Stokić DS, McKay WB, Scott L, *et al*. Intracortical inhibition of lower limb motor-evoked potentials after paired transcranial magnetic stimulation. *Exp Brain Res* 1997;117:437–43.
12 Terao Y, Ugawa Y, Hanajima R, *et al*. Predominant activation of i1-waves from the leg motor area by transcranial magnetic stimulation. *Brain Res* 2000;859:137–46.
13 Su B, Jia Y, Zhang L, *et al*. Reliability of tms measurements using conventional hand-hold method with different numbers of stimuli for tibialis anterior muscle in healthy adults. *Front Neural Circuits* 2022;16:986669.
14 Enzinger C, Johansen-Berg H, Dawes H, *et al*. Functional MRI correlates of lower limb function in stroke victims with gait impairment. *Stroke* 2008;39:1507–13.
15 Luft AR, Forrester L, Macko RF, *et al*. Brain activation of lower extremity movement in chronically impaired stroke survivors. *Neuroimage* 2005;26:184–94.
16 Zhang X, Tang Y, Maletic-Savatic M, *et al*. Altered neuronal spontaneous activity correlates with glutamate concentration in medial prefrontal cortex of major depressed females: an fMRI-MRS study. *J Affect Disord* 2016;201:153–61.
17 Li J, Zhang X, Zuo Z, *et al*. Cerebral functional reorganization in ischemic stroke after repetitive transcranial magnetic stimulation: an fMRI study. *CNS Neurosci Ther* 2016;22:952–60.
18 van Meer MPA, van der Marel K, Wang K, *et al*. Recovery of sensorimotor function after experimental stroke correlates with restoration of resting-state interhemispheric functional connectivity. *J Neurosci* 2010;30:3964–72.
19 Golestani A-M, Tymchuk S, Demchuk A, *et al*. Longitudinal evaluation of resting-state FMRI after acute stroke with hemiparesis. *Neurorehabil Neural Repair* 2013;27:153–63.
20 Wang L, Yu C, Chen H, *et al*. Dynamic functional reorganization of the motor execution network after stroke. *Brain (Bacau)* 2010;133:1224–38.
21 Stinear CM, Barber PA, Smale PR, *et al*. Functional potential in chronic stroke patients depends on corticospinal tract integrity. *Brain (Bacau)* 2007;130:170–80.
22 Guo AH, Hao FL, Liu LF, *et al*. An assessment of the correlation between early postinfarction pyramidal tract Wallerian degeneration and nerve function recovery using diffusion tensor imaging. *Genet Mol Res* 2017;16.
23 Thomalla G, Glauche V, Koch MA, *et al*. Diffusion tensor imaging detects early Wallerian degeneration of the pyramidal tract after ischemic stroke. *Neuroimage* 2004;22:1767–74.
24 Peters DM, Fridriksson J, Stewart JC, *et al*. Cortical disconnection of the ipsilesional primary motor cortex is associated with gait speed and upper extremity motor impairment in chronic left hemispheric stroke. *Hum Brain Mapp* 2018;39:120–32.
25 Li J, Wang H, Yuan Y, *et al*. Effects of high frequency rTMS of contralesional dorsal premotor cortex in severe subcortical chronic stroke: protocol of a randomized controlled trial with multimodal neuroimaging assessments. *BMC Neurol* 2022;22:125.
26 Klem GH, Lüders HO, Jasper HH, *et al*. The ten-twenty electrode system of the international federation. *Int Fed Clin Neurophysiol* 1999;3–6.
27 Rossini PM, Burke D, Chen R, *et al*. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. *Clin Neurophysiol* 2015;126:1071–107.
28 Groppa S, Oliviero A, Eisen A, *et al*. A practical guide to diagnostic transcranial magnetic stimulation: report of an IFCN committee. *Clin Neurophysiol* 2012;123:858–82.
29 Tscherpel C, Dern S, Hensel L, *et al*. Brain responsivity provides an individual readout for motor recovery after stroke. *Brain (Bacau)* 2020;143:1873–88.
30 Chen Y-J, Huang Y-Z, Chen C-Y, *et al*. Intermittent theta burst stimulation enhances upper limb motor function in patients with chronic stroke: a pilot randomized controlled trial. *BMC Neurol* 2019;19:69.
31 van Bloemendaal M, van de Water ATM, van de Port IGL. Walking tests for stroke survivors: a systematic review of their measurement properties. *Disabil Rehabil* 2012;34:2207–21.
32 Fugl-Meyer AR, Jääskö L, Leyman I. The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance a method for evaluation of physical performance. *Scand J Rehabil Med* 1975;7:13–31.
33 Barak S, Duncan PW. Issues in selecting outcome measures to assess functional recovery after stroke. *NeuroRx* 2006;3:505–24.
34 Sanford J, Moreland J, Swanson LR, *et al*. Reliability of the Fugl-Meyer assessment for testing motor performance in patients following stroke. *Phys Ther* 1993;73:447–54.
35 Ng SS, Hui-Chan CW. The timed up & go test: its reliability and association with lower-limb impairments and locomotor capacities in people with chronic stroke. *Arch Phys Med Rehabil* 2005;86:1641–7.
36 Wade DT, Collen FM, Robb GF, *et al*. Physiotherapy intervention late after stroke and mobility. *BMJ* 1992;304:609–13.
37 Mehrholz J, Wagner K, Rutte K, *et al*. Predictive validity and responsiveness of the functional ambulation category in hemiparetic patients after stroke. *Arch Phys Med Rehabil* 2007;88:1314–9.
38 Meseguer-Henarejos A-B, Rubio-Aparicio M, López-Pina J-A, *et al*. Characteristics that affect score reliability in the Berg Balance Scale: a meta-analytic reliability generalization study. *Eur J Phys Rehabil Med* 2019;55:570–84.
39 Maeda N, Urabe Y, Murakami M, *et al*. Discriminant analysis for predictor of falls in stroke patients by using the Berg Balance Scale. *smedj* 2015;56:280–3.
40 Sleutjes DKL, Harmsen IJ, van Bergen FS, *et al*. Validity of the mini-mental state examination-2 in diagnosing mild cognitive impairment and dementia in patients visiting an outpatient clinic in the Netherlands. *Alzheimer Dis Assoc Disord* 2020;34:278–81.
41 Srivastava A, Taly AB, Gupta A, *et al*. Post-stroke balance training: role of force platform with visual feedback technique. *J Neurol Sci* 2009;287:89–93.
42 Schoneburg B, Mancini M, Horak F, *et al*. Framework for understanding balance dysfunction in Parkinson's disease. *Mov Disord* 2013;28:1474–82.
43 Horak FB. Postural orientation and equilibrium: what do we need to know about neural control of balance to prevent falls? *Age Ageing* 2006;35 Suppl 2:ii7–11.
44 Cug M, Wikstrom EA. Learning effects associated with the least stable level of the biodex® stability system during dual and single limb stance. *J Sports Sci Med* 2014;13:387–92.
45 Rainoldi A, Bullock-Saxton JE, Cavarretta F, *et al*. Repeatability of maximal voluntary force and of surface EMG variables during voluntary isometric contraction of quadriceps muscles in healthy subjects. *J Electromyogr Kinesiol* 2001;11:425–38.
46 Mihcin S, Sahin AM, Yilmaz M, *et al*. Database covering the prayer movements which were not available previously. *Sci Data* 2023;10:276.
47 Dai W, Geng Y, Liu H, *et al*. Preconditioning with cathodal high-definition transcranial direct current stimulation sensitizes the primary motor cortex to subsequent intermittent theta burst stimulation. *Neural Plast* 2021;2021:8966584.
48 Liu H, Au-Yeung SSY. Reliability of transcranial magnetic stimulation induced corticomotor excitability measurements for a hand muscle in healthy and chronic stroke subjects. *J Neurol Sci* 2014;341:105–9.
49 Chieffo R, Giatsidis F, Santangelo R, *et al*. Repetitive Transcranial magnetic stimulation with H-coil coupled with cycling for improving

lower limb motor function after stroke: an exploratory study. *Neuromodulation* 2021;24:916–22.
50 Peters HT, Dunning K, Belagaje S, *et al*. Navigated transcranial magnetic stimulation: a biologically based assay of lower extremity impairment and gait velocity. *Neural Plast* 2017;2017:6971206.
51 Rossi S, Hallett M, Rossini PM, *et al*. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol* 2009;120:2008–39.
52 Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the safety of repetitive transcranial magnetic stimulation, June 5–7, 1996. *Electroencephalogr Clin Neurophysiol Evoked Potent Sect* 1998;108:1–16.
53 Grossheinrich N, Rau A, Pogarell O, *et al*. Theta burst stimulation of the prefrontal cortex: safety and impact on cognition, mood, and resting electroencephalogram. *Biol Psychiatry* 2009;65:778–84.
54 Thut G, Pascual-Leone A, Thut G, *et al*. Integrating TMS with EEG: How and what for? *Brain Topogr* 2010;22:215–8.
55 Tang Z, Han K, Wang R, *et al*. Excitatory repetitive transcranial magnetic stimulation over the ipsilesional hemisphere for upper limb motor function after stroke: a systematic review and meta-analysis. *Front Neurol* 2022;13:918597.
56 Chervyakov AV, Poydasheva AG, Lyukmanov RH, *et al*. Effects of navigated repetitive transcranial magnetic stimulation after stroke. *J Clin Neurophysiol* 2018;35:166–72.
57 Funke K, Benali A. Modulation of cortical inhibition by rTMS - findings obtained from animal models. *J Physiol* 2011;589:4423–35.
58 Cicinelli P, Pasqualetti P, Zaccagnini M, *et al*. Interhemispheric asymmetries of motor cortex excitability in the postacute stroke stage: a paired-pulse transcranial magnetic stimulation study. *Stroke* 2003;34:2653–8.
59 Liepert J, Dettmers C, Terborg C, *et al*. Inhibition of ipsilateral motor cortex during phasic generation of low force. *Clin Neurophysiol* 2001;112:114–21.
60 Ameli M, Grefkes C, Kemper F, *et al*. Differential effects of high-frequency repetitive transcranial magnetic stimulation over ipsilesional primary motor cortex in cortical and subcortical middle cerebral artery stroke. *Ann Neurol* 2009;66:298–309.
61 Wang L, Huang G, Zhang L, *et al*. Effects of the intermittent theta burst stimulation of the cerebellar vermis on balance recovery after stroke: a study protocol for a randomized controlled trial. *Front Aging Neurosci* 2022;14:881311.
62 Huppert T, Schmidt B, Beluk N, *et al*. Measurement of brain activation during an upright stepping reaction task using functional near-infrared spectroscopy. *Hum Brain Mapp* 2013;34:2817–28.
63 Chang W-H, Tang P-F, Wang Y-H, *et al*. Role of the premotor cortex in leg selection and anticipatory postural adjustments associated with a rapid stepping task in patients with stroke. *Gait Posture* 2010;32:487–93.