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The effectiveness of cerebellar vermis intermittent theta burst stimulation in improving trunk control and balance function for subacute stroke patients: a randomized controlled trial protocol

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Abstract

Introduction Balance impairments frequently occur in patients with stroke. Achieving effective core trunk stability is the key to improving balance ability. However, there still lacks of advanced well-defined rehabilitation protocols for balance improvement in stroke patients. Intermittent theta-burst stimulation (iTBS) is a non-invasive brain activity modulation strategy, which can produce long-term potentiation. Cerebellar vermis is a cardinal structure involved in balance and motor control. However, no study has demonstrated the therapeutic effect and potential mechanism of cerebellar vermis iTBS on balance in individuals with stroke.

Methods and Analysis This study will be a prospective single-center double-blind randomized controlled clinical trial with 3-week intervention and 3-week follow-up. Eligible participants will be randomly allocated in a 1:1 ratio to experimental group or control group, respectively. After routine conventional physical therapy, patients assigned to the experimental group will receive cerebellar vermis iTBS whereas patients assigned to the control group will receive sham stimulation. The overall intervention periods are five days a week for three consecutive weeks. The outcomes will be measured at baseline (T0), 3 weeks post-intervention (T1) and 3 weeks follow-up (T3). The primary outcomes are Berg balance scale (BBS) and trunk impairment scale (TIS) scores. The secondary outcomes are balance tests via the Balance Master system, muscle activation of trunk and lower limbs via the surface electromyography (sEMG) recording, cerebral cortex oxygen concentrations via the resting-state functional near-infrared spectroscopy (fNIRS), FMA-LE scores, and Barthel index (BI) scores.

Ethics and Dissemination This study was approved by the West China Hospital Clinical Trials and Biomedical Ethics Committee of Sichuan University. The trial registration number

is ChiCTR2200061225. All participants will sign the informed consent voluntarily. The results of this study will be published in peer-reviewed journals and disseminated at academic conferences.

Strengths and limitations of this study

- This prospective single-center double-blind randomized controlled clinical trial with 3-week intervention and 3-week follow-up is firstly designed to confirm the effect and potential mechanism of cerebellar vermis iTBS stimulation on balance in subacute stroke patients.
- Our study will comprehensively assess the trunk control and balance function by clinical scales, balance tests via the Smart Equitest Balance Master System and sEMG measurements. Additionally, we will also collect the concentration of HbO2 in cerebral cortex via the resting-state fNIRS. Integrated data results sufficiently verify the research hypothesis.
- Our study can provide valuable information to develop a novel treatment method for the rehabilitation of balance dysfunction after stroke.
- This study has sufficient research basis. Previously published articles by our research group provided evidence that iTBS of the cerebellar hemisphere could promotes upper limb spasticity, balance, and walking performance recovery in post-stroke patients. And, preliminary pilot study conducted by us found that cerebellar vermis iTBS contributed to increasing the excitability of the bilateral supplementary motor areas during balance tasks in healthy adults.

Introduction

Stroke is the third most common cause of disability worldwide.[1] The number of incidents, prevalent survivors, and disability-adjusted life-years lost of stroke is still increasing over the past two decades[2], which are considered to lead to heavy economic burdens on society.

Balance impairments frequently occur in patients with stroke, with the reported incidence ranging from 61% to 83%[3]. The main manifestations are postural instability, weak trunk control, and difficulty of weight shift,[4] which will ultimately result in falls, poor mobility, decreased physical activity, and reduced quality of life in patients.[5] Therefore, improvement of the balance function is a cardinal requirement in patients with stroke.

The trunk plays a fundamental role in trunk control, balance, and mobility during sitting and transferring.[6] The synchronized activity of trunk muscles is necessary for maintaining dynamic balance. In addition, proper trunk muscle control is essential in stabilizing distal limbs.[7] Muscle weakness of lower limbs is associated with a decreased standing balance control.[8] Impaired trunk control and core muscle weakness attenuate balance and physical function in individuals after stroke.[9] Therefore, achieving effective core trunk stability is crucial to improving balance ability after stroke.

The cerebellum, a central brain structure located in posterior cranial fossa, works in concert with the cerebral cortex, brainstem, and spinal cord and is involved in motor control.[10 11] It consists of two lateral hemispheres and a cerebellar vermis. Cerebellar vermis is a cardinal structure involved in balance and motor processing,[12 13] which is responsible for regulating the trunk, head, neck and proximal limb muscles to control posture and maintain balance.[14] And balance dysfunction in cerebellar disorders is most likely caused by lesions of the medial zone of the cerebellum.[15] At present, the main clinical interventions to improve the balance function in stroke rehabilitation are muscle strength training or balance training. It has a great potential to activate the cerebellar vermis in the central nervous system through the neuromodulation with non-invasive brain stimulation to enhance the balance function in stroke patients.

Repetitive transcranial magnetic stimulation (rTMS) is a safe, reliable, and standardized non-invasive brain activity modulation strategy to regulate cortical excitability and facilitate neural

plasticity.[16] Intermittent theta-burst stimulation (iTBS) is a novel form of rTMS, which can produce long-term potentiation and is more rapid and efficacious than standard rTMS.[17] Our group recently provided evidence that iTBS of the cerebellar hemisphere could promotes upper limb spasticity, balance, and walking performance recovery in post-stroke patients.[18-20] However, no study has demonstrated the therapeutic effect and potential mechanism of cerebellar vermis iTBS on balance in individuals with stroke since now. Preliminary pilot study conducted by us found that cerebellar vermis iTBS contributed to increasing the excitability of the bilateral supplementary motor areas (SMA) during balance tasks in healthy adults.[21]

Objective

A randomized controlled double-blind trial is conducted to determine the effects of cerebellar vermis iTBS on trunk control, muscle activation and balance function in subacute stroke patients since no clinical research have been reported to verify the effectiveness of cerebellar vermis iTBS stimulation. We hypothesize that cerebellar vermis iTBS can promote the activation of trunk and lower limbs muscles, and increase the excitability of SMA to improve trunk control and balance function in patients with subacute stroke.

Methods

Study design and setting

This study is a prospective single-center double-blind randomized controlled clinical trial with 3-week intervention and 3-week follow-up. The protocol is strictly followed the standard protocol guidelines: SPIRIT 2013 Statement.[22] Eligible participants will be randomly allocated in a 1:1 ratio to the experimental group or control group, respectively. After routine conventional physical therapy, patients assigned to the experimental group will receive

cerebellar vermis iTBS whereas patients assigned to the control group will receive sham stimulation. The overall intervention periods are five days a week for three consecutive weeks. The outcomes will be measured at baseline (T0), 3 weeks post-intervention (T1), and 3 weeks follow-up (T3). The whole study will be performed at the Department of Rehabilitation Medicine of Sichuan University West China Hospital (Chengdu, Sichuan Province, China). Figure 1 shows the flow diagram of the study design. We plan to start subject recruitment on the 15th of July 2022 and complete the trial in December 2024. Figure 2 illustrates the study schedule.

Sample size calculation

The sample size calculation was conducted via G*power of 3.1.9.2 based on the result of Berg balance scale (BBS) score in our published study, which indicated an estimated effect size f =0.38.[19] Other parameters were set as follows: significance level α=0.05 (two tails), power (1–β) =90%, correlation among repeated measures=0.5, nonsphericity correction ε=1, number of measurements=3, and number of groups=2. Therefore, the sample size of n=40 was obtained. After allowing for a 15% dropout rate, a minimum total of 46 participants are needed.

Participants

Recruitment

The participants will be recruited from the Department of Rehabilitation Medicine of Sichuan University West China Hospital in Chengdu, Sichuan Province, China. After carefully screening the inclusion and exclusion criteria, voluntary participants are required to provide written informed consent before the experiment.

Inclusion criteria

Participants will be considered for inclusion if they meet the following criteria:

(1) A diagnosis of a stroke according to the *Diagnostic criteria of cerebrovascular diseases in China (version 2019)*.[23]

(2) Aged between 18 and 65 years.

(3) First-ever unilateral stroke confirmed by imaging examination.

(4) Subacute stroke participants with the stroke onset ranged from 2 weeks to 6 months.[18]

(5) Having motor deficit and balance dysfunction, with the Fugl-Meyer assessment scale score for lower extremities (FMA-LE) <34 points and BBS score <56 points.[19]

Exclusion criteria

Participants will be excluded if they meet any of the following criteria:

(1) Diagnosis of coexisting other neurological diseases.

(2) Injury of cerebellum or brain stem.

(3) Having contraindications of iTBS (e.g., history of seizures, intracranial metallic implants, microprocessor implants in the body, suffering from tumorous, and pregnancy)

(4) Cognitive impairment with the mini-mental state examination (MMSE) score<27.

Interventions

All enrolled participants will receive 1 session of cerebellar vermis iTBS or sham stimulation from Monday to Friday, always before routine conventional physical therapy, for a total of 15 sessions. The experimental group patients will receive cerebellar vermis iTBS coupled with conventional physical therapy, and the control group patients will receive sham stimulation coupled with conventional physical therapy. The whole intervention period will last three consecutive weeks in total.

Cerebellar vermis iTBS stimulation

The stimulation protocol will strictly adhere to the safety guidelines and recommendations endorsed by the International Federation for Clinical Neurophysiology in 2021.[24] We will use a Magstim Rapid2 stimulator (The Magstim Company Limited) connected to a 70 mm figure-of-8 Double Rapid2 Air Cooled Coil (P/N 3910-00) to stimulate the cerebellar vermis (Figure 3). The center of the coil will be placed tangentially to the target scalp and the coil current direction will point downward. iTBS is applied over the cerebellar vermis, 1 cm inferior to the inion.[25] We will use a neuronavigation system (BrainSightt, Rogue Research Inc.) coupled with a Polaris Vicra infrared camera to ensure that cerebellar vermis iTBS is applied over the same spot across different sessions in the same participant (Figure 3). The pattern of iTBS consists of 600 pulses containing 3 pulses at 50Hz repeated at a rate of 5Hz, with 20 trains of 10 bursts given at 8s intervals.[26] The standard stimulus intensity is set at 80% of the active motor threshold (AMT), which is the lowest intensity evoking at least five out of ten motor-evoked potentials (MEP) with a peak to peak amplitude >200 μV in the abductor pollicis brevis muscle during 10% of maximum voluntary contraction measuring by a dynamometer.[20] If the participant cannot tolerate the preset standard stimulus intensity, the stimulator output intensity is set to the participant's maximum tolerated intensity (MTI).[27]

Sham stimulation

In the control group, participants are treated identically except for using the Magstim's sham coil (P/N 3950-00) to realize the sham stimulation.[28] The sham coil has the same external appearance, parameters and application methods to simulate the sensation produced by the real coil without induction of a magnetic field. Therefore, it can sufficiently ensure that the patients remain blind to the intervention.

Conventional physical therapy

After receiving cerebellar vermis iTBS or sham stimulation, all participants will receive conventional physical therapy, including limb positioning, balance exercise, trunk control, postural and transfer training, lasting 50 min per session during intervention phase.

Discontinuing allocated interventions criteria

Participants will stop receiving any interventions if any of the following events occurs:

(1) Serious adverse events happen during the stimulation, such as epilepsy, severe headache, persistent tinnitus and syncope.

(2) Participants withdraw from the trial.

(3) Participants are not compliant with the allocation and intervention plan.

(4) Participants join in extra studies during the trial.

(5) Group exposure for participants and outcomes evaluators lead to the failure of blindness.

Improving adherence strategies

In order to improve the participant compliance, the researcher in charge of the trial will contact the participants regularly to clarify the rehabilitation progress and discuss the subsequent physical therapy program. Additionally, patients who complete the entire procedure in accordance with the protocol are to be provided with a subject fee and an additional free rehabilitation consultation. Once the participant drops out, the specific reasons for withdrawal will be recorded.

Outcome Measures

At the day of enrollment, the basic characteristics information of participants, including age, gender, type of stroke, lesion site, course of diseases, degree of neurological deficit assessed by National Institutes of Health Stroke Scale (NIHSS), and cognitive function assessed by

MMSE, are documented. The outcome assessments are performed at the treatments site before intervention as a baseline (T0), after 3 weeks of intervention (T1) and after 3 weeks of follow-up (T3). The primary outcomes are BBS and trunk impairment scale (TIS) scores. The secondary outcomes are balance tests via the Balance Master system, muscle activation of trunk and lower limbs via the surface electromyography (sEMG) recording, cerebral cortex oxygen concentrations via the resting-state functional near-infrared spectroscopy (fNIRS), FMA-LE scores, and Barthel index (BI) scores. Each assessment is performed by a professional clinician or by a qualified physical therapist who is blinded to the experimental condition of the participant.

Primary outcomes

1. BBS

The BBS is a well-validated scale of balance among individuals with neurological disease.[29] It has high reliability and internal validity, with the intraclass correlation coefficient (ICC) for inter-measure reliability and intra-measure reliability is 0.97 and 0.98, respectively.[30] This scale is a 14-item measure with a total score of 56, and the score of each item ranges from 0 (poor balance) to 4 (good balance).[31]

2. TIS

TIS is a scale designed to assess motor impairment of the trunk after stroke, illustrating the most promising performance in psychometric properties with satisfactory reliability and validity.[32] It is a 17-item scale with a total score rates from 0 to 23 points to evaluate static and dynamic sitting balance and trunk coordination for stroke patients.[33] A higher score indicates better trunk control.

Secondary outcomes

1. balance tests via the Balance Master system

The assessments of dynamic balance and postural control abilities are performed by sensory organization test (SOT), limits of stability (LOS), and rhythmic weight shift (RWS) via the Smart Equitest Balance Master System® (NeuroCom Int., Inc., Clackamas, Oregon, USA). (Figure 4)

1.1 SOT: The SOT evaluates postural control when participants undergo different somatosensory, visual, and vestibular feedback perturbations. When testing, inaccurate interference information delivered to the patient's eyes, feet, and joints are controlled through calibrated sway referencing of the support surface and/or visual surround. The participant is required to maintain balance to keep their center of gravity (COG) as steady as possible. A composite equilibrium score is provided to characterize the participant's overall level of performance through six conditions described in Table 1. During SOT, each trial lasts for 20 s and is repeated three times.[34 35]

Table 1. Sensory organization test

Condition	Vision	Surface	Surround	Interference
1	Eyes open	Stable	Fixed	Null
2	Eyes closed	Stable	Fixed	Vision
3	Eyes open	Stable	Unfixed	Vision
4	Eyes open	Unstable	Fixed	Somatosensation
5	Eyes closed	Unstable	Fixed	Somatosensation and Vision
6	Eyes open	Unstable	Unfixed	Somatosensation and Vision

1.2 LOS: The LOS quantifies the voluntary ability to shift the COG towards eight different directions, which are forward, forward-right, right, backward-right, backward, backward-left, left, and forward -left. When the test is performed, a real-time display of their COG position in relation to targets placed at the center of the base of support and the stability limits is shown. Once the command is given, the participant needs to move the COG as quickly (up to 8 seconds) and accurately as possible from a central position out towards one of eight

targets.[36]

1.3 RWS: The RWS evaluates the participant's ability to perform rhythmic movements of their COG moves from left to right (lateral) and forward to backward (anterior/posterior) between two targets at three different speeds (slow, medium and fast).[37] Movement velocity and directional control are measured in each direction and speed.

2. sEMG recordings

The sEMG recordings will be conducted in accordance with SENIAM guidelines.[38] A 20-channel wireless BTS-FREEEMG 300 (BTS Biomechanics Ltd, Italy) is used to collect the sEMG signals of the following muscles: bilateral rectus abdominis (RA), external oblique muscle (EO), erector spinae (longissimus), rectus femoris (RF), biceps femoris (BF), tibialis anterior (TA) and soleus (Table 2 and Figure 5 illustrate the sensor locations on individual muscles). Before starting, the skin should be cleaned using 75% alcohol and would be shaved if needed to ensure a maximum skin impedance below 5kΩ. After skin preparation, the participant has to be placed in the starting posture that depends on the muscle at which the electrodes will be placed. A pair of pre-gelled electrodes certified for a medical use and complying with the directive 93/42/EEC (amended by 2007/47/EC) are placed on the belly of the target muscle with an interelectrode distance of 2 cm.[39] When the electrodes are placed and fixed, a certified physical therapist will teach the patient to perform the maximum voluntary isometric contraction (MVIC) of the target muscle. For individual muscles, we will record three 3s trails of MVIC with a 2min rest between each trail.

sEMG signals are sampled at 1000 Hz. Collected data are synchronously transmitted to a BTS EMG-Analyzer (BTS Bioengineering) with the band-pass filtered from 20 to 500Hz. We will rectify and filter the recorded signal and extract the data of averaged electromyography (AEMG), root mean square (RMS), mean power frequency (MPF) and median frequency

(MF) for subsequent analyses.

Table 2. The sensor locations of sEMG on individual muscles*

Muscle	Starting posture of participant	Electrode placement	
		Location	Orientation
RA	Supine or standing	At 2cm superior and 2-4cm lateral to the umbilicus	Vertical
EO	Supine or standing	At 2 finger width above the anterior half of the iliac crest	In the direction of the line from the outside of the 5-12 ribs to the anterior half of the iliac crest
longissimus	Prone with the lumbar vertebral columns slightly flexed	At 2 finger width lateral from the proc. spin. of L1.	Vertical
RF	Sitting on a table with the knees in slight flexion and the upper body slightly bend backward	At 50% on the line from the anterior spina iliaca superior to the superior part of the patella	In the direction of the line from the anterior spina iliaca superior to the superior part of the patella
BF	Lying on the belly with the face down with the thigh down on the table and the knees flexed (to less than 90 degrees) with the thigh in slight lateral rotation and the leg in slight lateral rotation with respect to the thigh	At 50% on the line between the ischial tuberosity and the lateral epicondyle of the tibia	In the direction of the line between the ischial tuberosity and the lateral epicondyle of the tibia
TA	Supine or sitting	At 1/3 on the line between the tip of the fibula and the tip of the medial malleolus	In the direction of the line between the tip of the fibula and the tip of the medial malleolus

soleus	Sitting with the knee approximately 90 degrees flexed and the heel / foot of the investigated leg on the floor	At 2/3 of the line between the medial condylis of the femur to the medial malleolus	In the direction of the line between the medial condylis to the medial malleolus

Abbreviations: sEMG, surface electromyography; RA, rectus abdominis; EO, external oblique muscle; RF, rectus femoris; BF, biceps femoris; TA, tibialis anterior.

* According to the SENIAM recommendations for sensor locations for muscles.

3. *resting-state fNIRS*

A multichannel fNIRS system with 24 sources and 24 detectors (NirScan, HuiChuang, China) will be used to record changes of oxygenated hemoglobin (HbO2), deoxygenated Hb and total Hb of the cerebral cortex when the participant is at rest. Relevant parameters are set as follows: the wavelengths are between 730 and 850 nm, the source-detector distance is 3 cm, and the sampling frequency is over 11Hz. The international 10/20 system is referenced for identifying optodes on the bilateral prefrontal and parietal lobes.[40] Collected fNIRS data are analyzed by the NirSpark software package with the band-pass filtered from 0.01 to 0.1 Hz. Extract the mean HbO2 value of each channel for statistical analyses.

4. *FMA-LE*

The lower extremity function of stroke patients is assessed by FMA-LE, which has good interrater reliability and concurrent validity.[41] The maximum score of this 17-item scale is 34. Each item is scored on a 3-point ordinal scale, with 0 for inability, 1 for partial ability, and 2 for full ability to perform the required movement.[42]

5. *BI*

The BI is a self-reported scale comprised of 10 items, including bathing, grooming, bladder management, bowel management, dressing, feeding, toilet use, transfers, ascending and descending stairs, and walking, to measure the basic activities of daily living (ADL). [43] The total scores vary from 0 (totally dependent) to 100 (independent). This scale has good clinimetric properties and excellent inter-rater reliability with standardized administration in stroke patients.[18 44]

Safety measurement

Possible stimulation-related adverse events, such as headache, nausea, neck pain, seizure, mood changes, fatigue, tinnitus, dizziness, sleepiness and syncope, are listed in the informed consent. An adverse reaction record is used to monitor and report in detail after each stimulation. In addition, any adverse events related to in conventional physical therapy will be also recorded using the adverse event case report form (CRF).

Randomization and blinding

The study is a randomized, double-blind, sham-controlled trial. Enrolled participants are randomly signed based on the computer-generated random numbers that are concealed in opaque numbered envelopes and opened in numerical order by a neutral non-involved researcher. We plan to blind the participants and evaluators. Once blinding fails, the participant will be removed. The sham coil is used to ensure the patients are blinded to the intervention. Outcome evaluations will be conducted by a professional clinician or by a qualified physical therapist who is blinded to the group assignment. An independent researcher is designated to complete the data analysis. Unblinding will be carried out after the data analysis is completed. In case of serious adverse events happen during interventions, emergency unblinding will be also implemented.

Data management and analysis

Data management

Data will be recorded on CRFs in a timely, complete and accurate manner. Two researchers independently input data into the Excel software of computer and proofread each other. Thus, electronic data will be stored and available by the relevant researcher only. The West China Hospital Clinical Trials and Biomedical Ethics Committee of Sichuan University are responsible for monitoring the safety and process of the study and has the right to terminate

the trial if serious advent events happened. All procedures will comply with the confidentiality standards for medical data.

Statistical analysis

Statistical analyses will be performed using GraphPad Prism 8.4.3 (GraphPad Software, Inc., La Jolla, CA, USA) based on the Intention-To-Treat (ITT) principle. Missing data are imputed using the last observation carried forward approach. The Shapiro-Wilk test is conducted to evaluate the normal distribution of data. The level of significance is set at $\alpha = 0.05$. Continuous variables, ordinal variables, and categorical variables are presented as mean (±standard deviation, SD), medians (interquartile range, IQR), and number (percentage, %), respectively. Based on different types of data, the independent-samples *t* test, Mann–Whitney U test, and chi-square test are used to compare the demographic and baseline data between groups. The two-way mixed measures analysis of variance (ANOVA) with group as a between-individual factor and time as a within-individual factor is performed for outcome measures analyses. Nonsphericity correct is conducted using the Greenhouse-Geisser correction if necessary, and Tukey's *post hoc* multiple comparison test is applied.

Patient and public involvement

Patients and the public are not involved in the study design, recruitment, implementation or report. However, the study results will be disseminated to the public through academic papers and conferences.

Ethical approval, trial registration and dissemination

The study was approved by the West China Hospital Clinical Trials and Biomedical Ethics Committee of Sichuan University on May 19, 2022 (ethics reference: 2022 (573)), and will be

conducted in accordance with the Declaration of Helsinki.

This protocol was registered on June 16, 2022, in the Chinese Clinical Trial Registry with the registration number is ChiCTR2200061225. All participants will be fully informed of the study procedures and sign the informed consent voluntarily before inclusion (see Appendix). The private information of all participants will be kept confidential through securing in a locked cabinet and only accessible to researchers of the study. However, the results of this study will be published in peer-reviewed journals and disseminated in academic conferences.

Discussion

At present, there is no research has revealed the effect and potential mechanism of cerebellar vermis iTBS stimulation on balance in subacute stroke patients. This prospective single-center double-blind randomized controlled clinical trial with 3-week intervention and 3-week follow-up is designed to confirm its effectiveness.

Our study will comprehensively assess the trunk control and balance function by clinical scales, balance tests via the Smart Equitest Balance Master System and sEMG measurements. Additionally, we will also collect the concentration of HbO2 in cerebral cortex via the resting-state fNIRS. Integrated data results sufficiently verify the research hypothesis.

For trunk control, the scores of TIS reveal the motor impairment of the trunk for stroke patients. sEMG signal reflects the activation of muscles directly and contains information about movement intention generated by the brain.[45] AEMG represents the degree of muscle activation and the synchronization of activated motor units. RMS quantifies the effort of the muscle. MPF and MF are kinds of frequency domain features and indicate muscle fatigue.[46 47]

For balance function, the scores of BBS reflect the overall performance of static and dynamic balance. Accurate integration of sensory information is critical to maintaining balance. The composite equilibrium score of SOT characterizes the impairments of individual sensory

systems.[48] Ability to voluntarily move the COG within the LOS is fundamental to mobility tasks. By LOS test, reaction time, movement velocities and excursions are recorded to measure the voluntary ability to shift the COG without losing balance. Reaction time reflects the ability of cognitive processing. Movement velocities indicate the high-level central nervous system function. Excursions can be restricted by biomechanical deficits.[49] Overall, limitations in the LOS are associated with instability during weight-shifting activities. RWS measures movement velocity and directional control during rhythmic movements. Rhythmic, reciprocal movement patterns are required in daily activities. Stroke patients with disrupted normal rhythmic movement control are exhibit reduced velocities and/or poor directional control ability.[50]

For cortical activation, fNIRS is a widespread non-invasive measurement which provides real-time monitoring hemodynamic signals to reflect the changes of brain activation.[51] Increased HbO2 is positively correlated with cortical excitability. Besides, balance function and postural stability are positively related to the changes of HbO2 signals in the bilateral SMA in stroke patients.[52] Additionally, our previous work have revealed single-session cerebellar vermis iTBS can increase the bilateral SMA excitability during the balance tasks in healthy adults.[21]

We hypothesize that cerebellar vermis iTBS can promote the activation of muscles in trunk and lower limbs, and increase the excitability of SMA to improve trunk control and balance function in patients after stroke. Cerebellar vermis plays an important role in balance and motor control. SMA contributes to anticipatory postural adjustments and postural stability during gait initiation.[53] iTBS consists of high-frequency stimulation bursts to strongly modulate the neural activity of cerebellar vermis. Given that studies in humans have shown iTBS drives acute changes to motor behavior and neuronal excitability.[54] The possible mechanism has been reported by an animal study that iTBS can promote neural structural

remodeling and functional recovery by enhancing neurogenesis and migration via miR-551b-5p/BDNF/TrkB pathway.[55] The study of cerebellar vermis stimulation was first reported in 1995, which investigated its effects on saccade metrics in man via TMS.[56] At present, researchers reported that cerebellar vermis is a safe and well-tolerated brain stimulation technology having a potential therapeutic effect on schizophrenia.[57] In addition, cerebellar vermis rTMS can induce a suppressive effect on pharyngeal motor cortical activity and swallowing behavior.[58] However, limited researches have reported that cerebellar vermis plays an important role in postural response and balance stability.[13 59] Therefore, we hopefully identify the effectiveness of cerebellar vermis iTBS in trunk control and balance function for subacute stroke individuals. Our results may provide valuable information to develop a novel treatment method for the rehabilitation of balance dysfunction after stroke.

Author contributions: Conceptualization, validation, and original draft: YC. Recruitment: LH, HHJ, and QCW. Data collection: YC, WS, and HXT. Data analysis: CFG and QFG. Manuscript review and editing: CFG and QG. QG designed the trial and was responsible for the manuscript. All authors read and approved the final manuscript.

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References

1. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;392(10159):1859-922. doi: 10.1016/s0140-6736(18)32335-3 [published Online First: 2018/11/13]
2. Hankey GJ. Stroke. *Lancet* 2017;389(10069):641-54. doi: 10.1016/s0140-6736(16)30962-x [published Online First: 2016/09/18]
3. Komiya M, Maeda N, Narahara T, et al. Effect of 6-Week Balance Exercise by Real-Time Postural Feedback System on Walking Ability for Patients with Chronic Stroke: A Pilot Single-Blind Randomized Controlled Trial. *Brain Sci* 2021;11(11) doi: 10.3390/brainsci11111493 [published Online First: 2021/11/28]
4. Zhang Y, Wang C, Yang J, et al. Comparing the Effects of Short-Term Liuzijue Exercise and Core Stability Training on Balance Function in Patients Recovering From Stroke: A Pilot Randomized Controlled Trial. *Front Neurol* 2022;13:748754. doi: 10.3389/fneur.2022.748754 [published Online First: 2022/03/05]
5. Chen Y, Gao Q, He CQ, et al. Effect of Virtual Reality on Balance in Individuals With Parkinson Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Phys Ther* 2020;100(6):933-45. doi: 10.1093/ptj/pzaa042 [published Online First: 2020/03/12]
6. Luque-Moreno C, Kiper P, Solís-Marcos I, et al. Virtual Reality and Physiotherapy in Post-Stroke Functional Re-Education of the Lower Extremity: A Controlled Clinical Trial on a New Approach. *J Pers Med* 2021;11(11) doi: 10.3390/jpm11111210 [published Online First: 2021/11/28]
7. Marchesi G, Ballardini G, Barone L, et al. Modified Functional Reach Test: Upper-Body Kinematics and Muscular Activity in Chronic Stroke Survivors. *Sensors (Basel)* 2021;22(1) doi: 10.3390/s22010230 [published Online First: 2022/01/12]
8. Schröder J, Saeys W, Yperzeele L, et al. Time Course and Mechanisms Underlying Standing Balance Recovery Early After Stroke: Design of a Prospective Cohort Study With Repeated Measurements. *Front Neurol* 2022;13:781416. doi: 10.3389/fneur.2022.781416 [published Online First: 2022/03/11]
9. Karthikbabu S, Verheyden G. Relationship between trunk control, core muscle strength and balance confidence in community-dwelling patients with chronic stroke. *Top Stroke*

Rehabil 2021;28(2):88-95. doi: 10.1080/10749357.2020.1783896 [published Online First: 2020/06/24]

10. D'Angelo E. Physiology of the cerebellum. *Handb Clin Neurol* 2018;154:85-108. doi: 10.1016/B978-0-444-63956-1.00006-0 [published Online First: 2018/06/16]
11. Roostaei T, Nazeri A, Sahraian MA, et al. The human cerebellum: a review of physiologic neuroanatomy. *Neurol Clin* 2014;32(4):859-69. doi: 10.1016/j.ncl.2014.07.013 [published Online First: 2014/12/03]
12. De Bartolo P, Florenzano F, Burello L, et al. Activity-dependent structural plasticity of Purkinje cell spines in cerebellar vermis and hemisphere. *Brain structure & function* 2015;220(5):2895-904. doi: 10.1007/s00429-014-0833-6 [published Online First: 2014/07/16]
13. Lam CK, Tokuno CD, Staines WR, et al. The direction of the postural response to a vestibular perturbation is mediated by the cerebellar vermis. *Exp Brain Res* 2016;234(12):3689-97. doi: 10.1007/s00221-016-4766-6 [published Online First: 2016/09/08]
14. Marfeo A. Neuroanatomy Through Clinical Cases: Inc. Publishers 2010.
15. Ilg W, Giese MA, Gizewski ER, et al. The influence of focal cerebellar lesions on the control and adaptation of gait. *Brain* 2008;131(Pt 11):2913-27. doi: 10.1093/brain/awn246 [published Online First: 2008/10/07]
16. Ille S, Kelm A, Schroeder A, et al. Navigated repetitive transcranial magnetic stimulation improves the outcome of postsurgical paresis in glioma patients - A randomized, double-blinded trial. *Brain Stimul* 2021;14(4):780-87. doi: 10.1016/j.brs.2021.04.026 [published Online First: 2021/05/14]
17. Chen SC, Yang LY, Adeel M, et al. Transcranial electrostimulation with special waveforms enhances upper-limb motor function in patients with chronic stroke: a pilot randomized controlled trial. *J Neuroeng Rehabil* 2021;18(1):106. doi: 10.1186/s12984-021-00901-8 [published Online First: 2021/07/02]
18. Chen Y, Wei QC, Zhang MZ, et al. Cerebellar Intermittent Theta-Burst Stimulation Reduces Upper Limb Spasticity After Subacute Stroke: A Randomized Controlled Trial. *Front Neural Circuits* 2021;15:655502. doi: 10.3389/fncir.2021.655502 [published Online First: 2021/11/16]
19. Liao LY, Xie YJ, 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(1):23-32. doi: 10.1177/1545968320971735 [published Online First: 2020/11/10]

20. Xie YJ, Wei QC, Chen Y, et al. Cerebellar Theta Burst Stimulation on Walking Function in Stroke Patients: A Randomized Clinical Trial. *Front Neurosci* 2021;15:688569. doi: 10.3389/fnins.2021.688569 [published Online First: 2021/11/13]
21. Tan H-X, Wei Q-C, Chen Y, et al. The Immediate Effects of Intermittent Theta Burst Stimulation of the Cerebellar Vermis on Cerebral Cortical Excitability During a Balance Task in Healthy Individuals: A Pilot Study. *Frontiers in Human Neuroscience* 2021;15 doi: 10.3389/fnhum.2021.748241
22. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158(3):200-7. doi: 10.7326/0003-4819-158-3-201302050-00583 [published Online First: 2013/01/09]
23. Chinese Society of Neurology CSS. Diagnostic criteria of cerebrovascular diseases in China (version 2019). *Chinese Journal of Neurology* 2019;52(09):710-15. doi: 10.3760/cma.j.issn.1006?7876.2019.09.003
24. Rossi S, Antal A, Bestmann S, et al. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. *Clin Neurophysiol* 2021;132(1):269-306. doi: 10.1016/j.clinph.2020.10.003 [published Online First: 2020/11/28]
25. Garg S, Sinha VK, Tikka SK, et al. The efficacy of cerebellar vermal deep high frequency (theta range) repetitive transcranial magnetic stimulation (rTMS) in schizophrenia: A randomized rater blind-sham controlled study. *Psychiatry Res* 2016;243:413-20. doi: 10.1016/j.psychres.2016.07.023 [published Online First: 2016/07/28]
26. Huang YZ, Edwards MJ, Rounis E, et al. Theta burst stimulation of the human motor cortex. *Neuron* 2005;45(2):201-6. doi: 10.1016/j.neuron.2004.12.033 [published Online First: 2005/01/25]
27. Spampinato D, Ibáñez J, Spanoudakis M, et al. Cerebellar transcranial magnetic stimulation: The role of coil type from distinct manufacturers. *Brain Stimul* 2020;13(1):153-56. doi: 10.1016/j.brs.2019.09.005 [published Online First: 2019/10/22]
28. Kumar N, Vishnubhatla S, Wadhawan AN, et al. A randomized, double blind, sham-controlled trial of repetitive transcranial magnetic stimulation (rTMS) in the treatment of negative symptoms in schizophrenia. *Brain Stimul* 2020;13(3):840-49. doi:

10.1016/j.brs.2020.02.016 [published Online First: 2020/04/15]

29. Meseguer-Henarejos AB, Rubio-Aparicio M, López-Pina JA, 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(5):570-84. doi: 10.23736/s1973-9087.19.05363-2 [published Online First: 2019/04/09]
30. Hyun SJ, Lee J, Lee BH. The Effects of Sit-to-Stand Training Combined with Real-Time Visual Feedback on Strength, Balance, Gait Ability, and Quality of Life in Patients with Stroke: A Randomized Controlled Trial. *Int J Environ Res Public Health* 2021;18(22) doi: 10.3390/ijerph182212229 [published Online First: 2021/11/28]
31. Chou HY, Lo YC, Tsai YW, et al. Increased Anxiety and Depression Symptoms in Post-Acute Care Patients with Stroke during the COVID-19 Pandemic. *Int J Environ Res Public Health* 2021;19(1) doi: 10.3390/ijerph19010162 [published Online First: 2022/01/12]
32. Zhao J, Chau JPC, Zang Y, et al. Psychometric properties of the Chinese version of the Trunk Impairment Scale in people with a stroke. *Health Qual Life Outcomes* 2021;19(1):85. doi: 10.1186/s12955-021-01730-y [published Online First: 2021/03/12]
33. Thijs L, Voets E, Wiskerke E, et al. Technology-supported sitting balance therapy versus usual care in the chronic stage after stroke: a pilot randomized controlled trial. *J Neuroeng Rehabil* 2021;18(1):120. doi: 10.1186/s12984-021-00910-7 [published Online First: 2021/07/30]
34. Yin L, Liu K, Liu C, et al. Effect of Kinesiology Tape on Muscle Activation of Lower Extremity and Ankle Kinesthesia in Individuals With Unilateral Chronic Ankle Instability. *Front Physiol* 2021;12:786584. doi: 10.3389/fphys.2021.786584 [published Online First: 2022/01/04]
35. Bultitude JH, Pidgeon DM, LeBlanc PR, et al. Two weeks of twice-daily prism adaptation treatment does not improve posture or gait in Parkinson's disease: a double-blind randomized controlled trial. *Trials* 2021;22(1):846. doi: 10.1186/s13063-021-05832-2 [published Online First: 2021/11/27]
36. Kolářová B, Janura M, Svoboda Z, et al. Postural Control Strategies and Balance-Related Factors in Individuals with Traumatic Transtibial Amputations. *Sensors (Basel)* 2021;21(21) doi: 10.3390/s21217284 [published Online First: 2021/11/14]
37. Rossi-Izquierdo M, Santos-Pérez S, Faraldo-García A, et al. Impact of obesity in elderly

patients with postural instability. *Aging Clin Exp Res* 2016;28(3):423-8. doi: 10.1007/s40520-015-0414-4 [published Online First: 2015/07/19]

38. Hermens HJ, Freriks B, Disselhorst-Klug C, et al. Development of recommendations for SEMG sensors and sensor placement procedures. *Journal of Electromyography and Kinesiology* 2000;10(5):361-74. doi: 10.1016/s1050-6411(00)00027-4

39. Shen Y, Chen L, Zhang L, et al. Effectiveness of a Novel Contralaterally Controlled Neuromuscular Electrical Stimulation for Restoring Lower Limb Motor Performance and Activities of Daily Living in Stroke Survivors: A Randomized Controlled Trial. *Neural Plast* 2022;2022:5771634. doi: 10.1155/2022/5771634 [published Online First: 2022/01/25]

40. Sun W, Wu X, Zhang T, et al. Narrowband Resting-State fNIRS Functional Connectivity in Autism Spectrum Disorder. *Front Hum Neurosci* 2021;15:643410. doi: 10.3389/fnhum.2021.643410 [published Online First: 2021/07/03]

41. Wang YL, Lin GH, Huang YJ, et al. Refining 3 Measures to Construct an Efficient Functional Assessment of Stroke. *Stroke* 2017;48(6):1630-35. doi: 10.1161/strokeaha.116.015516 [published Online First: 2017/05/05]

42. Akazawa N, Kishi M, Hino T, et al. Increased intramuscular adipose tissue of the quadriceps is related to decreased activities of daily living in patients who have had a stroke. *Nutrition* 2021;90:111277. doi: 10.1016/j.nut.2021.111277 [published Online First: 2021/05/20]

43. Liu F, Tsang RC, Zhou J, et al. Relationship of Barthel Index and its Short Form with the Modified Rankin Scale in acute stroke patients. *J Stroke Cerebrovasc Dis* 2020;29(9):105033. doi: 10.1016/j.jstrokecerebrovasdis.2020.105033 [published Online First: 2020/08/19]

44. Harrison JK, McArthur KS, Quinn TJ. Assessment scales in stroke: clinimetric and clinical considerations. *Clin Interv Aging* 2013;8:201-11. doi: 10.2147/cia.S32405 [published Online First: 2013/02/27]

45. Qing Z, Lu Z, Cai Y, et al. Elements Influencing sEMG-Based Gesture Decoding: Muscle Fatigue, Forearm Angle and Acquisition Time. *Sensors (Basel)* 2021;21(22) doi: 10.3390/s21227713 [published Online First: 2021/11/28]

46. Wei P, Zhang J, Wang B, et al. Surface Electromyography and Electroencephalogram-Based Gait Phase Recognition and Correlations Between Cortical and Locomotor Muscle in the Seven Gait Phases. *Front Neurosci* 2021;15:607905. doi:

10.3389/fnins.2021.607905 [published Online First: 2021/06/08]

47. Alhusuny A, Cook M, Khalil A, et al. The relationship between visual impairments and activity of the neck/shoulder muscles among surgeons during simulated surgical tasks. *Surg Endosc* 2022 doi: 10.1007/s00464-021-08913-0 [published Online First: 2022/01/09]
48. Acuña SA, Tyler ME, Thelen DG. Individuals with Chronic Mild-to-Moderate Traumatic Brain Injury Exhibit Decreased Neuromuscular Complexity During Gait. *Neurorehabil Neural Repair* 2022:15459683221081064. doi: 10.1177/15459683221081064 [published Online First: 2022/03/25]
49. Carvalho GF, Becnel AR, Miske C, et al. Postural control impairment in patients with headaches-A systematic review and meta-analysis. *Headache* 2022;62(3):241-70. doi: 10.1111/head.14281 [published Online First: 2022/03/23]
50. Chen CL, Chen FF, Lin CH, et al. Effect of Anterior Ankle-Foot Orthoses on Weight Shift in Persons With Stroke. *Arch Phys Med Rehabil* 2015;96(10):1795-801. doi: 10.1016/j.apmr.2015.05.003 [published Online First: 2015/05/23]
51. Kinoshita S, Tamashiro H, Okamoto T, et al. Association between imbalance of cortical brain activity and successful motor recovery in sub-acute stroke patients with upper limb hemiparesis: a functional near-infrared spectroscopy study. *Neuroreport* 2019;30(12):822-27. doi: 10.1097/wnr.0000000000001283 [published Online First: 2019/07/10]
52. Fujimoto H, Mihara M, Hattori N, et al. Cortical changes underlying balance recovery in patients with hemiplegic stroke. *Neuroimage* 2014;85 Pt 1:547-54. doi: 10.1016/j.neuroimage.2013.05.014 [published Online First: 2013/05/21]
53. Richard A, Van Hamme A, Drevelle X, et al. Contribution of the supplementary motor area and the cerebellum to the anticipatory postural adjustments and execution phases of human gait initiation. *Neuroscience* 2017;358:181-89. doi: 10.1016/j.neuroscience.2017.06.047 [published Online First: 2017/07/05]
54. Tang AD, Bennett W, Bindoff AD, et al. Subthreshold repetitive transcranial magnetic stimulation drives structural synaptic plasticity in the young and aged motor cortex. *Brain Stimul* 2021;14(6):1498-507. doi: 10.1016/j.brs.2021.10.001 [published Online First: 2021/10/16]
55. Wang L, Zhou Y, Chen X, et al. Long-term iTBS promotes neural structural and functional recovery by enhancing neurogenesis and migration via miR-551b-

5p/BDNF/TrkB pathway in a rat model of cerebral ischemia-reperfusion injury. *Brain Res Bull* 2022;184:46-55. doi: 10.1016/j.brainresbull.2022.03.002 [published Online First: 2022/03/09]

56. Hashimoto M, Ohtsuka K. Transcranial magnetic stimulation over the posterior cerebellum during visually guided saccades in man. *Brain* 1995;118 (Pt 5):1185-93. doi: 10.1093/brain/118.5.1185 [published Online First: 1995/10/01]

57. Escelsior A, Belvederi Murri M, Calcagno P, et al. Effectiveness of Cerebellar Circuitry Modulation in Schizophrenia: A Systematic Review. *The Journal of nervous and mental disease* 2019;207(11):977-86. doi: 10.1097/nmd.0000000000001064 [published Online First: 2019/09/11]

58. Sasegbon A, Niziolek N, Zhang M, et al. The Effects of Midline Cerebellar rTMS on Human Pharyngeal Cortical Activity in the Intact Swallowing Motor System. *Cerebellum* 2021;20(1):101-15. doi: 10.1007/s12311-020-01191-x [published Online First: 2020/09/27]

59. Colnaghi S, Honeine JL, Sozzi S, et al. Body Sway Increases After Functional Inactivation of the Cerebellar Vermis by cTBS. *Cerebellum* 2017;16(1):1-14. doi: 10.1007/s12311-015-0758-5 [published Online First: 2016/01/19]

Legends

Figure 1. The flow diagram of the study design.

Figure 2. The schedule of enrolment, interventions, and assessments.

Figure 3. The Magstim Rapid2 stimulator with a BrainSight neuronavigation system.

Figure 4. The Smart Equitest Balance Master System®.

Figure 5. The sensor locations on individual muscles for sEMG recording (A. rectus abdominis, B. external oblique muscle, C. rector spinae (longissimus), D. rectus femoris, E. biceps femoris, F. tibialis anterior, G. soleus

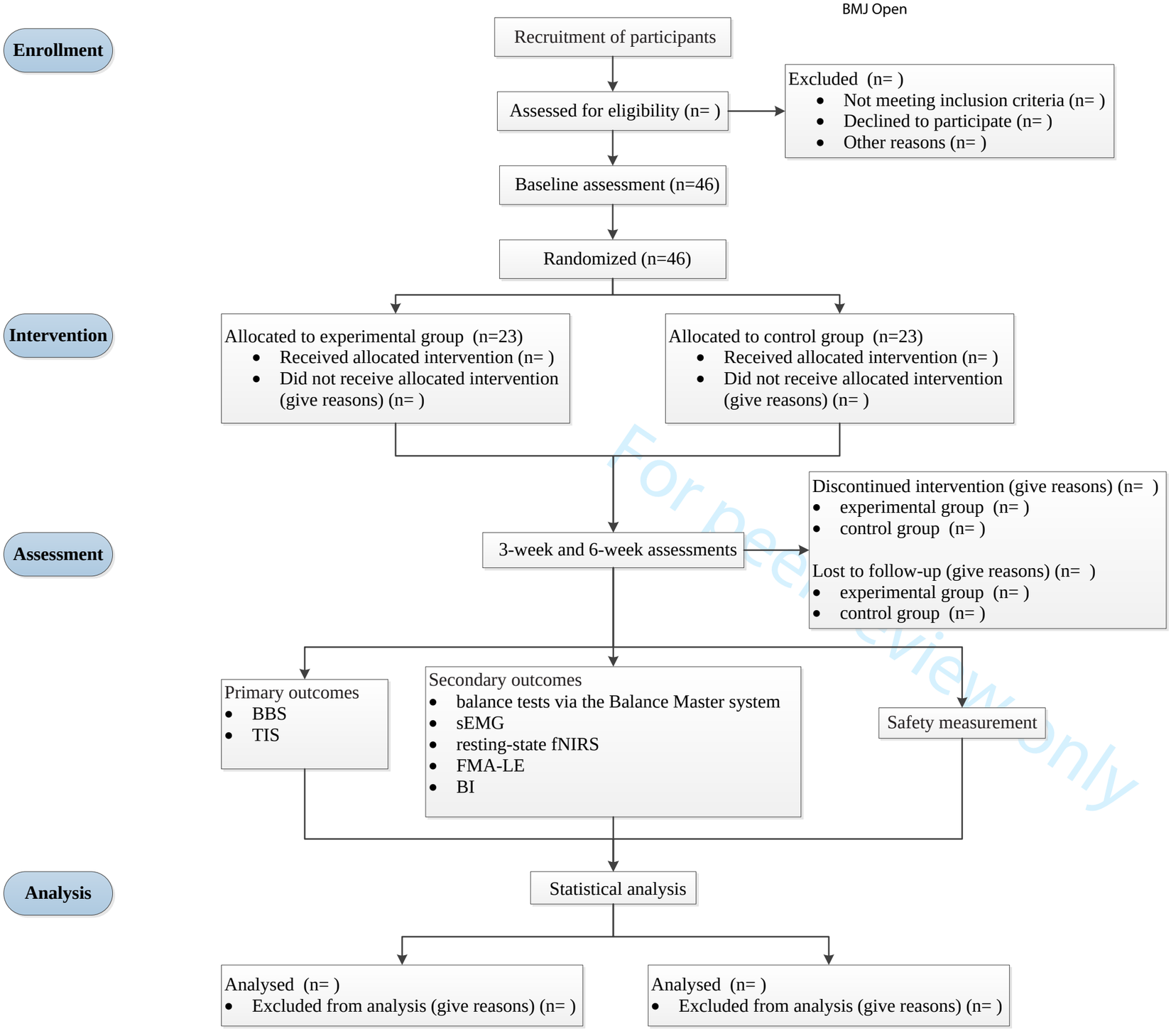

Figure 2. The schedule of enrolment, interventions, and assessments.

	Enrolment	**Allocation**	**Post-allocation**					
TIMEPOINT	$-t_1$	**0**	***W1***	***W2***	***W3***	***W4***	***W5***	***W6***
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Ethical approval and trial registration	X							
Allocation		X						
INTERVENTIONS:								
cerebellar vermis iTBS and conventional physical therapy			—	—	—			
sham stimulation and conventional physical therapy			—	—	—			
ASSESSMENTS:								
basic characteristics information		X						
BBS		X			X			X
TIS		X			X			X
balance tests via the Balance Master system		X			X			X
sEMG		X			X			X
resting-state fNIRS		X			X			X
FMA-LE		X			X			X
BI		X			X			X
Safety measurement			X	X	X	X	X	X

W, week; iTBS, intermittent theta-burst stimulation; BBS, Berg balance scale; TIS, trunk impairment scale; sEMG, surface electromyography; fNIRS, functional near-infrared spectroscopy; FMA-LE, Fugl-Meyer assessment scale score for lower extremities; BI, Barthel index.

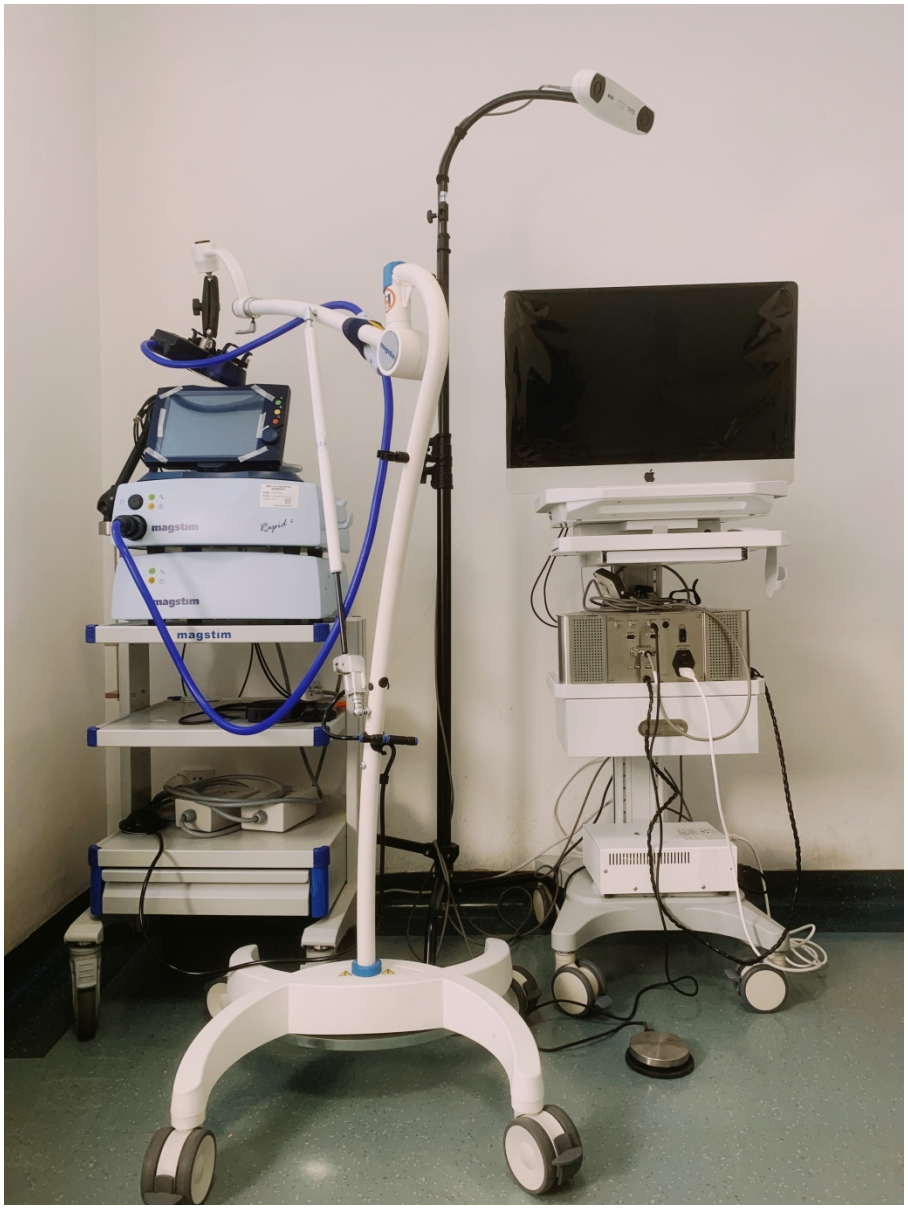

Figure 3. The Magstim Rapid2 stimulator with a BrainSight neuronavigation system.

1066x1422mm (72 x 72 DPI)

Figure 4. The Smart Equitest Balance Master System®.

1066x1422mm (72 x 72 DPI)

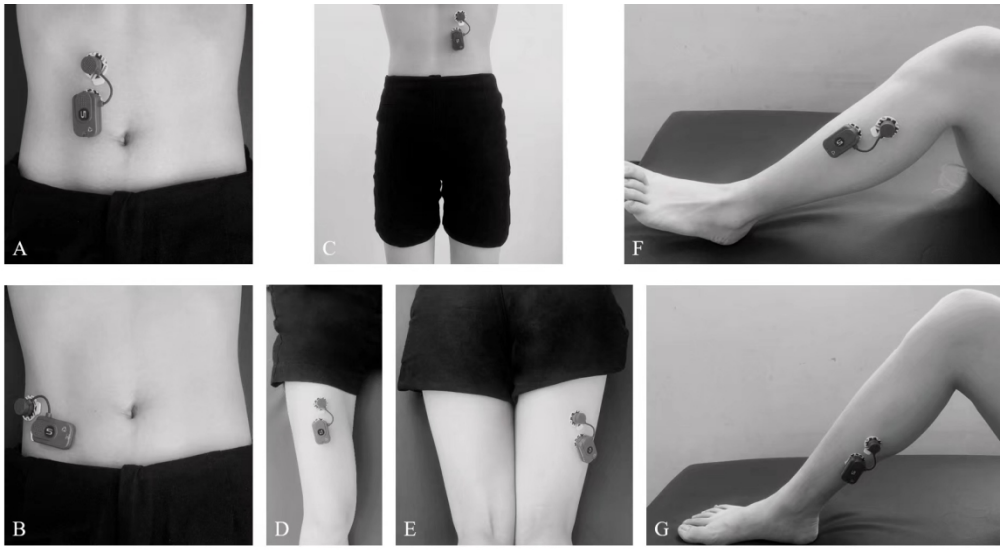

Figure 5. The sensor locations on individual muscles for sEMG recording (A. rectus abdominis, B. external oblique muscle, C. rector spinae (longissimus), D. rectus femoris, E. biceps femoris, F. tibialis anterior, G. soleus)

654x359mm (72 x 72 DPI)

Appendix. Informed Consent Form

West China Hospital, Sichuan University **Participant Informed Consent**			
Name:	**Gender:**	**Age:**	**Inpatient ID:**

Title of study: The effectiveness of cerebellar vermis intermittent theta burst stimulation in improving trunk control and balance function for subacute stroke patients: a randomized controlled trial

Investigator: Qiang Gao

Funding: NSFC 82172540 from the National Natural Science Foundation of China

What is the study about?

The aim of the study is to determine the effects of cerebellar vermis intermittent theta-burst stimulation (iTBS) on trunk control, muscle activation and balance function in stroke patients. We will recruit 46 patients who meet the inclusion criteria as follows: (1) a diagnosis of a stroke according to the Diagnostic criteria of cerebrovascular diseases in China (version 2019), (2) aged between 18 and 65 years, (3) first-ever unilateral stroke confirmed by imaging examination, (4) subacute stroke participants with the stroke onset ranged from 2 weeks to 6 months, (5) having motor deficit and balance dysfunction, with the Fugl-Meyer assessment scale score for lower extremities (FMA-LE) <34 points and BBS score <56 points. Patients were excluded if they presented one of the following: (1) coexisting other neurological diseases, (2) injury of cerebellar or brain stem, (3) having contraindications of iTBS (e.g., history of seizures, intracranial metallic implants, microprocessor implants in the body, suffering from tumorous, and pregnancy), (4) cognitive impairment with the mini-mental state examination (MMSE) score<27.

How long will I be in the study?

Your part in the study will last **6 weeks** with 3 weeks of intervention and 3 weeks of follow-up (excluding assessment).

What will happen in this study?

You will be randomized into either the experimental or control group according to the random number table. If you assigned to the experimental group will receive cerebellar vermis iTBS after routine daily conventional physical therapy, otherwise you will receive sham stimulation after routine daily conventional physical therapy. The overall intervention periods are five days a week for three consecutive weeks. You will be assessed before treatment, after 3 weeks of intervention and after 3 weeks of follow-up. The measures including clinical scales, balance tests via the Balance Master system, and the surface electromyography recording.

If you are eligible and wish to join the study, you must sign this consent form. If you do not sign the consent form you cannot join the study.

We will review this consent form with you. You will be given enough time to review the consent and have all your questions about the study answered. We will give you a signed copy of the consent for your records before treatment in person.

Study stuff will not know which group or study treatment you are assigned to. You should not join the study if you are not willing to take the study treatment (or join the group) you are assigned to.

What if I have questions?

You can contact the therapist at working hours if you have questions about the study. Qiang Gao (the director of therapists) is in charge of the study.

Do I have to be in the study?

You decide if you want to be in the study. Deciding not to take part will not affect your relationship with your therapist. If your therapist is an investigator for the

study, you may get a second opinion from another therapist not involved in the study.

You can leave the study at any time and you do not have to give a reason. Leaving the study will not affect your relationship with your therapist.

The study investigators may ask you to leave the study if it is in your best interest. The study investigator may ask you to leave the study if you do not follow the study rules.

What if I don't want to be in the study?

You can choose not to be in the study and you do not have to give a reason. You can choose to (talk to your doctor/therapist about other options, investigate outside resources on your own, etc.).

Are there any costs?

All study-related treatments are free.

Will I be paid for being in the study?

You will not be paid for being in the study.

Are there any risks?

There is always a small risk of a breech of confidentiality to your personal health information. However, these risks have been addressed and minimized as much as is possible.

You will be told about any new information that may affect your willingness to participate in the study.

There are some possible risks and side effects as follows: headache, nausea, neck pain, seizure, mood changes, fatigue, tinnitus, dizziness, sleepiness and syncope.

If you experience any side effects while on the study contact investigator (Qiang Gao) at any time as soon as possible.

What if I feel I've been hurt by taking part in the study?

If you feel you have been injured or harmed by taking part in this study, please contact investigator (Qiang Gao) at any time. If you feel you were harmed while taking part in this study, you may be treated at West China Hospital, Sichuan University. However, West China Hospital does not offer to pay the cost of this treatment.

If you feel your rights have been violated or you have harmed by this study, please contact your therapist.

Are there any benefits?

It is possible you may receive some benefit from cerebellar vermis iTBS and conventional physical therapy. iTBS is a novel form of rTMS, which can produce long-term potentiation and is more rapid and efficacious than standard rTMS. Cerebellar vermis is a cardinal structure involved in balance and motor control, which is responsible for regulating the trunk, head, neck and proximal limb muscles to control posture and maintain balance. There is no guarantee, however, that you will receive any benefit at all. Your participation will help us learn more about the effects of cerebellar vermis iTBS on trunk control, muscle activation and balance function in subacute stroke patients.

Your privacy is important

Protecting your privacy is very important to us.

During this study we will ask about your (past) and (current) medical history. This information will be used to determine your eligibility for the study and provide data for the study. Your personal health information will be kept private and only authorized study staff will have access to this information. We will use a study number instead of your name. All paper forms will be kept in a locked, secure office. All electronic data will be stored on password-protected computers. Your name will not be used in any publications or presentations about this study.

During the study, you may not be given access to medical information about you that is part of the study. When the study is over, you may request certain medical information collected about you that is part of your study medical record.

None of your personal information will be shared outside of West China Hospital.

By signing this consent form, you are stating that we can use your health information in the ways mentioned above for this study. You are not waiving any of your legal right by signing this form.

You have the right to take away your permission to use your health information collected as part of the study. In order to do this, you must send a written request to: Qiang Gao, department of rehabilitation, West China hospital, Sichuan University

Once your letter is received, no additional information about you will be collected from you for this study. Any data that were collected before we receive your letter will continue to be used for the study. Taking away your permission to use your health information will not affect your relationship with West China Hospital.

We are collecting only the personal health information that we need for the specific

purpose of this study. Your personal health information cannot be used for additional research purpose.

The West China hospital may be required to provide copies of your personal information to government agencies as required by law.

Your permission to use your identifiable health information when the study is complete.

Signatures:

By signing this consent form, it means the following:

- I know my rights have not been waived by signing.
- I have had all of my questions answered and I know whom to ask if I have more questions.
- I have read this form and understand it.
- I want to join the study.
- I know I can leave the study at any time and do not have to give a reason.

_____ _____

Signature of Participant Date

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 17-18
	2b	All items from the World Health Organization Trial Registration Data Set	nil
Protocol version	3	Date and version identifier	nil
Funding	4	Sources and types of financial, material, and other support	20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page, 20
	5b	Name and contact information for the trial sponsor	Title page
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	20
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	nil
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6-7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5, Fig.2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5-6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	16
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	16
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	16
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	16
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16-17
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	16
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15-16
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17-18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	nil
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	nil
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	nil
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	nil
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary material
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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The effectiveness of cerebellar vermis intermittent theta burst stimulation in improving trunk control and balance function for subacute stroke patients: a randomized controlled trial protocol

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The effectiveness of cerebellar vermis intermittent theta burst stimulation in improving trunk control and balance function for subacute stroke patients: a randomized controlled trial protocol

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Abstract

Introduction Balance impairments frequently occur in stroke patients. Achieving effective core trunk stability is the key to improving balance ability. However, there is still a lack of advanced well-defined rehabilitation protocols for balance improvement in stroke patients. Intermittent theta-burst stimulation (iTBS) is a noninvasive brain activity modulation strategy that can produce long-term potentiation. The cerebellar vermis is a fundamental structure involved in balance and motor control. However, no study has demonstrated the therapeutic effect and potential mechanism of cerebellar vermis iTBS on balance in individuals with stroke.

Methods and Analysis This study will be a prospective single-centre double-blind randomized controlled clinical trial with a 3-week intervention and 3-week follow-up. Eligible participants will be randomly allocated to the experimental group or the control group in a 1:1 ratio. After routine conventional physical therapy, patients in the experimental group will receive cerebellar vermis iTBS, whereas patients in the control group will receive sham stimulation. The overall intervention period will be five days a week for three consecutive weeks. The outcomes will be measured at baseline (T0), 3 weeks postintervention (T1) and at the 3-week follow-up (T3). The primary outcomes are Berg Balance Scale (BBS) and Trunk Impairment Scale (TIS) scores. The secondary outcomes are balance tests scores via the Balance Master system, muscle activation of the trunk and lower limbs via the surface electromyography (sEMG) recordings, cerebral cortex oxygen concentrations measured via the resting-state functional near-infrared spectroscopy (fNIRS), and Fugl-Meyer Assessment of Lower Extremity (FMA-LE) and Barthel index (BI) scores.

Ethics and Dissemination This study was approved by the West China Hospital Clinical Trials and Biomedical Ethics Committee of Sichuan University. The trial registration number

is ChiCTR2200065369. All participants will sign the informed consent form voluntarily. The results of this study will be published in peer-reviewed journals and disseminated at academic conferences.

Strengths and limitations of this study

- Our study comprehensively assesses the trunk control and balance function by clinical scales, balance tests via the Smart Equitest Balance Master System, and surface electromyography (sEMG) measurements.
- Resting-state functional near-infrared spectroscopy (fNIRS) will be used to collect the concentration of HbO2 in the cerebral cortex.
- This study lacks a long-term follow-up assessment.

Introduction

Stroke is the third most common cause of disability worldwide.[1] The incidents, prevalence, and disability-adjusted life-years of stroke have increased over the past two decades[2], and are considered to place heavy economic burdens on society. Balance impairments frequently occur in patients with stroke, with a reported incidence ranging from 61% to 83%[3]. The main manifestations are postural instability, weak trunk control, and difficulty shifting weight,[4] which ultimately result in falls, poor mobility, decreased physical activity, and reduced quality of life in patients.[5] Therefore, improvement of balance function is a cardinal requirement in patients with stroke.

The trunk plays a fundamental role in trunk control, balance, and mobility during sitting and transferring.[6] The synchronized activity of trunk muscles is necessary for maintaining dynamic balance. In addition, proper trunk muscle control is essential for stabilizing distal

limbs.[7] Muscle weakness of the lower limbs is associated with decreased standing balance control.[8] Impaired trunk control and core muscle weakness attenuate balance and physical function in individuals after stroke.[9] Therefore, achieving effective core trunk stability is crucial to improving balance ability after stroke.

The cerebellum, a central brain structure located in the posterior cranial fossa, works in concert with the cerebral cortex, brainstem, and spinal cord and is involved in motor control.[10] [11] It consists of two lateral hemispheres and the cerebellar vermis. The cerebellar vermis is a fundamental structure involved in balance and motor processing,[12] [13] and is responsible for regulating the trunk, head, neck and proximal limb muscles to control posture and maintain balance.[14] Balance dysfunction in cerebellar disorders is most likely caused by lesions of the medial zone of the cerebellum.[15] At present, the main clinical interventions to improve the balance function in stroke rehabilitation are muscle strength training or balance training. The activation of the cerebellar vermis in the central nervous system through neuromodulation with noninvasive brain stimulation has great potential for enhancing balance function in stroke patients.

Repetitive transcranial magnetic stimulation (rTMS) is a safe, reliable, and standardized noninvasive brain activity modulation strategy to regulate cortical excitability and facilitate neural plasticity.[16] Intermittent theta-burst stimulation (iTBS) is a novel form of rTMS that can produce long-term potentiation and is more rapid and efficacious than standard rTMS.[17] Previously published studies revealed that iTBS over the cerebellar hemisphere could promote gait and balance recovery in patients with chronic ischemic stroke.[18] Similarly, our research group recently provided evidence that iTBS over the cerebellar hemisphere could promote upper limb spasticity, balance, and walking performance recovery in poststroke patients.[19-21] However, one of the results indicated that the difference in Berg Balance Scale (BBS) scores between the cerebellar iTBS group and the sham stimulation group weas 1.58

points, which did not reach the minimal clinically important difference.[22] Therefore, the identification of a more effective stimulation target for improving balance function after stroke is necessary. No study has demonstrated the therapeutic effect and potential mechanism of cerebellar vermis iTBS on balance in individuals with stroke. Our preliminary pilot study found that cerebellar vermis iTBS contributed to increasing the excitability of the bilateral supplementary motor areas (SMAs) during balance tasks in healthy adults.[23]

Objective

Since no clinical research verifying the effectiveness of cerebellar vermis iTBS stimulation has been reported, a randomized controlled double-blind trial will be conducted to determine the effects of cerebellar vermis iTBS on trunk control, muscle activation and balance function in subacute ischemic stroke patients. We hypothesize that cerebellar vermis iTBS can promote the activation of trunk and lower limb muscles and increase the excitability of SMAs to improve trunk control and balance function in patients with subacute ischemic stroke.

Methods

Study design and setting

This study will be a prospective single-centre double-blind randomized controlled clinical trial with a 3-week intervention and 3-week follow-up. The protocol strictly follows the Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) 2013 Statement.[24] Eligible participants will be randomly allocated to the experimental group or control group in a 1:1 ratio. After routine conventional physical therapy, patients assigned to the experimental group will receive cerebellar vermis iTBS, whereas patients assigned to the control group will receive sham stimulation. The overall intervention period will be five days a week for three consecutive weeks. The outcomes will be measured at baseline (T0), 3 weeks

postintervention (T1), and at the 3-week follow-up (T3). The whole study will be performed at the Department of Rehabilitation Medicine of Sichuan University West China Hospital (Chengdu, Sichuan Province, China). Figure 1 shows the flow diagram of the study design. We plan to start subject recruitment on the 1st of December 2022 and complete the trial in December 2025. Figure 2 illustrates the study schedule.

Sample size calculation

The sample size calculation was conducted via G*power of 3.1.9.2 based on the result of the BBS score in our published study, which indicated an estimated effect size of f =0.38.[20] Other parameters were set as follows: a significance level of α=0.05 (two tails), power (1–β) =90%, correlation among repeated measures=0.5, nonsphericity correction ε=1, number of measurements=3, and number of groups=2. Therefore, a sample size of n=40 was obtained. After allowing for a 15% dropout rate, a minimum total of 46 participants is needed.

Participants

Recruitment

The participants will be recruited from the Department of Rehabilitation Medicine of Sichuan University West China Hospital in Chengdu, Sichuan Province, China. After carefully screening the inclusion and exclusion criteria, voluntary participants will be required to provide written informed consent before the experiment.

Inclusion criteria

Participants will be considered for inclusion if they meet the following criteria:

(1) A diagnosis of ischemic stroke according to the *Diagnostic criteria of cerebrovascular diseases in China (version 2019)*.[25]

(2) Aged between 18 and 65 years.

(3) First-ever unilateral ischemic stroke confirmed by imaging examination.

(4) Subacute stroke participants with the stroke onset ranging from 2 weeks to 6 months.[26-28]

(5) Having motor deficit and balance dysfunction, with a Fugl-Meyer Assessment for Lower Extremities (FMA-LE) score <34 points and BBS score <56 points.[20]

Exclusion criteria

Participants will be excluded if they meet any of the following criteria:

(1) Diagnosis of coexisting other neurological diseases.

(2) Injury of cerebellum or brain stem.

(3) Having contraindications for iTBS (e.g., history of seizures, intracranial metallic implants, microprocessor implants in the body, tumours, and pregnancy)

(4) Cognitive impairment defined as a Mini-Mental State Examination (MMSE) score<27.

(5) Treatment with benzodiazepines, baclofen, antiepileptics and antidepressants.

Interventions

All enrolled participants will receive 1 session of cerebellar vermis iTBS or sham stimulation before routine conventional physical therapy from Monday to Friday, with a total of 15 sessions. Patients in the experimental group will receive cerebellar vermis iTBS coupled with conventional physical therapy, and those in the control group will receive sham stimulation coupled with conventional physical therapy. The whole intervention period will last for a total of three consecutive weeks.

Cerebellar vermis iTBS stimulation

The stimulation protocol will strictly adhere to the safety guidelines and recommendations endorsed by the International Federation for Clinical Neurophysiology in 2021.[29] We will use a Magstim Rapid2 stimulator (The Magstim Company Limited) connected to a 70 mm figure-

of-8 Double Rapid2 Air Cooled Coil (P/N 3910-00) to stimulate the cerebellar vermis (Figure 3). The centre of the coil will be placed tangentially to the target scalp area, and the coil current direction will point downwards. iTBS will be applied over the cerebellar vermis, 1 cm inferior to the inion.[30] We will use a neuronavigation system (BrainSightt, Rogue Research Inc.) coupled with a Polaris Vicra infrared camera to ensure that cerebellar vermis iTBS is applied over the same spot for the same participant across different sessions (Figure 3). The pattern of iTBS consists of 600 pulses containing 3 pulses at 50 Hz repeated at a rate of 5 Hz, with 20 trains of 10 bursts given at 8 seconds intervals.[31] The standard stimulus intensity will be set at 80% of the active motor threshold (AMT), which is the lowest intensity evoking at least five out of ten motor-evoked potentials (MEPs) with a peak-to-peak amplitude >200 μV in the abductor pollicis brevis muscle during 10% of the maximum voluntary contraction measured by a dynamometer.[21] If the participant cannot elicit MEPs or cannot tolerate the preset standard stimulus intensity, the stimulator output intensity will be set to the participant's maximum tolerated intensity.[32]

Sham stimulation

Participants in the control group will be treated identically to those in the experimental group, except the Magstim sham coil (P/N 3950-00) will be used to deliver the sham stimulation.[33] The sham coil has the same external appearance, parameters and application methods for stimulating the sensation produced by the real coil without inducing a magnetic field. Therefore, it can sufficiently ensure that the patients remain blinded to the intervention.

Conventional physical therapy

After receiving cerebellar vermis iTBS or sham stimulation, all participants will receive conventional physical therapy, including limb positioning, balance exercise, trunk control,

and postural and transfer training, with each session lasting 50 minutes during the intervention phase.

Criteria for discontinuing the allocated interventions

Interventions will be discontinued for participants if any of the following events occur:

(1) Serious adverse events, such as epilepsy, severe headache, persistent tinnitus and syncope, occur during the stimulation.

(2) Participants withdraw from the trial.

(3) Participants are not compliant with the allocation and intervention plan.

(4) Participants join in additional studies during the trial.

(5) Group exposure for participants and outcome evaluators lead to the failure of blindness.

Improving adherence strategies

To improve the participant compliance, the researcher in charge of the trial will contact the participants regularly to clarify their rehabilitation progress and discuss the subsequent physical therapy programme. Additionally, patients who complete the entire procedure in accordance with the protocol will be provided with a subject fee and an additional free rehabilitation consultation. If a participant drops out, the specific reasons for withdrawal will be recorded.

Outcome Measures

On the day of enrolment, the basic characteristics of the participants, including age, sex, type of stroke, lesion site, course of disease, degree of neurological deficit as assessed by the National Institutes of Health Stroke Scale (NIHSS), and cognitive function as assessed by the MMSE, will be documented. The outcome assessments will be conducted at the treatment site

at T0, T1 and T3. The primary outcomes are BBS and Trunk Impairment Scale (TIS) scores. The secondary outcomes are balance tests via the Balance Master system, muscle activation of the trunk and lower limbs via the surface electromyography (sEMG) recordings, cerebral cortex oxygen concentrations measured via the resting-state functional near-infrared spectroscopy (fNIRS), FMA-LE scores, and Barthel Index (BI) scores. Each assessment will be performed by a professional clinician or by a qualified physical therapist who will be blinded to the experimental condition of the participant.

Primary outcomes

1. BBS

The BBS is a well-validated scale for assessing balance among individuals with neurological disease.[34] It has high reliability and internal validity, with an intraclass correlation coefficient for inter-measure reliability and intra-measure reliability of 0.97 and 0.98, respectively.[35] This scale is a 14-item measure with a total score of 56, and the score of each item ranges from 0 (poor balance) to 4 (good balance).[36]

2. TIS

The TIS is a scale designed to assess motor impairment of the trunk after stroke, demonstrating the most promising performance in psychometric properties with satisfactory reliability and validity.[37] It is a 17-item scale used to evaluate static and dynamic sitting balance and trunk coordination for stroke patients, with a total score ranging from 0 to 23 points.[38] A higher score indicates better trunk control.

Secondary outcomes

1. Balance tests via the Balance Master system

The assessments of dynamic balance and postural control abilities will be performed by the

Sensory Organization Test (SOT), Limits of Stability (LOS), and Rhythmic Weight Shift (RWS) via the Smart Equitest Balance Master System® (NeuroCom Int., Inc., Clackamas, Oregon, USA). (Figure 4)

1.1 SOT: The SOT evaluates postural control when participants undergo different somatosensory, visual, and vestibular feedback perturbations. During testing, inaccurate interference information is delivered to the patient's eyes, feet, and joints and is controlled through calibrated sway referencing of the support surface and/or visual surroundings. The participant is required to maintain balance to keep their centre of gravity (COG) as steady as possible. A composite equilibrium score is provided to characterize the participant's overall level of performance through the six conditions described in Table 1. During the SOT, each trial lasts for 20 seconds and is repeated three times.[39 40]

Table 1. Sensory Organization Test

Condition	Vision	Surface	Surround	Interference
1	Eyes open	Stable	Fixed	Null
2	Eyes closed	Stable	Fixed	Vision
3	Eyes open	Stable	Unfixed	Vision
4	Eyes open	Unstable	Fixed	Somatosensation
5	Eyes closed	Unstable	Fixed	Somatosensation and Vision
6	Eyes open	Unstable	Unfixed	Somatosensation and Vision

1.2 LOS: The LOS quantifies the voluntary ability to shift the COG in eight different directions: forwards, forwards-right, right, backwards-right, backwards, backwards-left, left, and forwards-left. When the test is performed, a real-time display of the participant's COG position in relation to targets placed at the centre of the base of support and the stability limits is shown. Once the command is given, the participant must move their COG from a central position out towards one of the eight targets as quickly (up to 8 seconds) and accurately as

possible.[41]

1.3 RWS: The RWS evaluates a participant's ability to perform rhythmic movements of their COG from left to right (lateral) and forwards to backwards (anterior/posterior) between two targets at three different speeds (slow, medium and fast).[42] Movement velocity and directional control are measured for each direction and speed.

2. sEMG recordings

The sEMG recordings will be conducted in accordance with the Surface ElectroMyoGraphy for the Non-Invasive Assessment of Muscles (SENIAM) guidelines.[43] A 20-channel wireless BTS-FREEEMG 300 (BTS Biomechanics Ltd, Italy) will be used to collect the sEMG signals of the following muscles: bilateral rectus abdominis (RA), external oblique muscle (EO), erector spinae (longissimus), rectus femoris (RF), biceps femoris (BF), tibialis anterior (TA) and soleus (Table 2 and Figure 5 illustrate the sensor locations on the individual muscles). Before starting, the skin will be cleaned using 75% alcohol and would be shaved if needed to ensure a maximum skin impedance below 5 kΩ. After skin preparation, the participant will be put into the starting posture, depending on the muscle at which the electrodes will be placed. A pair of pre-gelled electrodes certified for medical use and in compliance with the directive 93/42/EEC (amended by 2007/47/EC) will be placed on the belly of the target muscle with an interelectrode distance of 2 cm.[44] When the electrodes are placed and fixed, a certified physical therapist will teach the patient to perform the maximum voluntary isometric contraction (MVIC) of the target muscle. For individual muscles, we will record three we will record three 3 seconds MVIC trials with a 2 minutes rest period between each trial. sEMG signals will be sampled at 1000 Hz. Collected data will be synchronously transmitted to a BTS EMG-Analyzer (BTS Bioengineering) with the bandpass filtered from 20 to 500 Hz. We will rectify and filter the recorded signal and extract the data of averaged electromyography (AEMG), root mean square (RMS), mean power frequency (MPF) and

median frequency (MF) data for subsequent analyses.

Table 2. The sensor locations on individual muscles for sEMG recordings *

Muscle	Starting posture of participant	Electrode placement	
		Location	Orientation
RA	Supine or standing	2 cm superior and 2-4 cm lateral to the umbilicus	Vertical
EO	Supine or standing	At a 2-finger width above the anterior half of the iliac crest	In the direction of the line from the outside of the 5-12 ribs to the anterior half of the iliac crest
Longissimus	Prone with the lumbar vertebral columns slightly flexed	At a 2-finger width lateral from the proc. spin. of L1.	Vertical
RF	Sitting on a table with the knees in slight flexion and the upper body bend slightly backwards	At 50% on the line from the anterior spina iliaca superior to the superior part of the patella	In the direction of the line from the anterior spina iliaca superior to the superior part of the patella
BF	Lying on the belly with the face down with the thigh down on the table, the knees flexed (to less than 90 degrees), the thigh in a slight lateral rotation and the leg in a slight lateral rotation with respect to the thigh	At 50% on the line between the ischial tuberosity and the lateral epicondyle of the tibia	In the direction of the line between the ischial tuberosity and the lateral epicondyle of the tibia
TA	Supine or sitting	At 1/3 on the line between the tip of the fibula and the tip of the medial malleolus	In the direction of the line between the tip of the fibula and the tip of the medial malleolus

Soleus	Sitting with the knee flexed approximately 90 degrees and the heel/foot of the investigated leg on the floor	At 2/3 of the line between the medial condyle of the femur to the medial malleolus	In the direction of the line between the medial condyle to the medial malleolus

Abbreviations: sEMG, surface electromyography; RA, rectus abdominis; EO, external oblique muscle; RF, rectus femoris; BF, biceps femoris; TA, tibialis anterior.

* According to the SENIAM recommendations for sensor locations for muscles.

3. Resting-state fNIRS

A multichannel fNIRS system with 24 sources and 24 detectors (NirScan, HuiChuang, China) will be used to record changes in oxygenated haemoglobin (HbO2), deoxygenated Hb and total Hb of the cerebral cortex when the participant is at rest. Relevant parameters will be set as follows: the wavelengths are between 730 and 850 nm, the source-detector distance is 3 cm, and the sampling frequency is over 11 Hz. The international 10/20 system is referenced for identifying optodes on the bilateral prefrontal and parietal lobes.[45] Collected fNIRS data will be analyses by the NirSpark software package with the bandpass filtering from 0.01 to 0.1 Hz. The mean HbO2 value of each channel will be extracted for statistical analyses.

4. FMA-LE

The lower extremity function of stroke patients will be assessed by FMA-LE, which has good interrater reliability and concurrent validity.[46] The maximum score of this 17-item scale is 34 points. Each item is scored on a 3-point ordinal scale, with 0 points for inability, 1 point for partial ability, and 2 points for full ability to perform the required movement.[47]

5. BI

The BI is a self-reported scale comprising of 10 items, including bathing, grooming, bladder management, bowel management, dressing, feeding, toilet use, transfers, ascending and descending stairs, and walking, to measure basic activities of daily living.[48] The total scores vary from 0 (totally dependent) to 100 (independent). This scale has good clinimetric properties and excellent interrater reliability with standardized administration for stroke patients.[19 49]

Safety measurements

Possible stimulation-related adverse events, such as headache, nausea, neck pain, seizure, mood changes, fatigue, tinnitus, dizziness, sleepiness and syncope, are listed in the informed

consent form. An adverse reaction record will be used to monitor and provide detailed reports after each stimulation. In addition, any adverse events related to in conventional physical therapy will also be recorded using the adverse event case report form (CRF).

Randomization and blinding

The study will be a randomized, double-blind, sham-controlled trial. Enrolled participants will be randomly assigned based on the computer-generated random numbers that are concealed in opaque numbered envelopes and opened in numerical order by a neutral noninvolved researcher. We plan to blind the participants and evaluators. If blinding fails, the participants will be removed. A sham coil will be used to ensure that the patients are blinded to the intervention. Outcome evaluations will be conducted by a professional clinician or by a qualified physical therapist who is blinded to the group assignment. An independent researcher will be designated to complete the data analysis. Unblinding will be carried out after the data analysis is completed. In the case of serious adverse events occurring during interventions, emergency unblinding will also be implemented.

Data management and analysis

Data management

Data will be recorded on CRFs in a timely, complete and accurate manner. Two researchers will independently input data into Excel software and cross-check each other. Thus, electronic data will be stored and available to the relevant researcher only. The West China Hospital Clinical Trials and Biomedical Ethics Committee of Sichuan University are responsible for monitoring the safety and process of the study and have the right to terminate the trial if serious advent events occur. All procedures will comply with the confidentiality standards for medical data.

Statistical analysis

Statistical analyses will be performed using GraphPad Prism 8.4.3 (GraphPad Software, Inc., La Jolla, CA, USA) based on the intention-to-treat principle. Missing data will be imputed using the last observation carried forwards approach. The Shapiro-Wilk test will be conducted to evaluate the normal distribution of the data. The level of significance is set at $\alpha = 0.05$. Continuous variables, ordinal variables, and categorical variables will be presented as mean (±standard deviation, SD), medians (interquartile range, IQR), and number (percentage, %), respectively. Based on different types of data, the independent-samples *t* test, Mann–Whitney U test, and chi-square test will be used to compare demographic and baseline data between groups. Two-way mixed measures analysis of variance with group as the between-individual factor and time as the within-individual factor will be performed for outcome measures analyses. Nonsphericity correction will be conducted using the Greenhouse-Geisser correction if necessary, and Tukey's *post hoc* multiple comparison test will be applied.

Patient and public involvement

Patients and the public will not be involved in the study design, recruitment, implementation or reporting. However, the study results will be disseminated to the public through academic papers and conferences.

Ethical approval, trial registration and dissemination

The study was approved by the West China Hospital Clinical Trials and Biomedical Ethics Committee of Sichuan University on May 19, 2022 (ethics reference: 2022 (573)), and will be conducted in accordance with the Declaration of Helsinki.

This protocol was registered on November 3rd, 2022, in the Chinese Clinical Trial Registry

with the registration number ChiCTR2200065369. All participants will be fully informed of the study procedures and sign the informed consent form voluntarily before inclusion (see the Appendix). The private information of all participants will be kept confidential and securely placed in a locked cabinet and will only be accessible to researchers of the study. However, the results of this study will be published in peer-reviewed journals and disseminated at academic conferences.

Discussion

At present, no research has revealed the effect and potential mechanism of cerebellar vermis iTBS on balance in subacute stroke patients. This prospective single-centre double-blind randomized controlled clinical trial with a 3-week intervention and 3-week follow-up is designed to confirm its effectiveness.

Our study will comprehensively assess trunk control and balance function by clinical scales, balance tests via the Smart Equitest Balance Master System and sEMG measurements. Additionally, we will also collect the concentration of HbO2 in the cerebral cortex via resting-state fNIRS. The integrated data results will be sufficient verify the research hypothesis.

For trunk control, the TIS scores can reveal motor impairment of the trunk in stroke patients. The sEMG signal directly reflects the activation of muscles directly and contains information about movement intentions generated by the brain.[50] AEMG represents the degree of muscle activation and the synchronization of activated motor units. RMS quantifies the effort of the muscle. MPF and MF are frequency domain features and indicate muscle fatigue.[51 52]

For balance function, the BBS score reflects the overall performance of static and dynamic balance. Accurate integration of sensory information is critical to maintaining balance. The composite equilibrium score of the SOT characterizes the impairments of individual sensory systems.[53] The ability to voluntarily move the COG within the LOS is fundamental to

mobility tasks. By the LOS test, reaction time, movement velocities and excursions are recorded to measure the voluntary ability to shift the COG without losing balance. Reaction time reflects the cognitive processing ability. Movement velocities indicate high-level central nervous system function. Excursions can be restricted by biomechanical deficits.[54] Overall, limitations in the LOS are associated with instability during weight-shifting activities. RWS measures movement velocity and directional control during rhythmic movements. Rhythmic, reciprocal movement patterns are required in daily activities. Stroke patients with disrupted normal rhythmic movement control exhibit reduced velocities and/or poor directional control ability.[55]

For cortical activation, fNIRS is a widespread noninvasive measurement that provides real-time monitoring of haemodynamic signals to reflect changes in brain activation.[56] Increased HbO2 is positively correlated with cortical excitability. In addition, balance function and postural stability are positively related to the changes in HbO2 signals in the bilateral SMAs in stroke patients.[57] Additionally, our previous work revealed that single-session cerebellar vermis iTBS can increase bilateral SMAs excitability during balance tasks in healthy adults.[23] We hypothesize that cerebellar vermis iTBS can promote the activation of muscles in the trunk and lower limbs, and increase the excitability of the SMAs to improve trunk control and balance function in patients after stroke. The cerebellar vermis plays an important role in postural tone, balance, and locomotion through descending spinal pathways since the vermis receives vestibulocerebellar and proprioceptive spinocerebellar afferents.[58] SMA contributes to anticipatory postural adjustments and postural stability during gait initiation.[59] iTBS consists of high-frequency stimulation bursts that strongly modulate the neural activity of the cerebellar vermis. Studies with humans have shown that iTBS drives acute changes to motor behaviour and neuronal excitability.[60] A possible mechanism has been reported by an animal study showing that iTBS can promote neural structural remodelling and functional recovery

by enhancing neurogenesis and migration via the miR-551b-5p/BDNF/TrkB pathway.[61] The first study of cerebellar vermis stimulation was reported in 1995, which investigated its effects on saccade metrics in a man via TMS.[62] At present, researchers have reported that cerebellar vermis stimulation is a safe and well-tolerated brain stimulation technology with a potential therapeutic effect on schizophrenia.[63] In addition, cerebellar vermis rTMS can induce a suppressive effect on pharyngeal motor cortical activity and swallowing behaviour.[64] However, limited studies have reported that the cerebellar vermis plays an important role in postural response and balance stability.[13 65] Therefore, we hope to identify the effectiveness of cerebellar vermis iTBS in trunk control and balance function for subacute ischemic stroke patients. Our results may provide valuable information for developing a novel treatment method for the rehabilitation of balance dysfunction after stroke.

Author contributions: Conceptualization, validation, and original draft: YC. Recruitment: LH, HHJ, and QCW. Data collection: YC, WS, and HXT. Data analysis: CFG and QFG. Manuscript review and editing: CFG and QG. QG designed the trial and was responsible for the manuscript. All authors read and approved the final manuscript.

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References

1. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;392(10159):1859-922. doi: 10.1016/s0140-6736(18)32335-3 [published Online First: 2018/11/13]
2. Hankey GJ. Stroke. *Lancet* 2017;389(10069):641-54. doi: 10.1016/s0140-6736(16)30962-x [published Online First: 2016/09/18]
3. Komiya M, Maeda N, Narahara T, et al. Effect of 6-Week Balance Exercise by Real-Time Postural Feedback System on Walking Ability for Patients with Chronic Stroke: A Pilot Single-Blind Randomized Controlled Trial. *Brain Sci* 2021;11(11) doi: 10.3390/brainsci11111493 [published Online First: 2021/11/28]
4. Zhang Y, Wang C, Yang J, et al. Comparing the Effects of Short-Term Liuzijue Exercise and Core Stability Training on Balance Function in Patients Recovering From Stroke: A Pilot Randomized Controlled Trial. *Front Neurol* 2022;13:748754. doi: 10.3389/fneur.2022.748754 [published Online First: 2022/03/05]
5. Chen Y, Gao Q, He CQ, et al. Effect of Virtual Reality on Balance in Individuals With Parkinson Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Phys Ther* 2020;100(6):933-45. doi: 10.1093/ptj/pzaa042 [published Online First: 2020/03/12]
6. Luque-Moreno C, Kiper P, Solís-Marcos I, et al. Virtual Reality and Physiotherapy in Post-Stroke Functional Re-Education of the Lower Extremity: A Controlled Clinical Trial on a New Approach. *J Pers Med* 2021;11(11) doi: 10.3390/jpm11111210 [published Online First: 2021/11/28]
7. Marchesi G, Ballardini G, Barone L, et al. Modified Functional Reach Test: Upper-Body Kinematics and Muscular Activity in Chronic Stroke Survivors. *Sensors (Basel)* 2021;22(1) doi: 10.3390/s22010230 [published Online First: 2022/01/12]
8. Schröder J, Saeys W, Yperzeele L, et al. Time Course and Mechanisms Underlying Standing Balance Recovery Early After Stroke: Design of a Prospective Cohort Study With Repeated Measurements. *Front Neurol* 2022;13:781416. doi: 10.3389/fneur.2022.781416 [published Online First: 2022/03/11]
9. Karthikbabu S, Verheyden G. Relationship between trunk control, core muscle strength and balance confidence in community-dwelling patients with chronic stroke. *Top Stroke Rehabil* 2021;28(2):88-95. doi: 10.1080/10749357.2020.1783896 [published Online First: 2020/06/24]
10. D'Angelo E. Physiology of the cerebellum. *Handb Clin Neurol* 2018;154:85-108. doi: 10.1016/B978-0-444-63956-1.00006-0 [published Online First: 2018/06/16]
11. Roostaei T, Nazeri A, Sahraian MA, et al. The human cerebellum: a review of physiologic neuroanatomy. *Neurol Clin* 2014;32(4):859-69. doi: 10.1016/j.ncl.2014.07.013 [published Online First: 2014/12/03]
12. De Bartolo P, Florenzano F, Burello L, et al. Activity-dependent structural plasticity of Purkinje cell spines in cerebellar vermis and hemisphere. *Brain structure & function* 2015;220(5):2895-904. doi: 10.1007/s00429-014-0833-6 [published Online First: 2014/07/16]
13. Lam CK, Tokuno CD, Staines WR, et al. The direction of the postural response to a vestibular perturbation is mediated by the cerebellar vermis. *Exp Brain Res* 2016;234(12):3689-97. doi: 10.1007/s00221-016-4766-6 [published Online First: 2016/09/08]
14. Marfeo A. Neuroanatomy Through Clinical Cases: Inc. Publishers 2010.
15. Ilg W, Giese MA, Gizewski ER, et al. The influence of focal cerebellar lesions on the control and adaptation of gait. *Brain* 2008;131(Pt 11):2913-27. doi: 10.1093/brain/awn246 [published Online First: 2008/10/07]
16. Ille S, Kelm A, Schroeder A, et al. Navigated repetitive transcranial magnetic stimulation improves the outcome of postsurgical paresis in glioma patients - A randomized, double-blinded trial. *Brain Stimul* 2021;14(4):780-87. doi: 10.1016/j.brs.2021.04.026 [published Online First: 2021/05/14]
17. Chen SC, Yang LY, Adeel M, et al. Transcranial electrostimulation with special waveforms enhances upper-limb motor function in patients with chronic stroke: a pilot randomized controlled trial. *J Neuroeng Rehabil* 2021;18(1):106. doi: 10.1186/s12984-021-00901-8 [published Online First: 2021/07/02]
18. 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(2):170-78. doi: 10.1001/jamaneurol.2018.3639 [published Online First: 2018/11/27]
19. Chen Y, Wei QC, Zhang MZ, et al. Cerebellar Intermittent Theta-Burst Stimulation Reduces Upper Limb Spasticity After Subacute Stroke: A Randomized Controlled Trial. *Front Neural Circuits* 2021;15:655502. doi: 10.3389/fncir.2021.655502 [published Online First: 2021/11/16]
20. Liao LY, Xie YJ, 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(1):23-32. doi: 10.1177/1545968320971735 [published Online First: 2020/11/10]
21. Xie YJ, Wei QC, Chen Y, et al. Cerebellar Theta Burst Stimulation on Walking Function in Stroke Patients: A Randomized Clinical Trial. *Front Neurosci* 2021;15:688569. doi: 10.3389/fnins.2021.688569

[published Online First: 2021/11/13]
22. Badke MB, Sherman J, Boyne P, et al. Tongue-based biofeedback for balance in stroke: results of an 8-week pilot study. *Arch Phys Med Rehabil* 2011;92(9):1364-70. doi: 10.1016/j.apmr.2011.03.030 [published Online First: 2011/09/01]
23. Tan H-X, Wei Q-C, Chen Y, et al. The Immediate Effects of Intermittent Theta Burst Stimulation of the Cerebellar Vermis on Cerebral Cortical Excitability During a Balance Task in Healthy Individuals: A Pilot Study. *Frontiers in Human Neuroscience* 2021;15 doi: 10.3389/fnhum.2021.748241
24. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158(3):200-7. doi: 10.7326/0003-4819-158-3-201302050-00583 [published Online First: 2013/01/09]
25. Chinese Society of Neurology CSS. Diagnostic criteria of cerebrovascular diseases in China (version 2019). *Chinese Journal of Neurology* 2019;52(09):710-15. doi: 10.3760/cma.j.issn.1006?7876.2019.09.003
26. Hayward KS, Kramer SF, Dalton EJ, et al. Timing and Dose of Upper Limb Motor Intervention After Stroke: A Systematic Review. *Stroke* 2021;52(11):3706-17. doi: 10.1161/strokeaha.121.034348 [published Online First: 2021/10/05]
27. Soulard J, Huber C, Baillieul S, et al. Motor tract integrity predicts walking recovery: A diffusion MRI study in subacute stroke. *Neurology* 2020;94(6):e583-e93. doi: 10.1212/wnl.0000000000008755 [published Online First: 2020/01/04]
28. Bernhardt J, Hayward KS, Kwakkel G, et al. Agreed definitions and a shared vision for new standards in stroke recovery research: The Stroke Recovery and Rehabilitation Roundtable taskforce. *Int J Stroke* 2017;12(5):444-50. doi: 10.1177/1747493017711816 [published Online First: 2017/07/13]
29. Rossi S, Antal A, Bestmann S, et al. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. *Clin Neurophysiol* 2021;132(1):269-306. doi: 10.1016/j.clinph.2020.10.003 [published Online First: 2020/11/28]
30. Garg S, Sinha VK, Tikka SK, et al. The efficacy of cerebellar vermal deep high frequency (theta range) repetitive transcranial magnetic stimulation (rTMS) in schizophrenia: A randomized rater blind-sham controlled study. *Psychiatry Res* 2016;243:413-20. doi: 10.1016/j.psychres.2016.07.023 [published Online First: 2016/07/28]
31. Huang YZ, Edwards MJ, Rounis E, et al. Theta burst stimulation of the human motor cortex. *Neuron* 2005;45(2):201-6. doi: 10.1016/j.neuron.2004.12.033 [published Online First: 2005/01/25]
32. Spampinato D, Ibáñez J, Spanoudakis M, et al. Cerebellar transcranial magnetic stimulation: The role of coil type from distinct manufacturers. *Brain Stimul* 2020;13(1):153-56. doi: 10.1016/j.brs.2019.09.005 [published Online First: 2019/10/22]
33. Kumar N, Vishnubhatla S, Wadhawan AN, et al. A randomized, double blind, sham-controlled trial of repetitive transcranial magnetic stimulation (rTMS) in the treatment of negative symptoms in schizophrenia. *Brain Stimul* 2020;13(3):840-49. doi: 10.1016/j.brs.2020.02.016 [published Online First: 2020/04/15]
34. Meseguer-Henarejos AB, Rubio-Aparicio M, López-Pina JA, 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(5):570-84. doi: 10.23736/s1973-9087.19.05363-2 [published Online First: 2019/04/09]
35. Hyun SJ, Lee J, Lee BH. The Effects of Sit-to-Stand Training Combined with Real-Time Visual Feedback on Strength, Balance, Gait Ability, and Quality of Life in Patients with Stroke: A Randomized Controlled Trial. *Int J Environ Res Public Health* 2021;18(22) doi: 10.3390/ijerph182212229 [published Online First: 2021/11/28]
36. Chou HY, Lo YC, Tsai YW, et al. Increased Anxiety and Depression Symptoms in Post-Acute Care Patients with Stroke during the COVID-19 Pandemic. *Int J Environ Res Public Health* 2021;19(1) doi: 10.3390/ijerph19010162 [published Online First: 2022/01/12]
37. Zhao J, Chau JPC, Zang Y, et al. Psychometric properties of the Chinese version of the Trunk Impairment Scale in people with a stroke. *Health Qual Life Outcomes* 2021;19(1):85. doi: 10.1186/s12955-021-01730-y [published Online First: 2021/03/12]
38. Thijs L, Voets E, Wiskerke E, et al. Technology-supported sitting balance therapy versus usual care in the chronic stage after stroke: a pilot randomized controlled trial. *J Neuroeng Rehabil* 2021;18(1):120. doi: 10.1186/s12984-021-00910-7 [published Online First: 2021/07/30]
39. Yin L, Liu K, Liu C, et al. Effect of Kinesiology Tape on Muscle Activation of Lower Extremity and Ankle Kinesthesia in Individuals With Unilateral Chronic Ankle Instability. *Front Physiol* 2021;12:786584. doi: 10.3389/fphys.2021.786584 [published Online First: 2022/01/04]
40. Bultitude JH, Pidgeon DM, LeBlanc PR, et al. Two weeks of twice-daily prism adaptation treatment does not improve posture or gait in Parkinson's disease: a double-blind randomized controlled trial. *Trials* 2021;22(1):846. doi: 10.1186/s13063-021-05832-2 [published Online First: 2021/11/27]
41. Kolářová B, Janura M, Svoboda Z, et al. Postural Control Strategies and Balance-Related Factors in Individuals

with Traumatic Transtibial Amputations. *Sensors (Basel)* 2021;21(21) doi: 10.3390/s21217284 [published Online First: 2021/11/14]
42. Rossi-Izquierdo M, Santos-Pérez S, Faraldo-García A, et al. Impact of obesity in elderly patients with postural instability. *Aging Clin Exp Res* 2016;28(3):423-8. doi: 10.1007/s40520-015-0414-4 [published Online First: 2015/07/19]
43. Hermens HJ, Freriks B, Disselhorst-Klug C, et al. Development of recommendations for SEMG sensors and sensor placement procedures. *Journal of Electromyography and Kinesiology* 2000;10(5):361-74. doi: 10.1016/s1050-6411(00)00027-4
44. Shen Y, Chen L, Zhang L, et al. Effectiveness of a Novel Contralaterally Controlled Neuromuscular Electrical Stimulation for Restoring Lower Limb Motor Performance and Activities of Daily Living in Stroke Survivors: A Randomized Controlled Trial. *Neural Plast* 2022;2022:5771634. doi: 10.1155/2022/5771634 [published Online First: 2022/01/25]
45. Sun W, Wu X, Zhang T, et al. Narrowband Resting-State fNIRS Functional Connectivity in Autism Spectrum Disorder. *Front Hum Neurosci* 2021;15:643410. doi: 10.3389/fnhum.2021.643410 [published Online First: 2021/07/03]
46. Wang YL, Lin GH, Huang YJ, et al. Refining 3 Measures to Construct an Efficient Functional Assessment of Stroke. *Stroke* 2017;48(6):1630-35. doi: 10.1161/strokeaha.116.015516 [published Online First: 2017/05/05]
47. Akazawa N, Kishi M, Hino T, et al. Increased intramuscular adipose tissue of the quadriceps is related to decreased activities of daily living in patients who have had a stroke. *Nutrition* 2021;90:111277. doi: 10.1016/j.nut.2021.111277 [published Online First: 2021/05/20]
48. Liu F, Tsang RC, Zhou J, et al. Relationship of Barthel Index and its Short Form with the Modified Rankin Scale in acute stroke patients. *J Stroke Cerebrovasc Dis* 2020;29(9):105033. doi: 10.1016/j.jstrokecerebrovasdis.2020.105033 [published Online First: 2020/08/19]
49. Harrison JK, McArthur KS, Quinn TJ. Assessment scales in stroke: clinimetric and clinical considerations. *Clin Interv Aging* 2013;8:201-11. doi: 10.2147/cia.S32405 [published Online First: 2013/02/27]
50. Qing Z, Lu Z, Cai Y, et al. Elements Influencing sEMG-Based Gesture Decoding: Muscle Fatigue, Forearm Angle and Acquisition Time. *Sensors (Basel)* 2021;21(22) doi: 10.3390/s21227713 [published Online First: 2021/11/28]
51. Wei P, Zhang J, Wang B, et al. Surface Electromyography and Electroencephalogram-Based Gait Phase Recognition and Correlations Between Cortical and Locomotor Muscle in the Seven Gait Phases. *Front Neurosci* 2021;15:607905. doi: 10.3389/fnins.2021.607905 [published Online First: 2021/06/08]
52. Alhusuny A, Cook M, Khalil A, et al. The relationship between visual impairments and activity of the neck/shoulder muscles among surgeons during simulated surgical tasks. *Surg Endosc* 2022 doi: 10.1007/s00464-021-08913-0 [published Online First: 2022/01/09]
53. Acuña SA, Tyler ME, Thelen DG. Individuals with Chronic Mild-to-Moderate Traumatic Brain Injury Exhibit Decreased Neuromuscular Complexity During Gait. *Neurorehabil Neural Repair* 2022:15459683221081064. doi: 10.1177/15459683221081064 [published Online First: 2022/03/25]
54. Carvalho GF, Becnel AR, Miske C, et al. Postural control impairment in patients with headaches-A systematic review and meta-analysis. *Headache* 2022;62(3):241-70. doi: 10.1111/head.14281 [published Online First: 2022/03/23]
55. Chen CL, Chen FF, Lin CH, et al. Effect of Anterior Ankle-Foot Orthoses on Weight Shift in Persons With Stroke. *Arch Phys Med Rehabil* 2015;96(10):1795-801. doi: 10.1016/j.apmr.2015.05.003 [published Online First: 2015/05/23]
56. Kinoshita S, Tamashiro H, Okamoto T, et al. Association between imbalance of cortical brain activity and successful motor recovery in sub-acute stroke patients with upper limb hemiparesis: a functional near-infrared spectroscopy study. *Neuroreport* 2019;30(12):822-27. doi: 10.1097/wnr.0000000000001283 [published Online First: 2019/07/10]
57. Fujimoto H, Mihara M, Hattori N, et al. Cortical changes underlying balance recovery in patients with hemiplegic stroke. *Neuroimage* 2014;85 Pt 1:547-54. doi: 10.1016/j.neuroimage.2013.05.014 [published Online First: 2013/05/21]
58. Maiti B, Rawson KS, Tanenbaum AB, et al. Functional Connectivity of Vermis Correlates with Future Gait Impairments in Parkinson's Disease. *Movement disorders : official journal of the Movement Disorder Society* 2021;36(11):2559-68. doi: 10.1002/mds.28684 [published Online First: 2021/06/11]
59. Richard A, Van Hamme A, Drevelle X, et al. Contribution of the supplementary motor area and the cerebellum to the anticipatory postural adjustments and execution phases of human gait initiation. *Neuroscience* 2017;358:181-89. doi: 10.1016/j.neuroscience.2017.06.047 [published Online First: 2017/07/05]
60. Tang AD, Bennett W, Bindoff AD, et al. Subthreshold repetitive transcranial magnetic stimulation drives structural synaptic plasticity in the young and aged motor cortex. *Brain Stimul* 2021;14(6):1498-507. doi: 10.1016/j.brs.2021.10.001 [published Online First: 2021/10/16]

61. Wang L, Zhou Y, Chen X, et al. Long-term iTBS promotes neural structural and functional recovery by enhancing neurogenesis and migration via miR-551b-5p/BDNF/TrkB pathway in a rat model of cerebral ischemia-reperfusion injury. *Brain Res Bull* 2022;184:46-55. doi: 10.1016/j.brainresbull.2022.03.002 [published Online First: 2022/03/09]
62. Hashimoto M, Ohtsuka K. Transcranial magnetic stimulation over the posterior cerebellum during visually guided saccades in man. *Brain* 1995;118 (Pt 5):1185-93. doi: 10.1093/brain/118.5.1185 [published Online First: 1995/10/01]
63. Escelsior A, Belvederi Murri M, Calcagno P, et al. Effectiveness of Cerebellar Circuitry Modulation in Schizophrenia: A Systematic Review. *The Journal of nervous and mental disease* 2019;207(11):977-86. doi: 10.1097/nmd.0000000000001064 [published Online First: 2019/09/11]
64. Sasegbon A, Niziolek N, Zhang M, et al. The Effects of Midline Cerebellar rTMS on Human Pharyngeal Cortical Activity in the Intact Swallowing Motor System. *Cerebellum* 2021;20(1):101-15. doi: 10.1007/s12311-020-01191-x [published Online First: 2020/09/27]
65. Colnaghi S, Honeine JL, Sozzi S, et al. Body Sway Increases After Functional Inactivation of the Cerebellar Vermis by cTBS. *Cerebellum* 2017;16(1):1-14. doi: 10.1007/s12311-015-0758-5 [published Online First: 2016/01/19]

Legends

Figure 1. The flow diagram of the study design.

Figure 2. The schedule of enrolment, interventions, and assessments.

Figure 3. The Magstim Rapid2 stimulator with a BrainSight neuronavigation system.

Figure 4. The Smart Equitest Balance Master System®.

Figure 5. The sensor locations on individual muscles for sEMG recording (A. rectus abdominis, B. external oblique muscle, C. rector spinae (longissimus), D. rectus femoris, E. biceps femoris, F. tibialis anterior, G. soleus

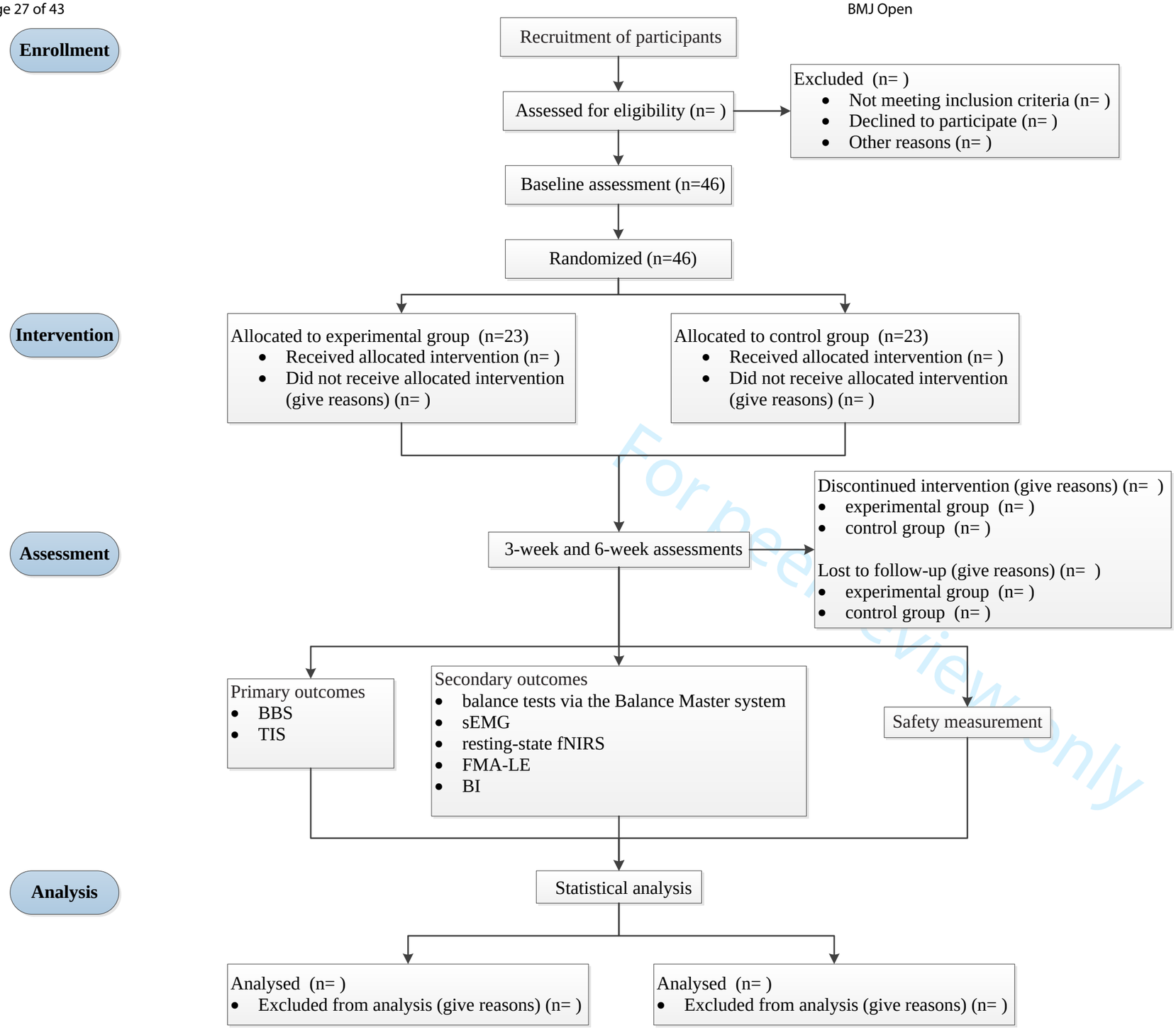

Figure 2. The schedule of enrolment, interventions, and assessments.

	Enrolment	**Allocation**	**Post-allocation**					
TIMEPOINT	$-t_1$	**0**	***W1***	***W2***	***W3***	***W4***	***W5***	***W6***
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Ethical approval and trial registration	X							
Allocation		X						
INTERVENTIONS:								
cerebellar vermis iTBS and conventional physical therapy			—	—	—			
sham stimulation and conventional physical therapy			—	—	—			
ASSESSMENTS:								
basic characteristics information		X						
BBS		X			X			X
TIS		X			X			X
balance tests via the Balance Master system		X			X			X
sEMG		X			X			X
resting-state fNIRS		X			X			X
FMA-LE		X			X			X
BI		X			X			X
Safety measurement			X	X	X	X	X	X

W, week; iTBS, intermittent theta-burst stimulation; BBS, Berg balance scale; TIS, trunk impairment scale; sEMG, surface electromyography; fNIRS, functional near-infrared spectroscopy; FMA-LE, Fugl-Meyer assessment scale score for lower extremities; BI, Barthel index.

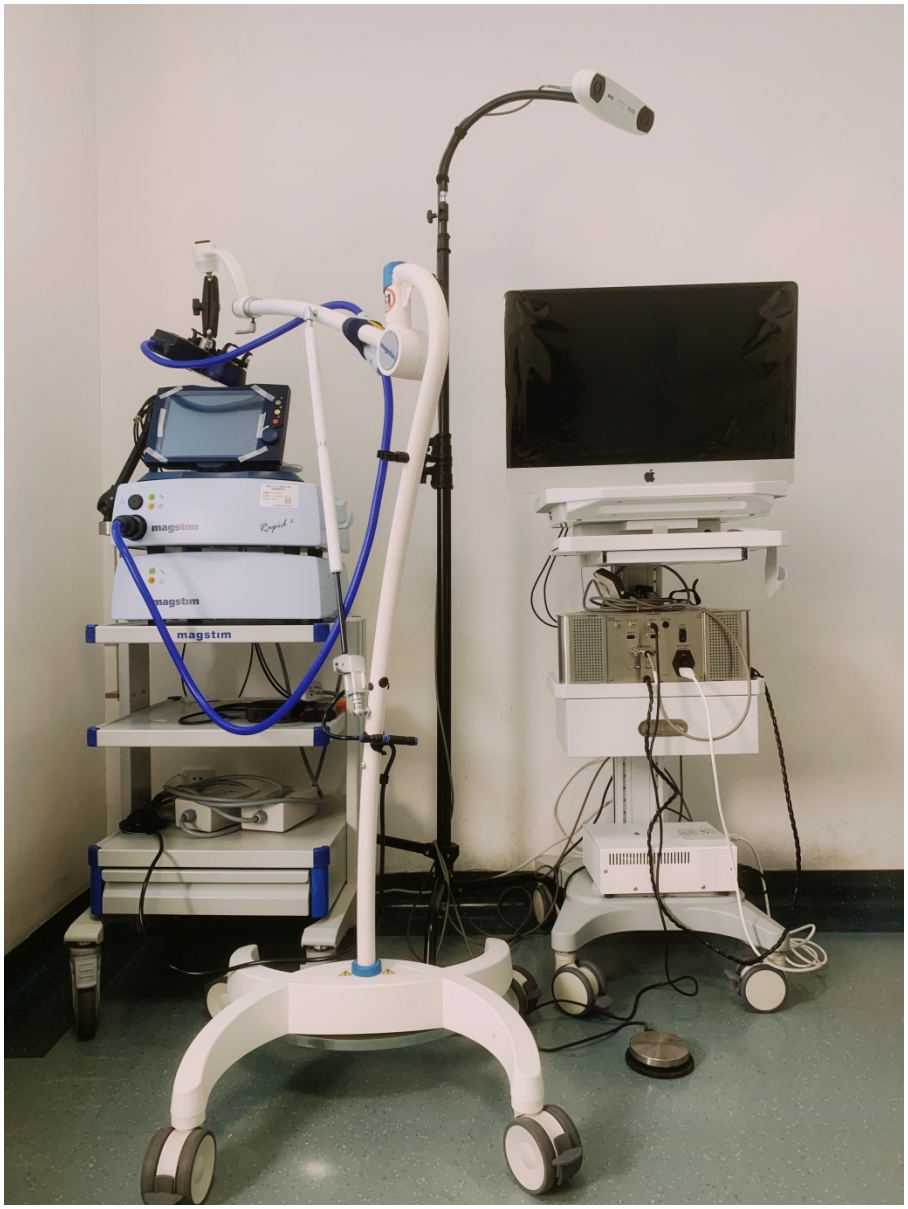

Figure 3. The Magstim Rapid2 stimulator with a BrainSight neuronavigation system.

1066x1422mm (72 x 72 DPI)

Figure 4. The Smart Equitest Balance Master System®.

1066x1422mm (72 x 72 DPI)

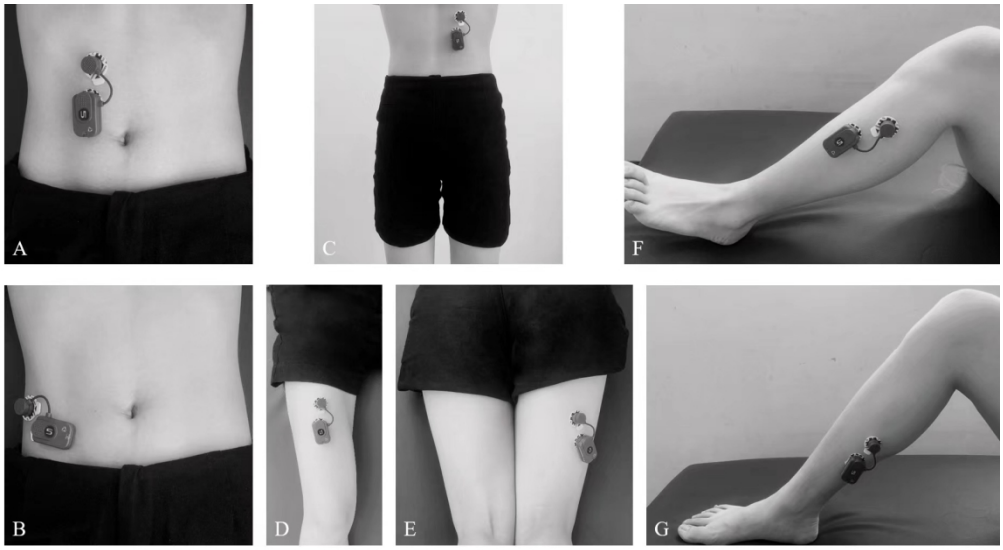

Figure 5. The sensor locations on individual muscles for sEMG recording (A. rectus abdominis, B. external oblique muscle, C. rector spinae (longissimus), D. rectus femoris, E. biceps femoris, F. tibialis anterior, G. soleus)

654x359mm (72 x 72 DPI)

Appendix. Informed Consent Form

West China Hospital, Sichuan University **Participant Informed Consent**			
Name:	**Gender:**	**Age:**	**Inpatient ID:**

Title of study: The effectiveness of cerebellar vermis intermittent theta burst stimulation in improving trunk control and balance function for subacute stroke patients: a randomized controlled trial

Investigator: Qiang Gao

Funding: NSFC 82172540 from the National Natural Science Foundation of China

What is the study about?

(1) The aim of the study is to determine the effects of cerebellar vermis intermittent theta-burst stimulation (iTBS) on trunk control, muscle activation and balance function in stroke patients. We will recruit 46 patients who meet the inclusion criteria as follows: (1) a diagnosis of ischemic stroke according to the *Diagnostic criteria of cerebrovascular diseases in China (version 2019)*, (2) aged between 18 and 65 years, (3) first-ever unilateral ischemic stroke confirmed by imaging examination, (4) subacute stroke participants with the stroke onset ranging from 2 weeks to 6 months, (5) having motor deficit and balance dysfunction, with a Fugl-Meyer Assessment for Lower Extremities (FMA-LE) <34 points and BBS score <56 points. Patients were excluded if they presented one of the following: (1) diagnosis of coexisting other neurological diseases, (2) injury of cerebellar or brain stem, (3) having contraindications for iTBS (e.g., history of seizures, intracranial metallic implants, microprocessor implants in the body, tumours, and pregnancy), (4) cognitive impairment with a Mini-Mental State Examination (MMSE) score <27, (5) treatment with benzodiazepines, baclofen, antiepileptics and antidepressants.

.

How long will I be in the study?

Your part in the study will last **6 weeks** with 3 weeks of intervention and 3 weeks of follow-up (excluding assessment).

What will happen in this study?

You will be randomized into either the experimental or control group according to the random number table. If you assigned to the experimental group will receive cerebellar vermis iTBS after routine daily conventional physical therapy, otherwise you will receive sham stimulation after routine daily conventional physical therapy. The overall intervention periods are five days a week for three consecutive weeks. You will be assessed before treatment, after 3 weeks of intervention and after 3 weeks of follow-up. The measures including clinical scales, balance tests via the Balance Master system, and the surface electromyography recording.

If you are eligible and wish to join the study, you must sign this consent form. If you do not sign the consent form you cannot join the study.

We will review this consent form with you. You will be given enough time to review the consent and have all your questions about the study answered. We will give you a signed copy of the consent for your records before treatment in person.

Study stuff will not know which group or study treatment you are assigned to. You should not join the study if you are not willing to take the study treatment (or join the group) you are assigned to.

What if I have questions?

You can contact the therapist at working hours if you have questions about the study. Qiang Gao (the director of therapists) is in charge of the study.

Do I have to be in the study?

You decide if you want to be in the study. Deciding not to take part will not affect your relationship with your therapist. If your therapist is an investigator for the study, you may get a second opinion from another therapist not involved in the study.

You can leave the study at any time and you do not have to give a reason. Leaving the study will not affect your relationship with your therapist.

The study investigators may ask you to leave the study if it is in your best interest. The study investigator may ask you to leave the study if you do not follow the study rules.

What if I don't want to be in the study?

You can choose not to be in the study and you do not have to give a reason. You can choose to (talk to your doctor/therapist about other options, investigate outside resources on your own, etc.).

Are there any costs?

All study-related treatments are free.

Will I be paid for being in the study?

You will not be paid for being in the study.

Are there any risks?

There is always a small risk of a breech of confidentiality to your personal health information. However, these risks have been addressed and minimized as much as is possible.

You will be told about any new information that may affect your willingness to participate in the study.

There are some possible risks and side effects as follows: headache, nausea, neck pain, seizure, mood changes, fatigue, tinnitus, dizziness, sleepiness and syncope.

If you experience any side effects while on the study contact investigator (Qiang Gao) at any time as soon as possible.

What if I feel I've been hurt by taking part in the study?

If you feel you have been injured or harmed by taking part in this study, please contact investigator (Qiang Gao) at any time. If you feel you were harmed while taking part in this study, you may be treated at West China Hospital, Sichuan University. However, West China Hospital does not offer to pay the cost of this treatment.

If you feel your rights have been violated or you have harmed by this study, please contact your therapist.

Are there any benefits?

It is possible you may receive some benefit from cerebellar vermis iTBS and conventional physical therapy. iTBS is a novel form of rTMS, which can produce long-term potentiation and is more rapid and efficacious than standard rTMS. Cerebellar vermis is a cardinal structure involved in balance and motor control, which is responsible for regulating the trunk, head, neck and proximal limb muscles to control posture and maintain balance. There is no guarantee, however, that you will receive any benefit at all. Your participation will help us learn more about the effects of cerebellar vermis iTBS on trunk control, muscle activation and balance function in subacute stroke patients.

Your privacy is important

Protecting your privacy is very important to us.

During this study we will ask about your (past) and (current) medical history. This information will be used to determine your eligibility for the study and provide data for the study. Your personal health information will be kept private and only authorized study staff will have access to this information. We will use a study number instead of your name. All paper forms will be kept in a locked, secure office. All electronic data will be stored on password-protected computers. Your name will not be used in any publications or presentations about this study.

During the study, you may not be given access to medical information about you that is part of the study. When the study is over, you may request certain medical information collected about you that is part of your study medical record.

None of your personal information will be shared outside of West China Hospital.

By signing this consent form, you are stating that we can use your health information in the ways mentioned above for this study. You are not waiving any of your legal right by signing this form.

You have the right to take away your permission to use your health information collected as part of the study. In order to do this, you must send a written request to: Qiang Gao, department of rehabilitation, West China hospital, Sichuan University

Once your letter is received, no additional information about you will be collected from you for this study. Any data that were collected before we receive your letter will continue to be used for the study. Taking away your permission to use your

health information will not affect your relationship with West China Hospital.

We are collecting only the personal health information that we need for the specific purpose of this study. Your personal health information cannot be used for additional research purpose.

The West China hospital may be required to provide copies of your personal information to government agencies as required by law.

Your permission to use your identifiable health information when the study is complete.

Signatures:

By signing this consent form, it means the following:

- I know my rights have not been waived by signing.
- I have had all of my questions answered and I know whom to ask if I have more questions.
- I have read this form and understand it.
- I want to join the study.
- I know I can leave the study at any time and do not have to give a reason.

_____ _____

Signature of Participant Date

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 17-18
	2b	All items from the World Health Organization Trial Registration Data Set	nil
Protocol version	3	Date and version identifier	nil
Funding	4	Sources and types of financial, material, and other support	20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page, 20
	5b	Name and contact information for the trial sponsor	Title page
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	20
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	nil
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5-6

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-16
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5-6, Fig.2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	16
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	16
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	16
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	16
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16-17
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	16
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15-16
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16-18
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17-18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	nil
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16-18

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	nil
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17-18
	31b	Authorship eligibility guidelines and any intended use of professional writers	nil
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	nil
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary material
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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The effectiveness of cerebellar vermis intermittent theta burst stimulation in improving trunk control and balance function for patients with subacute stroke: a randomized controlled trial protocol

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The effectiveness of cerebellar vermis intermittent theta burst stimulation in improving trunk control and balance function for patients with subacute stroke: a randomized controlled trial protocol

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Abstract

Introduction Balance impairments frequently occur after stroke. Achieving effective core trunk stability is the key to improving balance ability. However, there is still a lack of advanced well-defined rehabilitation protocols for balance improvement in patients with stroke. Intermittent theta-burst stimulation (iTBS) is a noninvasive brain activity modulation strategy that can produce long-term potentiation. The cerebellar vermis is a fundamental structure involved in balance and motor control. However, no study has demonstrated the therapeutic effect and potential mechanism of cerebellar vermis iTBS on balance after stroke.

Methods and Analysis This study will be a prospective single-centre double-blind randomized controlled clinical trial with a 3-week intervention and 3-week follow-up. Eligible participants will be randomly allocated to the experimental group or the control group in a 1:1 ratio. After routine conventional physical therapy, patients in the experimental group will receive cerebellar vermis iTBS, whereas patients in the control group will receive sham stimulation. The overall intervention period will be five days a week for three consecutive weeks. The outcomes will be measured at baseline (T0), 3 weeks postintervention (T1) and at the 3-week follow-up (T2). The primary outcomes are Berg Balance Scale (BBS) and Trunk Impairment Scale (TIS) scores. The secondary outcomes are balance tests scores via the Balance Master system, muscle activation of the trunk and lower limbs via the surface electromyography (sEMG) recordings, cerebral cortex oxygen concentrations measured via the resting-state functional near-infrared spectroscopy (fNIRS), and Fugl-Meyer Assessment of Lower Extremity (FMA-LE) and Barthel index (BI) scores.

Ethics and Dissemination This study was approved by the West China Hospital Clinical Trials and Biomedical Ethics Committee of Sichuan University. The trial registration number is ChiCTR2200065369. All participants will sign the informed consent form voluntarily. The

results of this study will be published in peer-reviewed journals and disseminated at academic conferences.

Strengths and limitations of this study

- Our study comprehensively assesses the trunk control and balance function by clinical scales, balance tests via the Smart Equitest Balance Master System, and surface electromyography (sEMG) measurements.
- Resting-state functional near-infrared spectroscopy (fNIRS) will be used to collect the concentration of HbO2 in the cerebral cortex.
- This study lacks a long-term follow-up assessment.

Introduction

Stroke is the third most common cause of disability worldwide.[1] The incidents, prevalence, and disability-adjusted life-years of stroke have increased over the past two decades[2], and are considered to place heavy economic burdens on society. Balance impairments frequently occur in patients with stroke, with a reported incidence ranging from 61% to 83%[3]. The main manifestations are postural instability, weak trunk control, and difficulty shifting weight,[4] which ultimately result in falls, poor mobility, decreased physical activity, and reduced quality of life in patients.[5] Therefore, improvement of balance function is a cardinal requirement in patients with stroke.

The trunk plays a fundamental role in trunk control, balance, and mobility during sitting and transferring.[6] The synchronized activity of trunk muscles is necessary for maintaining dynamic balance. In addition, proper trunk muscle control is essential for stabilizing distal limbs.[7] Muscle weakness of the lower limbs is associated with decreased standing balance

control.[8] Impaired trunk control and core muscle weakness attenuate balance and physical function in individuals after stroke.[9] Therefore, achieving effective core trunk stability is crucial to improving balance ability after stroke.

The cerebellum, a central brain structure located in the posterior cranial fossa, works in concert with the cerebral cortex, brainstem, and spinal cord and is involved in motor control.[10] [11] It consists of two lateral hemispheres and the cerebellar vermis. The cerebellar vermis is a fundamental structure involved in balance and motor processing,[12] [13] and is responsible for regulating the trunk, head, neck and proximal limb muscles to control posture and maintain balance.[14] Balance dysfunction in cerebellar disorders is most likely caused by lesions of the medial zone of the cerebellum.[15] At present, the main clinical interventions to improve the balance function in stroke rehabilitation are muscle strength training or balance training. The activation of the cerebellar vermis in the central nervous system through neuromodulation with noninvasive brain stimulation has great potential for enhancing balance function in patients with stroke.

Repetitive transcranial magnetic stimulation (rTMS) is a safe, reliable, and standardized noninvasive brain activity modulation strategy to regulate cortical excitability and facilitate neural plasticity.[16] Intermittent theta-burst stimulation (iTBS) is a novel form of rTMS that can produce long-term potentiation and is more rapid and efficacious than standard rTMS.[17] Previously published studies revealed that iTBS over the cerebellar hemisphere could promote gait and balance recovery in patients with chronic ischemic stroke.[18] Similarly, our research group recently provided evidence that iTBS over the cerebellar hemisphere could promote upper limb spasticity, balance, and walking performance recovery in patients with stroke.[19-21] However, one of the results indicated that the difference in Berg Balance Scale (BBS) scores between the cerebellar iTBS group and the sham stimulation group weas 1.58 points, which did not reach the minimal clinically important difference.[22] Therefore, the

identification of a more effective stimulation target for improving balance function after stroke is necessary. No study has demonstrated the therapeutic effect and potential mechanism of cerebellar vermis iTBS on balance in individuals with stroke. Our preliminary pilot study found that cerebellar vermis iTBS contributed to increasing the excitability of the bilateral supplementary motor areas (SMAs) during balance tasks in healthy adults.[23]

Objective

Since no clinical research verifying the effectiveness of cerebellar vermis iTBS stimulation has been reported, a randomized controlled double-blind trial will be conducted to determine the effects of cerebellar vermis iTBS on trunk control, muscle activation and balance function in patients with subacute ischemic stroke. We hypothesize that cerebellar vermis iTBS can promote the activation of trunk and lower limb muscles and increase the excitability of SMAs to improve trunk control and balance function in patients with subacute ischemic stroke.

Methods

Study design and setting

This study will be a prospective single-centre double-blind randomized controlled clinical trial with a 3-week intervention and 3-week follow-up. The protocol strictly follows the Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) 2013 Statement.[24] Eligible participants will be randomly allocated to the experimental group or control group in a 1:1 ratio. After routine conventional physical therapy, patients assigned to the experimental group will receive cerebellar vermis iTBS, whereas patients assigned to the control group will receive sham stimulation. The overall intervention period will be five days a week for three consecutive weeks. The outcomes will be measured at baseline (T0), 3 weeks postintervention (T1), and at the 3-week follow-up (T2). The whole study will be performed

at the Department of Rehabilitation Medicine of Sichuan University West China Hospital (Chengdu, Sichuan Province, China). Figure 1 shows the flow diagram of the study design. We plan to start subject recruitment on the 1st of December 2022 and complete the trial in December 2025. Figure 2 illustrates the study schedule.

Sample size calculation

The sample size calculation was conducted via G*power of 3.1.9.2 based on the result of the BBS score in our published study, which indicated an estimated effect size of f=0.38.[20] Other parameters were set as follows: a significance level of α=0.05 (two tails), power (1–β) =90%, correlation among repeated measures=0.5, nonsphericity correction ε=1, number of measurements=3, and number of groups=2. Therefore, a sample size of n=40 was obtained. After allowing for a 15% dropout rate, a minimum total of 46 participants is needed.

Participants

Recruitment

The participants will be recruited from the Department of Rehabilitation Medicine of Sichuan University West China Hospital in Chengdu, Sichuan Province, China. After carefully screening the inclusion and exclusion criteria, voluntary participants will be required to provide written informed consent before the experiment.

Inclusion criteria

Participants will be considered for inclusion if they meet the following criteria:

(1) A diagnosis of ischemic stroke according to the *Diagnostic criteria of cerebrovascular diseases in China (version 2019)*.[25]

(2) Aged between 18 and 65 years.

(3) First-ever unilateral ischemic stroke confirmed by imaging examination.

(4) Participants with subacute stroke, the stroke onset ranging from 2 weeks to 6 months.[26-28]

(5) Having motor deficit and balance dysfunction, with a Fugl-Meyer Assessment for Lower Extremities (FMA-LE) score <34 points and BBS score <56 points.[20]

Exclusion criteria

Participants will be excluded if they meet any of the following criteria:

(1) Diagnosis of coexisting other neurological diseases.

(2) Injury of cerebellum or brain stem.

(3) Having contraindications for iTBS (e.g., history of seizures, intracranial metallic implants, microprocessor implants in the body, tumours, and pregnancy)

(4) Cognitive impairment defined as a Mini-Mental State Examination (MMSE) score<27.

(5) Treatment with benzodiazepines, baclofen, antiepileptics and antidepressants.

Interventions

All enrolled participants will receive 1 session of cerebellar vermis iTBS or sham stimulation before routine conventional physical therapy from Monday to Friday, with a total of 15 sessions. Patients in the experimental group will receive cerebellar vermis iTBS coupled with conventional physical therapy, and those in the control group will receive sham stimulation coupled with conventional physical therapy. The whole intervention period will last for a total of three consecutive weeks.

Cerebellar vermis iTBS stimulation

The stimulation protocol will strictly adhere to the safety guidelines and recommendations endorsed by the International Federation for Clinical Neurophysiology in 2021.[29] We will use a Magstim Rapid2 stimulator (The Magstim Company Limited) connected to a 70 mm figure-of-8 Double Rapid2 Air Cooled Coil (P/N 3910-00) to stimulate the cerebellar vermis (Figure

3). The centre of the coil will be placed tangentially to the target scalp area, and the coil current direction will point downwards. iTBS will be applied over the cerebellar vermis, 1 cm inferior to the inion.[30] We will use a neuronavigation system (BrainSightt, Rogue Research Inc.) coupled with a Polaris Vicra infrared camera to ensure that cerebellar vermis iTBS is applied over the same spot for the same participant across different sessions (Figure 3). The pattern of iTBS consists of 600 pulses containing 3 pulses at 50 Hz repeated at a rate of 5 Hz, with 20 trains of 10 bursts given at 8 seconds intervals.[31] The standard stimulus intensity will be set at 80% of the active motor threshold (AMT), which is the lowest intensity evoking at least five out of ten motor-evoked potentials (MEPs) with a peak-to-peak amplitude >200 μV in the abductor pollicis brevis muscle during 10% of the maximum voluntary contraction measured by a dynamometer.[21] If the participant cannot elicit MEPs or cannot tolerate the preset standard stimulus intensity, the stimulator output intensity will be set to the participant's maximum tolerated intensity.[32]

Sham stimulation

Participants in the control group will be treated identically to those in the experimental group, except the Magstim sham coil (P/N 3950-00) will be used to deliver the sham stimulation.[33] The sham coil has the same external appearance, parameters and application methods for stimulating the sensation produced by the real coil without inducing a magnetic field. Therefore, it can sufficiently ensure that the patients remain blinded to the intervention.

Conventional physical therapy

After receiving cerebellar vermis iTBS or sham stimulation, all participants will receive conventional physical therapy, including limb positioning, balance exercise, trunk control, and postural and transfer training, with each session lasting 50 minutes during the intervention

phase.

Criteria for discontinuing the allocated interventions

Interventions will be discontinued for participants if any of the following events occur:

(1) Serious adverse events, such as epilepsy, severe headache, persistent tinnitus and syncope, occur during the stimulation.

(2) Participants withdraw from the trial.

(3) Participants are not compliant with the allocation and intervention plan.

(4) Participants join in additional studies during the trial.

(5) Group exposure for participants and outcome evaluators lead to the failure of blindness.

Improving adherence strategies

To improve the participant compliance, the researcher in charge of the trial will contact the participants regularly to clarify their rehabilitation progress and discuss the subsequent physical therapy programme. Additionally, patients who complete the entire procedure in accordance with the protocol will be provided with a subject fee and an additional free rehabilitation consultation. If a participant drops out, the specific reasons for withdrawal will be recorded.

Outcome Measures

On the day of enrolment, the basic characteristics of the participants, including age, sex, type of stroke, lesion site, course of disease, degree of neurological deficit as assessed by the National Institutes of Health Stroke Scale (NIHSS), and cognitive function as assessed by the MMSE, will be documented. The outcome assessments will be conducted at the treatment site at T0, T1 and T2. The primary outcomes are BBS and Trunk Impairment Scale (TIS) scores.

The secondary outcomes are balance tests via the Balance Master system, muscle activation of the trunk and lower limbs via the surface electromyography (sEMG) recordings, cerebral cortex oxygen concentrations measured via the resting-state functional near-infrared spectroscopy (fNIRS), FMA-LE scores, and Barthel Index (BI) scores. Each assessment will be performed by a professional clinician or by a qualified physical therapist who will be blinded to the experimental condition of the participant.

Primary outcomes

1. BBS

The BBS is a well-validated scale for assessing balance among individuals with neurological disease.[34] It has high reliability and internal validity, with an intraclass correlation coefficient for inter-measure reliability and intra-measure reliability of 0.97 and 0.98, respectively.[35] This scale is a 14-item measure with a total score of 56, and the score of each item ranges from 0 (poor balance) to 4 (good balance).[36]

2. TIS

The TIS is a scale designed to assess motor impairment of the trunk after stroke, demonstrating the most promising performance in psychometric properties with satisfactory reliability and validity.[37] It is a 17-item scale used to evaluate static and dynamic sitting balance and trunk coordination for patients with stroke, with a total score ranging from 0 to 23 points.[38] A higher score indicates better trunk control.

Secondary outcomes

1. Balance tests via the Balance Master system

The assessments of dynamic balance and postural control abilities will be performed by the Sensory Organization Test (SOT), Limits of Stability (LOS), and Rhythmic Weight Shift

(RWS) via the Smart Equitest Balance Master System® (NeuroCom Int., Inc., Clackamas, Oregon, USA). (Figure 4)

1.1 SOT: The SOT evaluates postural control when participants undergo different somatosensory, visual, and vestibular feedback perturbations. During testing, inaccurate interference information is delivered to the patient's eyes, feet, and joints and is controlled through calibrated sway referencing of the support surface and/or visual surroundings. The participant is required to maintain balance to keep their centre of gravity (COG) as steady as possible. A composite equilibrium score is provided to characterize the participant's overall level of performance through the six conditions described in Table 1. During the SOT, each trial lasts for 20 seconds and is repeated three times.[39 40]

Table 1. Sensory Organization Test

Condition	Vision	Surface	Surround	Interference
1	Eyes open	Stable	Fixed	Null
2	Eyes closed	Stable	Fixed	Vision
3	Eyes open	Stable	Unfixed	Vision
4	Eyes open	Unstable	Fixed	Somatosensation
5	Eyes closed	Unstable	Fixed	Somatosensation and Vision
6	Eyes open	Unstable	Unfixed	Somatosensation and Vision

1.2 LOS: The LOS quantifies the voluntary ability to shift the COG in eight different directions: forwards, forwards-right, right, backwards-right, backwards, backwards-left, left, and forwards-left. When the test is performed, a real-time display of the participant's COG position in relation to targets placed at the centre of the base of support and the stability limits is shown. Once the command is given, the participant must move their COG from a central position out towards one of the eight targets as quickly (up to 8 seconds) and accurately as possible.[41]

1.3 RWS: The RWS evaluates a participant's ability to perform rhythmic movements of their COG from left to right (lateral) and forwards to backwards (anterior/posterior) between two targets at three different speeds (slow, medium and fast).[42] Movement velocity and directional control are measured for each direction and speed.

2. sEMG recordings

The sEMG recordings will be conducted in accordance with the Surface ElectroMyoGraphy for the Non-Invasive Assessment of Muscles (SENIAM) guidelines.[43] A 20-channel wireless BTS-FREEEMG 300 (BTS Biomechanics Ltd, Italy) will be used to collect the sEMG signals of the following muscles: bilateral rectus abdominis (RA), external oblique muscle (EO), erector spinae (longissimus), rectus femoris (RF), biceps femoris (BF), tibialis anterior (TA) and soleus (Table 2 and Figure 5 illustrate the sensor locations on the individual muscles). Before starting, the skin will be cleaned using 75% alcohol and would be shaved if needed to ensure a maximum skin impedance below 5 kΩ. After skin preparation, the participant will be put into the starting posture, depending on the muscle at which the electrodes will be placed. A pair of pre-gelled electrodes certified for medical use and in compliance with the directive 93/42/EEC (amended by 2007/47/EC) will be placed on the belly of the target muscle with an interelectrode distance of 2 cm.[44] When the electrodes are placed and fixed, a certified physical therapist will teach the patient to perform the maximum voluntary isometric contraction (MVIC) of the target muscle. For individual muscles, we will record three we will record three 3 seconds MVIC trials with a 2 minutes rest period between each trial. sEMG signals will be sampled at 1000 Hz. Collected data will be synchronously transmitted to a BTS EMG-Analyzer (BTS Bioengineering) with the bandpass filtered from 20 to 500 Hz. We will rectify and filter the recorded signal and extract the data of averaged electromyography (AEMG), root mean square (RMS), mean power frequency (MPF) and median frequency (MF) data for subsequent analyses.

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Table 2. The sensor locations on individual muscles for sEMG recordings *

Muscle	Starting posture of participant	Electrode placement	
		Location	Orientation
RA	Supine or standing	2 cm superior and 2-4 cm lateral to the umbilicus	Vertical
EO	Supine or standing	At a 2-finger width above the anterior half of the iliac crest	In the direction of the line from the outside of the 5-12 ribs to the anterior half of the iliac crest
Longissimus	Prone with the lumbar vertebral columns slightly flexed	At a 2-finger width lateral from the proc. spin. of L1.	Vertical
RF	Sitting on a table with the knees in slight flexion and the upper body bend slightly backwards	At 50% on the line from the anterior spina iliaca superior to the superior part of the patella	In the direction of the line from the anterior spina iliaca superior to the superior part of the patella
BF	Lying on the belly with the face down with the thigh down on the table, the knees flexed (to less than 90 degrees), the thigh in a slight lateral rotation and the leg in a slight lateral rotation with respect to the thigh	At 50% on the line between the ischial tuberosity and the lateral epicondyle of the tibia	In the direction of the line between the ischial tuberosity and the lateral epicondyle of the tibia
TA	Supine or sitting	At 1/3 on the line between the tip of the fibula and the tip of the medial malleolus	In the direction of the line between the tip of the fibula and the tip of the medial malleolus

Soleus	Sitting with the knee flexed approximately 90 degrees and the heel/foot of the investigated leg on the floor	At 2/3 of the line between the medial condyle of the femur to the medial malleolus	In the direction of the line between the medial condyle to the medial malleolus

Abbreviations: sEMG, surface electromyography; RA, rectus abdominis; EO, external oblique muscle; RF, rectus femoris; BF, biceps femoris; TA, tibialis anterior.

* According to the SENIAM recommendations for sensor locations for muscles.

3. Resting-state fNIRS

A multichannel fNIRS system with 24 sources and 24 detectors (NirScan, HuiChuang, China) will be used to record changes in oxygenated haemoglobin (HbO2), deoxygenated Hb and total Hb of the cerebral cortex when the participant is at rest. Relevant parameters will be set as follows: the wavelengths are between 730 and 850 nm, the source-detector distance is 3 cm, and the sampling frequency is over 11 Hz. The international 10/20 system is referenced for identifying optodes on the bilateral prefrontal and parietal lobes.[45] Collected fNIRS data will be analyses by the NirSpark software package with the bandpass filtering from 0.01 to 0.1 Hz. The mean HbO2 value of each channel will be extracted for statistical analyses.

4. FMA-LE

The lower extremity function of patients with stroke will be assessed by FMA-LE, which has good interrater reliability and concurrent validity.[46] The maximum score of this 17-item scale is 34 points. Each item is scored on a 3-point ordinal scale, with 0 points for inability, 1 point for partial ability, and 2 points for full ability to perform the required movement.[47]

5. BI

The BI is a self-reported scale comprising of 10 items, including bathing, grooming, bladder management, bowel management, dressing, feeding, toilet use, transfers, ascending and descending stairs, and walking, to measure basic activities of daily living.[48] The total scores vary from 0 (totally dependent) to 100 (independent). This scale has good clinimetric properties and excellent interrater reliability with standardized administration for patients with stroke.[19 49]

Safety measurements

Possible stimulation-related adverse events, such as headache, nausea, neck pain, seizure, mood changes, fatigue, tinnitus, dizziness, sleepiness and syncope, are listed in the informed

consent form. An adverse reaction record will be used to monitor and provide detailed reports after each stimulation. In addition, any adverse events related to in conventional physical therapy will also be recorded using the adverse event case report form (CRF).

Randomization and blinding

The study will be a randomized, double-blind, sham-controlled trial. Enrolled participants will be randomly assigned based on the computer-generated random numbers that are concealed in opaque numbered envelopes and opened in numerical order by a neutral noninvolved researcher. We plan to blind the participants and evaluators. If blinding fails, the participants will be removed. A sham coil will be used to ensure that the patients are blinded to the intervention. Outcome evaluations will be conducted by a professional clinician or by a qualified physical therapist who is blinded to the group assignment. An independent researcher will be designated to complete the data analysis. Unblinding will be carried out after the data analysis is completed. In the case of serious adverse events occurring during interventions, emergency unblinding will also be implemented.

Data management and analysis

Data management

Data will be recorded on CRFs in a timely, complete and accurate manner. Two researchers will independently input data into Excel software and cross-check each other. Thus, electronic data will be stored and available to the relevant researcher only. The West China Hospital Clinical Trials and Biomedical Ethics Committee of Sichuan University are responsible for monitoring the safety and process of the study and have the right to terminate the trial if serious advent events occur. All procedures will comply with the confidentiality standards for medical data.

Statistical analysis

Statistical analyses will be performed using GraphPad Prism 8.4.3 (GraphPad Software, Inc., La Jolla, CA, USA) based on the intention-to-treat principle. Missing data will be imputed using the last observation carried forwards approach. The Shapiro-Wilk test will be conducted to evaluate the normal distribution of the data. The level of significance is set at $\alpha = 0.05$. Continuous variables, ordinal variables, and categorical variables will be presented as mean (±standard deviation, SD), medians (interquartile range, IQR), and number (percentage, %), respectively. Based on different types of data, the independent-samples *t* test, Mann–Whitney U test, and chi-square test will be used to compare demographic and baseline data between groups. Two-way mixed measures analysis of variance with group as the between-individual factor and time as the within-individual factor will be performed for outcome measures analyses. Nonsphericity correction will be conducted using the Greenhouse-Geisser correction if necessary, and Tukey's *post hoc* multiple comparison test will be applied.

Patient and public involvement

Patients and the public will not be involved in the study design, recruitment, implementation or reporting. However, the study results will be disseminated to the public through academic papers and conferences.

Ethical approval, trial registration and dissemination

The study was approved by the West China Hospital Clinical Trials and Biomedical Ethics Committee of Sichuan University on May 19, 2022 (ethics reference: 2022 (573)), and will be conducted in accordance with the Declaration of Helsinki.

This protocol was registered on November 3rd, 2022, in the Chinese Clinical Trial Registry

with the registration number ChiCTR2200065369. This trial is a sub-project of the National Natural Science Foundation of China with the registration number is ChiCTR2200061225. All participants will be fully informed of the study procedures and sign the informed consent form voluntarily before inclusion (see the Appendix). The private information of all participants will be kept confidential and securely placed in a locked cabinet and will only be accessible to researchers of the study. However, the results of this study will be published in peer-reviewed journals and disseminated at academic conferences.

Discussion

At present, no research has revealed the effect and potential mechanism of cerebellar vermis iTBS on balance in patients with subacute stroke. This prospective single-centre double-blind randomized controlled clinical trial with a 3-week intervention and 3-week follow-up is designed to confirm its effectiveness.

Our study will comprehensively assess trunk control and balance function by clinical scales, balance tests via the Smart Equitest Balance Master System and sEMG measurements. Additionally, we will also collect the concentration of HbO2 in the cerebral cortex via resting-state fNIRS. The integrated data results will be sufficient verify the research hypothesis.

For trunk control, the TIS scores can reveal motor impairment of the trunk in patients with stroke. The sEMG signal directly reflects the activation of muscles directly and contains information about movement intentions generated by the brain.[50] AEMG represents the degree of muscle activation and the synchronization of activated motor units. RMS quantifies the effort of the muscle. MPF and MF are frequency domain features and indicate muscle fatigue.[51 52]

For balance function, the BBS score reflects the overall performance of static and dynamic balance. Accurate integration of sensory information is critical to maintaining balance. The

composite equilibrium score of the SOT characterizes the impairments of individual sensory systems.[53] The ability to voluntarily move the COG within the LOS is fundamental to mobility tasks. By the LOS test, reaction time, movement velocities and excursions are recorded to measure the voluntary ability to shift the COG without losing balance. Reaction time reflects the cognitive processing ability. Movement velocities indicate high-level central nervous system function. Excursions can be restricted by biomechanical deficits.[54] Overall, limitations in the LOS are associated with instability during weight-shifting activities. RWS measures movement velocity and directional control during rhythmic movements. Patients with disrupted normal rhythmic movement control exhibit reduced velocities and/or poor directional control ability.[55]

For cortical activation, fNIRS is a widespread noninvasive measurement that provides real-time monitoring of haemodynamic signals to reflect changes in brain activation.[56] Increased HbO2 is positively correlated with cortical excitability. In addition, balance function and postural stability are positively related to the changes in HbO2 signals in the bilateral SMAs in patients with stroke.[57] Additionally, our previous work revealed that single-session cerebellar vermis iTBS can increase bilateral SMAs excitability during balance tasks in healthy adults.[23]

We hypothesize that cerebellar vermis iTBS can promote the activation of muscles in the trunk and lower limbs, and increase the excitability of the SMAs to improve trunk control and balance function in patients after stroke. The cerebellar vermis plays an important role in postural tone, balance, and locomotion through descending spinal pathways since the vermis receives vestibulocerebellar and proprioceptive spinocerebellar afferents.[58] SMA contributes to anticipatory postural adjustments and postural stability during gait initiation.[59] iTBS consists of high-frequency stimulation bursts that strongly modulate the neural activity of the cerebellar vermis. Studies with humans have shown that iTBS drives acute changes to motor

behaviour and neuronal excitability.[60] A possible mechanism has been reported by an animal study showing that iTBS can promote neural structural remodelling and functional recovery by enhancing neurogenesis and migration via the miR-551b-5p/BDNF/TrkB pathway.[61] The first study of cerebellar vermis stimulation was reported in 1995, which investigated its effects on saccade metrics in a man via TMS.[62] At present, researchers have reported that cerebellar vermis stimulation is a safe and well-tolerated brain stimulation technology with a potential therapeutic effect on schizophrenia.[63] In addition, cerebellar vermis rTMS can induce a suppressive effect on pharyngeal motor cortical activity and swallowing behaviour.[64] However, limited studies have reported that the cerebellar vermis plays an important role in postural response and balance stability.[13 65] Therefore, we hope to identify the effectiveness of cerebellar vermis iTBS in trunk control and balance function for patients with subacute ischemic stroke. Our results may provide valuable information for developing a novel treatment method for the rehabilitation of balance dysfunction after stroke.

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References

1. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;392(10159):1859-922. doi: 10.1016/s0140-6736(18)32335-3 [published Online First: 2018/11/13]
2. Hankey GJ. Stroke. *Lancet* 2017;389(10069):641-54. doi: 10.1016/s0140-6736(16)30962-x [published Online First: 2016/09/18]
3. Komiya M, Maeda N, Narahara T, et al. Effect of 6-Week Balance Exercise by Real-Time Postural Feedback System on Walking Ability for Patients with Chronic Stroke: A Pilot Single-Blind Randomized Controlled Trial. *Brain Sci* 2021;11(11) doi: 10.3390/brainsci11111493 [published Online First: 2021/11/28]
4. Zhang Y, Wang C, Yang J, et al. Comparing the Effects of Short-Term Liuzijue Exercise and Core Stability Training on Balance Function in Patients Recovering From Stroke: A Pilot Randomized Controlled Trial. *Front Neurol* 2022;13:748754. doi: 10.3389/fneur.2022.748754 [published Online First: 2022/03/05]
5. Chen Y, Gao Q, He CQ, et al. Effect of Virtual Reality on Balance in Individuals With Parkinson Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Phys Ther* 2020;100(6):933-45. doi: 10.1093/ptj/pzaa042 [published Online First: 2020/03/12]
6. Luque-Moreno C, Kiper P, Solís-Marcos I, et al. Virtual Reality and Physiotherapy in Post-Stroke Functional Re-Education of the Lower Extremity: A Controlled Clinical Trial on a New Approach. *J Pers Med* 2021;11(11) doi: 10.3390/jpm11111210 [published Online First: 2021/11/28]
7. Marchesi G, Ballardini G, Barone L, et al. Modified Functional Reach Test: Upper-Body Kinematics and Muscular Activity in Chronic Stroke Survivors. *Sensors (Basel)* 2021;22(1) doi: 10.3390/s22010230 [published Online First: 2022/01/12]
8. Schröder J, Saeys W, Yperzeele L, et al. Time Course and Mechanisms Underlying Standing Balance Recovery Early After Stroke: Design of a Prospective Cohort Study With Repeated Measurements. *Front Neurol* 2022;13:781416. doi: 10.3389/fneur.2022.781416 [published Online First: 2022/03/11]
9. Karthikbabu S, Verheyden G. Relationship between trunk control, core muscle strength and balance confidence in community-dwelling patients with chronic stroke. *Top Stroke Rehabil* 2021;28(2):88-95. doi: 10.1080/10749357.2020.1783896 [published Online First: 2020/06/24]
10. D'Angelo E. Physiology of the cerebellum. *Handb Clin Neurol* 2018;154:85-108. doi: 10.1016/B978-0-444-63956-1.00006-0 [published Online First: 2018/06/16]
11. Roostaei T, Nazeri A, Sahraian MA, et al. The human cerebellum: a review of physiologic neuroanatomy. *Neurol Clin* 2014;32(4):859-69. doi: 10.1016/j.ncl.2014.07.013 [published Online First: 2014/12/03]
12. De Bartolo P, Florenzano F, Burello L, et al. Activity-dependent structural plasticity of Purkinje cell spines in cerebellar vermis and hemisphere. *Brain structure & function* 2015;220(5):2895-904. doi: 10.1007/s00429-014-0833-6 [published Online First: 2014/07/16]
13. Lam CK, Tokuno CD, Staines WR, et al. The direction of the postural response to a vestibular perturbation is mediated by the cerebellar vermis. *Exp Brain Res* 2016;234(12):3689-97. doi: 10.1007/s00221-016-4766-6 [published Online First: 2016/09/08]
14. Marfeo A. Neuroanatomy Through Clinical Cases: Inc. Publishers 2010.
15. Ilg W, Giese MA, Gizewski ER, et al. The influence of focal cerebellar lesions on the control and adaptation of gait. *Brain* 2008;131(Pt 11):2913-27. doi: 10.1093/brain/awn246 [published Online First: 2008/10/07]
16. Ille S, Kelm A, Schroeder A, et al. Navigated repetitive transcranial magnetic stimulation improves the outcome of postsurgical paresis in glioma patients - A randomized, double-blinded trial. *Brain Stimul* 2021;14(4):780-87. doi: 10.1016/j.brs.2021.04.026 [published Online First: 2021/05/14]
17. Chen SC, Yang LY, Adeel M, et al. Transcranial electrostimulation with special waveforms enhances upper-limb motor function in patients with chronic stroke: a pilot randomized controlled trial. *J Neuroeng Rehabil* 2021;18(1):106. doi: 10.1186/s12984-021-00901-8 [published Online First: 2021/07/02]
18. 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(2):170-78. doi: 10.1001/jamaneurol.2018.3639 [published Online First: 2018/11/27]
19. Chen Y, Wei QC, Zhang MZ, et al. Cerebellar Intermittent Theta-Burst Stimulation Reduces Upper Limb Spasticity After Subacute Stroke: A Randomized Controlled Trial. *Front Neural Circuits* 2021;15:655502. doi: 10.3389/fncir.2021.655502 [published Online First: 2021/11/16]

20. Liao LY, Xie YJ, 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(1):23-32. doi: 10.1177/1545968320971735 [published Online First: 2020/11/10]
21. Xie YJ, Wei QC, Chen Y, et al. Cerebellar Theta Burst Stimulation on Walking Function in Stroke Patients: A Randomized Clinical Trial. *Front Neurosci* 2021;15:688569. doi: 10.3389/fnins.2021.688569 [published Online First: 2021/11/13]
22. Badke MB, Sherman J, Boyne P, et al. Tongue-based biofeedback for balance in stroke: results of an 8-week pilot study. *Arch Phys Med Rehabil* 2011;92(9):1364-70. doi: 10.1016/j.apmr.2011.03.030 [published Online First: 2011/09/01]
23. Tan H-X, Wei Q-C, Chen Y, et al. The Immediate Effects of Intermittent Theta Burst Stimulation of the Cerebellar Vermis on Cerebral Cortical Excitability During a Balance Task in Healthy Individuals: A Pilot Study. *Frontiers in Human Neuroscience* 2021;15 doi: 10.3389/fnhum.2021.748241
24. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158(3):200-7. doi: 10.7326/0003-4819-158-3-201302050-00583 [published Online First: 2013/01/09]
25. Chinese Society of Neurology CSS. Diagnostic criteria of cerebrovascular diseases in China (version 2019). *Chinese Journal of Neurology* 2019;52(09):710-15. doi: 10.3760/cma.j.issn.1006?7876.2019.09.003
26. Hayward KS, Kramer SF, Dalton EJ, et al. Timing and Dose of Upper Limb Motor Intervention After Stroke: A Systematic Review. *Stroke* 2021;52(11):3706-17. doi: 10.1161/strokeaha.121.034348 [published Online First: 2021/10/05]
27. Soulard J, Huber C, Baillieul S, et al. Motor tract integrity predicts walking recovery: A diffusion MRI study in subacute stroke. *Neurology* 2020;94(6):e583-e93. doi: 10.1212/wnl.0000000000008755 [published Online First: 2020/01/04]
28. Bernhardt J, Hayward KS, Kwakkel G, et al. Agreed definitions and a shared vision for new standards in stroke recovery research: The Stroke Recovery and Rehabilitation Roundtable taskforce. *Int J Stroke* 2017;12(5):444-50. doi: 10.1177/1747493017711816 [published Online First: 2017/07/13]
29. Rossi S, Antal A, Bestmann S, et al. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. *Clin Neurophysiol* 2021;132(1):269-306. doi: 10.1016/j.clinph.2020.10.003 [published Online First: 2020/11/28]
30. Garg S, Sinha VK, Tikka SK, et al. The efficacy of cerebellar vermal deep high frequency (theta range) repetitive transcranial magnetic stimulation (rTMS) in schizophrenia: A randomized rater blind-sham controlled study. *Psychiatry Res* 2016;243:413-20. doi: 10.1016/j.psychres.2016.07.023 [published Online First: 2016/07/28]
31. Huang YZ, Edwards MJ, Rounis E, et al. Theta burst stimulation of the human motor cortex. *Neuron* 2005;45(2):201-6. doi: 10.1016/j.neuron.2004.12.033 [published Online First: 2005/01/25]
32. Spampinato D, Ibáñez J, Spanoudakis M, et al. Cerebellar transcranial magnetic stimulation: The role of coil type from distinct manufacturers. *Brain Stimul* 2020;13(1):153-56. doi: 10.1016/j.brs.2019.09.005 [published Online First: 2019/10/22]
33. Kumar N, Vishnubhatla S, Wadhawan AN, et al. A randomized, double blind, sham-controlled trial of repetitive transcranial magnetic stimulation (rTMS) in the treatment of negative symptoms in schizophrenia. *Brain Stimul* 2020;13(3):840-49. doi: 10.1016/j.brs.2020.02.016 [published Online First: 2020/04/15]
34. Meseguer-Henarejos AB, Rubio-Aparicio M, López-Pina JA, 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(5):570-84. doi: 10.23736/s1973-9087.19.05363-2 [published Online First: 2019/04/09]
35. Hyun SJ, Lee J, Lee BH. The Effects of Sit-to-Stand Training Combined with Real-Time Visual Feedback on Strength, Balance, Gait Ability, and Quality of Life in Patients with Stroke: A Randomized Controlled Trial. *Int J Environ Res Public Health* 2021;18(22) doi: 10.3390/ijerph182212229 [published Online First: 2021/11/28]
36. Chou HY, Lo YC, Tsai YW, et al. Increased Anxiety and Depression Symptoms in Post-Acute Care Patients with Stroke during the COVID-19 Pandemic. *Int J Environ Res Public Health* 2021;19(1) doi: 10.3390/ijerph19010162 [published Online First: 2022/01/12]
37. Zhao J, Chau JPC, Zang Y, et al. Psychometric properties of the Chinese version of the Trunk Impairment Scale in people with a stroke. *Health Qual Life Outcomes* 2021;19(1):85. doi: 10.1186/s12955-021-01730-y [published Online First: 2021/03/12]
38. Thijs L, Voets E, Wiskerke E, et al. Technology-supported sitting balance therapy versus usual care in the chronic stage after stroke: a pilot randomized controlled trial. *J Neuroeng Rehabil* 2021;18(1):120. doi: 10.1186/s12984-021-00910-7 [published Online First: 2021/07/30]
39. Yin L, Liu K, Liu C, et al. Effect of Kinesiology Tape on Muscle Activation of Lower Extremity and Ankle Kinesthesia in Individuals With Unilateral Chronic Ankle Instability. *Front Physiol* 2021;12:786584. doi:

10.3389/fphys.2021.786584 [published Online First: 2022/01/04]
40. Bultitude JH, Pidgeon DM, LeBlanc PR, et al. Two weeks of twice-daily prism adaptation treatment does not improve posture or gait in Parkinson's disease: a double-blind randomized controlled trial. *Trials* 2021;22(1):846. doi: 10.1186/s13063-021-05832-2 [published Online First: 2021/11/27]
41. Kolářová B, Janura M, Svoboda Z, et al. Postural Control Strategies and Balance-Related Factors in Individuals with Traumatic Transtibial Amputations. *Sensors (Basel)* 2021;21(21) doi: 10.3390/s21217284 [published Online First: 2021/11/14]
42. Rossi-Izquierdo M, Santos-Pérez S, Faraldo-García A, et al. Impact of obesity in elderly patients with postural instability. *Aging Clin Exp Res* 2016;28(3):423-8. doi: 10.1007/s40520-015-0414-4 [published Online First: 2015/07/19]
43. Hermens HJ, Freriks B, Disselhorst-Klug C, et al. Development of recommendations for SEMG sensors and sensor placement procedures. *Journal of Electromyography and Kinesiology* 2000;10(5):361-74. doi: 10.1016/s1050-6411(00)00027-4
44. Shen Y, Chen L, Zhang L, et al. Effectiveness of a Novel Contralaterally Controlled Neuromuscular Electrical Stimulation for Restoring Lower Limb Motor Performance and Activities of Daily Living in Stroke Survivors: A Randomized Controlled Trial. *Neural Plast* 2022;2022:5771634. doi: 10.1155/2022/5771634 [published Online First: 2022/01/25]
45. Sun W, Wu X, Zhang T, et al. Narrowband Resting-State fNIRS Functional Connectivity in Autism Spectrum Disorder. *Front Hum Neurosci* 2021;15:643410. doi: 10.3389/fnhum.2021.643410 [published Online First: 2021/07/03]
46. Wang YL, Lin GH, Huang YJ, et al. Refining 3 Measures to Construct an Efficient Functional Assessment of Stroke. *Stroke* 2017;48(6):1630-35. doi: 10.1161/strokeaha.116.015516 [published Online First: 2017/05/05]
47. Akazawa N, Kishi M, Hino T, et al. Increased intramuscular adipose tissue of the quadriceps is related to decreased activities of daily living in patients who have had a stroke. *Nutrition* 2021;90:111277. doi: 10.1016/j.nut.2021.111277 [published Online First: 2021/05/20]
48. Liu F, Tsang RC, Zhou J, et al. Relationship of Barthel Index and its Short Form with the Modified Rankin Scale in acute stroke patients. *J Stroke Cerebrovasc Dis* 2020;29(9):105033. doi: 10.1016/j.jstrokecerebrovasdis.2020.105033 [published Online First: 2020/08/19]
49. Harrison JK, McArthur KS, Quinn TJ. Assessment scales in stroke: clinimetric and clinical considerations. *Clin Interv Aging* 2013;8:201-11. doi: 10.2147/cia.S32405 [published Online First: 2013/02/27]
50. Qing Z, Lu Z, Cai Y, et al. Elements Influencing sEMG-Based Gesture Decoding: Muscle Fatigue, Forearm Angle and Acquisition Time. *Sensors (Basel)* 2021;21(22) doi: 10.3390/s21227713 [published Online First: 2021/11/28]
51. Wei P, Zhang J, Wang B, et al. Surface Electromyography and Electroencephalogram-Based Gait Phase Recognition and Correlations Between Cortical and Locomotor Muscle in the Seven Gait Phases. *Front Neurosci* 2021;15:607905. doi: 10.3389/fnins.2021.607905 [published Online First: 2021/06/08]
52. Alhusuny A, Cook M, Khalil A, et al. The relationship between visual impairments and activity of the neck/shoulder muscles among surgeons during simulated surgical tasks. *Surg Endosc* 2022 doi: 10.1007/s00464-021-08913-0 [published Online First: 2022/01/09]
53. Acuña SA, Tyler ME, Thelen DG. Individuals with Chronic Mild-to-Moderate Traumatic Brain Injury Exhibit Decreased Neuromuscular Complexity During Gait. *Neurorehabil Neural Repair* 2022:15459683221081064. doi: 10.1177/15459683221081064 [published Online First: 2022/03/25]
54. Carvalho GF, Becnel AR, Miske C, et al. Postural control impairment in patients with headaches-A systematic review and meta-analysis. *Headache* 2022;62(3):241-70. doi: 10.1111/head.14281 [published Online First: 2022/03/23]
55. Chen CL, Chen FF, Lin CH, et al. Effect of Anterior Ankle-Foot Orthoses on Weight Shift in Persons With Stroke. *Arch Phys Med Rehabil* 2015;96(10):1795-801. doi: 10.1016/j.apmr.2015.05.003 [published Online First: 2015/05/23]
56. Kinoshita S, Tamashiro H, Okamoto T, et al. Association between imbalance of cortical brain activity and successful motor recovery in sub-acute stroke patients with upper limb hemiparesis: a functional near-infrared spectroscopy study. *Neuroreport* 2019;30(12):822-27. doi: 10.1097/wnr.0000000000001283 [published Online First: 2019/07/10]
57. Fujimoto H, Mihara M, Hattori N, et al. Cortical changes underlying balance recovery in patients with hemiplegic stroke. *Neuroimage* 2014;85 Pt 1:547-54. doi: 10.1016/j.neuroimage.2013.05.014 [published Online First: 2013/05/21]
58. Maiti B, Rawson KS, Tanenbaum AB, et al. Functional Connectivity of Vermis Correlates with Future Gait Impairments in Parkinson's Disease. *Movement disorders : official journal of the Movement Disorder Society* 2021;36(11):2559-68. doi: 10.1002/mds.28684 [published Online First: 2021/06/11]
59. Richard A, Van Hamme A, Drevelle X, et al. Contribution of the supplementary motor area and the cerebellum

to the anticipatory postural adjustments and execution phases of human gait initiation. *Neuroscience* 2017;358:181-89. doi: 10.1016/j.neuroscience.2017.06.047 [published Online First: 2017/07/05]

60. Tang AD, Bennett W, Bindoff AD, et al. Subthreshold repetitive transcranial magnetic stimulation drives structural synaptic plasticity in the young and aged motor cortex. *Brain Stimul* 2021;14(6):1498-507. doi: 10.1016/j.brs.2021.10.001 [published Online First: 2021/10/16]
61. Wang L, Zhou Y, Chen X, et al. Long-term iTBS promotes neural structural and functional recovery by enhancing neurogenesis and migration via miR-551b-5p/BDNF/TrkB pathway in a rat model of cerebral ischemia-reperfusion injury. *Brain Res Bull* 2022;184:46-55. doi: 10.1016/j.brainresbull.2022.03.002 [published Online First: 2022/03/09]
62. Hashimoto M, Ohtsuka K. Transcranial magnetic stimulation over the posterior cerebellum during visually guided saccades in man. *Brain* 1995;118 (Pt 5):1185-93. doi: 10.1093/brain/118.5.1185 [published Online First: 1995/10/01]
63. Escelsior A, Belvederi Murri M, Calcagno P, et al. Effectiveness of Cerebellar Circuitry Modulation in Schizophrenia: A Systematic Review. *The Journal of nervous and mental disease* 2019;207(11):977-86. doi: 10.1097/nmd.0000000000001064 [published Online First: 2019/09/11]
64. Sasegbon A, Niziolek N, Zhang M, et al. The Effects of Midline Cerebellar rTMS on Human Pharyngeal Cortical Activity in the Intact Swallowing Motor System. *Cerebellum* 2021;20(1):101-15. doi: 10.1007/s12311-020-01191-x [published Online First: 2020/09/27]
65. Colnaghi S, Honeine JL, Sozzi S, et al. Body Sway Increases After Functional Inactivation of the Cerebellar Vermis by cTBS. *Cerebellum* 2017;16(1):1-14. doi: 10.1007/s12311-015-0758-5 [published Online First: 2016/01/19]

Legends

Figure 1. The flow diagram of the study design.

Figure 2. The schedule of enrolment, interventions, and assessments.

Figure 3. The Magstim Rapid2 stimulator with a BrainSight neuronavigation system.

Figure 4. The Smart Equitest Balance Master System®.

Figure 5. The sensor locations on individual muscles for sEMG recording (A. rectus abdominis, B. external oblique muscle, C. rector spinae (longissimus), D. rectus femoris, E. biceps femoris, F. tibialis anterior, G. soleus

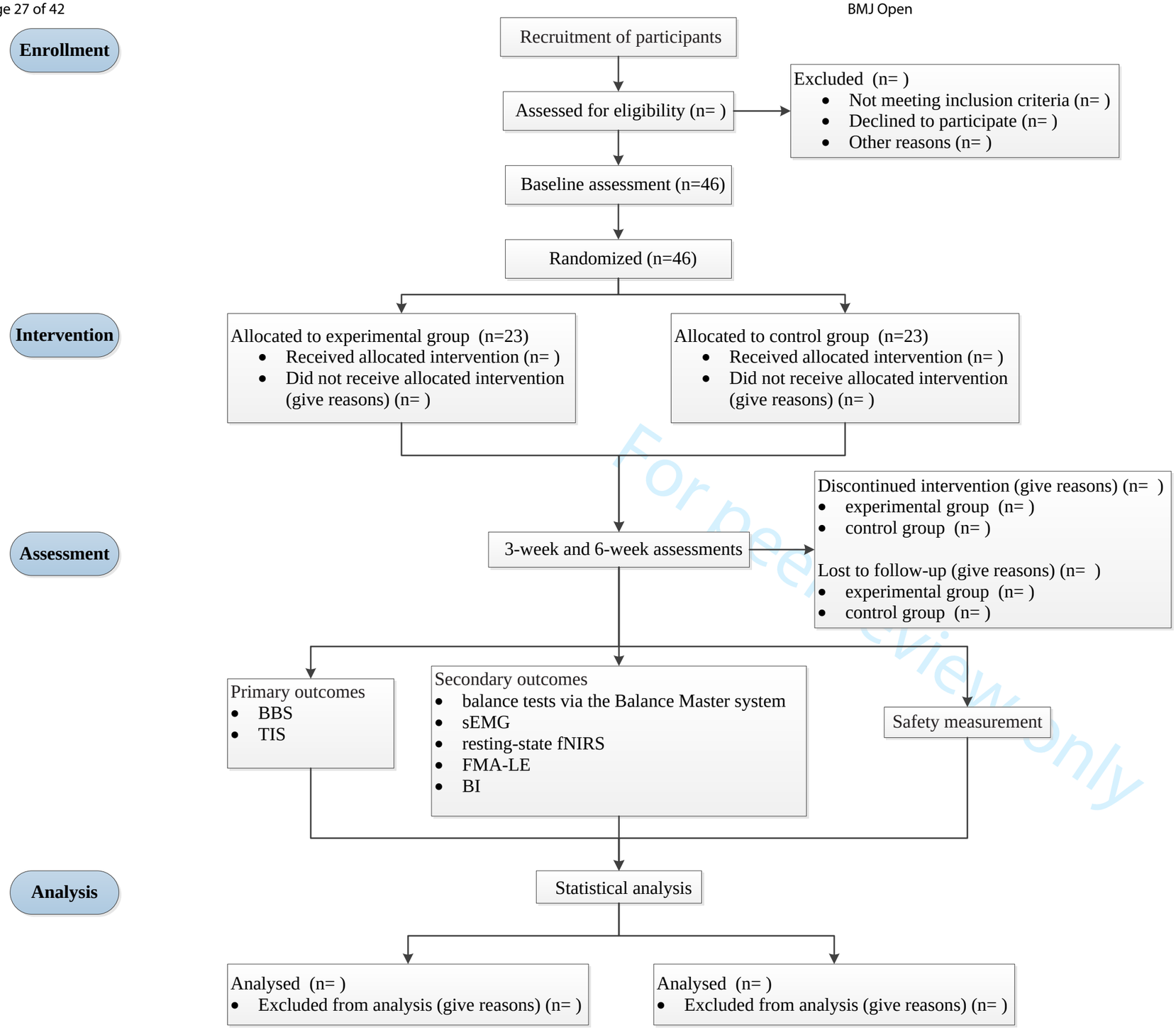

Figure 2. The schedule of enrolment, interventions, and assessments.

	Enrolment	**Allocation**	**Post-allocation**					
TIMEPOINT	$-t_1$	**0**	***W1***	***W2***	***W3***	***W4***	***W5***	***W6***
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Ethical approval and trial registration	X							
Allocation		X						
INTERVENTIONS:								
cerebellar vermis iTBS and conventional physical therapy			—	—	—			
sham stimulation and conventional physical therapy			—	—	—			
ASSESSMENTS:								
basic characteristics information		X						
BBS		X			X			X
TIS		X			X			X
balance tests via the Balance Master system		X			X			X
sEMG		X			X			X
resting-state fNIRS		X			X			X
FMA-LE		X			X			X
BI		X			X			X
Safety measurement			X	X	X	X	X	X

W, week; iTBS, intermittent theta-burst stimulation; BBS, Berg balance scale; TIS, trunk impairment scale; sEMG, surface electromyography; fNIRS, functional near-infrared spectroscopy; FMA-LE, Fugl-Meyer assessment scale score for lower extremities; BI, Barthel index.

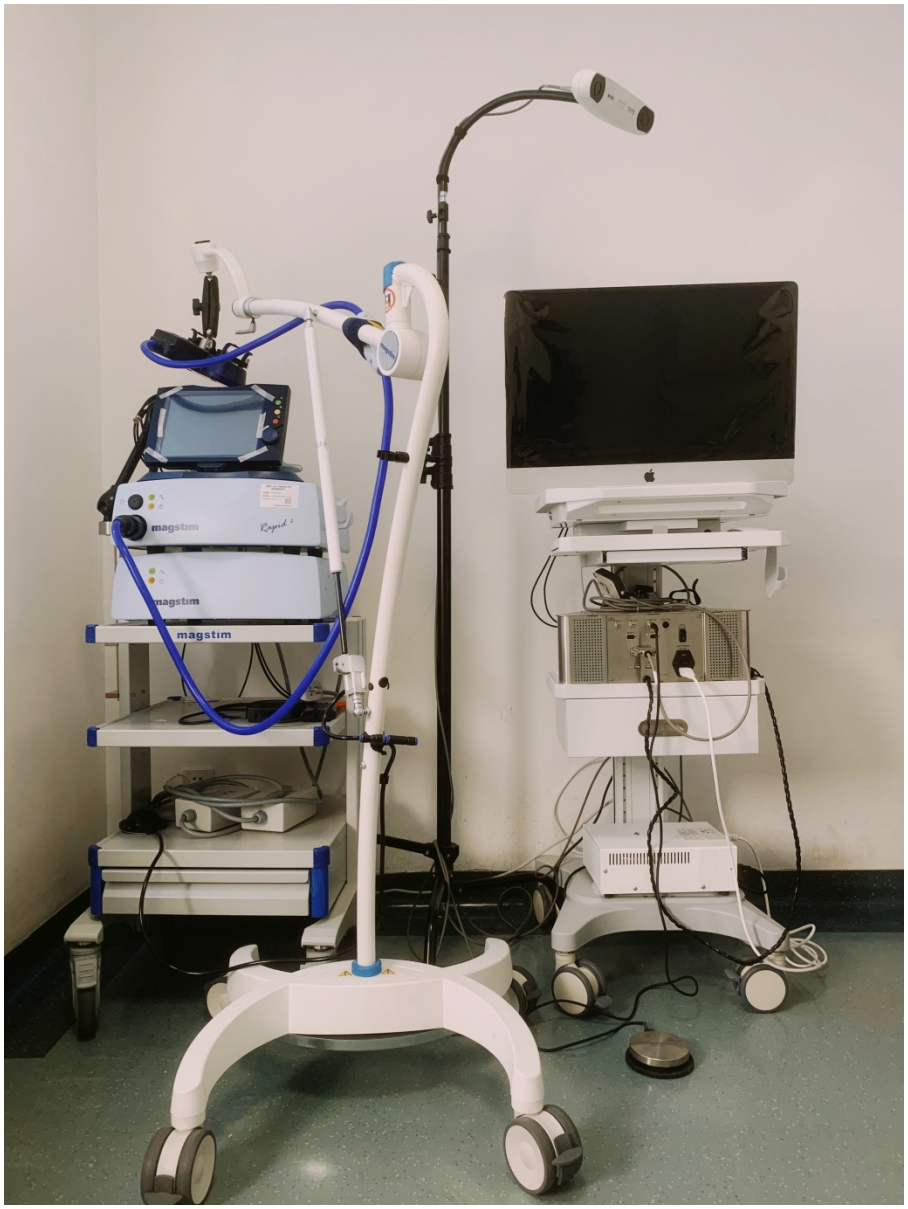

Figure 3. The Magstim Rapid2 stimulator with a BrainSight neuronavigation system.

1066x1422mm (72 x 72 DPI)

Figure 4. The Smart Equitest Balance Master System®.

1066x1422mm (72 x 72 DPI)

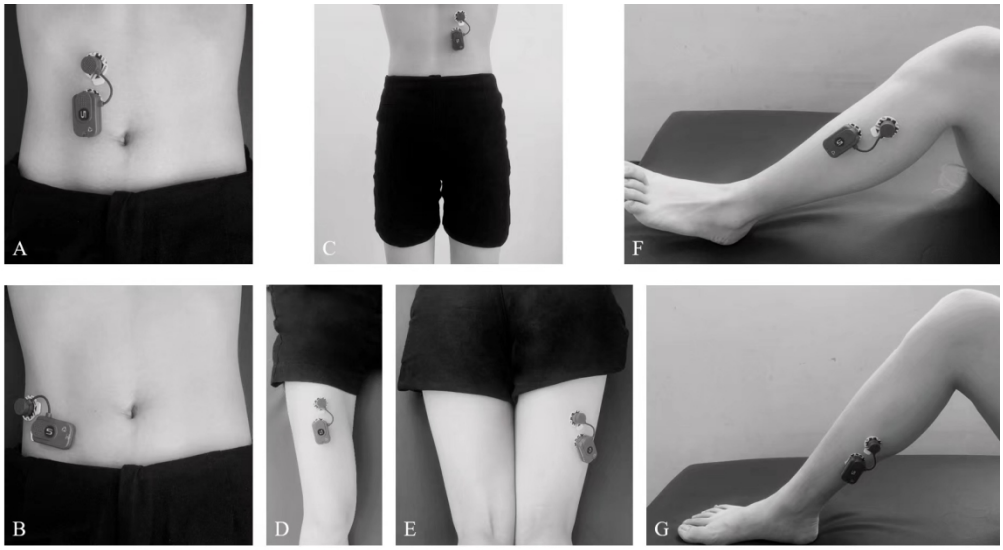

Figure 5. The sensor locations on individual muscles for sEMG recording (A. rectus abdominis, B. external oblique muscle, C. rector spinae (longissimus), D. rectus femoris, E. biceps femoris, F. tibialis anterior, G. soleus)

654x359mm (72 x 72 DPI)

Appendix. Informed Consent Form

West China Hospital, Sichuan University **Participant Informed Consent**			
Name:	**Gender:**	**Age:**	**Inpatient ID:**

Title of study: The effectiveness of cerebellar vermis intermittent theta burst stimulation in improving trunk control and balance function for patients with subacute stroke: a randomized controlled trial

Investigator: Qiang Gao

Funding: NSFC 82172540 from the National Natural Science Foundation of China

What is the study about?

(1) The aim of the study is to determine the effects of cerebellar vermis intermittent theta-burst stimulation (iTBS) on trunk control, muscle activation and balance function in stroke patients. We will recruit 46 patients who meet the inclusion criteria as follows: (1) a diagnosis of ischemic stroke according to the *Diagnostic criteria of cerebrovascular diseases in China (version 2019)*, (2) aged between 18 and 65 years, (3) first-ever unilateral ischemic stroke confirmed by imaging examination, (4) subacute stroke participants with the stroke onset ranging from 2 weeks to 6 months, (5) having motor deficit and balance dysfunction, with a Fugl-Meyer Assessment for Lower Extremities (FMA-LE) <34 points and BBS score <56 points. Patients were excluded if they presented one of the following: (1) diagnosis of coexisting other neurological diseases, (2) injury of cerebellar or brain stem, (3) having contraindications for iTBS (e.g., history of seizures, intracranial metallic implants, microprocessor implants in the body, tumours, and pregnancy), (4) cognitive impairment with a Mini-Mental State Examination (MMSE) score <27, (5) treatment with benzodiazepines, baclofen, antiepileptics and antidepressants.

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How long will I be in the study?

Your part in the study will last **6 weeks** with 3 weeks of intervention and 3 weeks of follow-up (excluding assessment).

What will happen in this study?

You will be randomized into either the experimental or control group according to the random number table. If you assigned to the experimental group will receive cerebellar vermis iTBS after routine daily conventional physical therapy, otherwise you will receive sham stimulation after routine daily conventional physical therapy. The overall intervention periods are five days a week for three consecutive weeks. You will be assessed before treatment, after 3 weeks of intervention and after 3 weeks of follow-up. The measures including clinical scales, balance tests via the Balance Master system, and the surface electromyography recording.

If you are eligible and wish to join the study, you must sign this consent form. If you do not sign the consent form you cannot join the study.

We will review this consent form with you. You will be given enough time to review the consent and have all your questions about the study answered. We will give you a signed copy of the consent for your records before treatment in person.

Study stuff will not know which group or study treatment you are assigned to. You should not join the study if you are not willing to take the study treatment (or join the group) you are assigned to.

What if I have questions?

You can contact the therapist at working hours if you have questions about the study. Qiang Gao (the director of therapists) is in charge of the study.

Do I have to be in the study?

You decide if you want to be in the study. Deciding not to take part will not affect your relationship with your therapist. If your therapist is an investigator for the study, you may get a second opinion from another therapist not involved in the study.

You can leave the study at any time and you do not have to give a reason. Leaving the study will not affect your relationship with your therapist.

The study investigators may ask you to leave the study if it is in your best interest. The study investigator may ask you to leave the study if you do not follow the study rules.

What if I don't want to be in the study?

You can choose not to be in the study and you do not have to give a reason. You can choose to (talk to your doctor/therapist about other options, investigate outside resources on your own, etc.).

Are there any costs?

All study-related treatments are free.

Will I be paid for being in the study?

You will not be paid for being in the study.

Are there any risks?

There is always a small risk of a breech of confidentiality to your personal health information. However, these risks have been addressed and minimized as much as is possible.

You will be told about any new information that may affect your willingness to participate in the study.

There are some possible risks and side effects as follows: headache, nausea, neck pain, seizure, mood changes, fatigue, tinnitus, dizziness, sleepiness and syncope.

If you experience any side effects while on the study contact investigator (Qiang Gao) at any time as soon as possible.

What if I feel I've been hurt by taking part in the study?

If you feel you have been injured or harmed by taking part in this study, please contact investigator (Qiang Gao) at any time. If you feel you were harmed while taking part in this study, you may be treated at West China Hospital, Sichuan University. However, West China Hospital does not offer to pay the cost of this treatment.

If you feel your rights have been violated or you have harmed by this study, please contact your therapist.

Are there any benefits?

It is possible you may receive some benefit from cerebellar vermis iTBS and conventional physical therapy. iTBS is a novel form of rTMS, which can produce long-term potentiation and is more rapid and efficacious than standard rTMS. Cerebellar vermis is a cardinal structure involved in balance and motor control, which is responsible for regulating the trunk, head, neck and proximal limb muscles to control posture and maintain balance. There is no guarantee, however, that you will receive any benefit at all. Your participation will help us learn more about the effects of cerebellar vermis iTBS on trunk control, muscle activation and balance function in subacute stroke patients.

Your privacy is important

Protecting your privacy is very important to us.

During this study we will ask about your (past) and (current) medical history. This information will be used to determine your eligibility for the study and provide data for the study. Your personal health information will be kept private and only authorized study staff will have access to this information. We will use a study number instead of your name. All paper forms will be kept in a locked, secure office. All electronic data will be stored on password-protected computers. Your name will not be used in any publications or presentations about this study.

During the study, you may not be given access to medical information about you that is part of the study. When the study is over, you may request certain medical information collected about you that is part of your study medical record.

None of your personal information will be shared outside of West China Hospital.

By signing this consent form, you are stating that we can use your health information in the ways mentioned above for this study. You are not waiving any of your legal right by signing this form.

You have the right to take away your permission to use your health information collected as part of the study. In order to do this, you must send a written request to: Qiang Gao, department of rehabilitation, West China hospital, Sichuan University

Once your letter is received, no additional information about you will be collected from you for this study. Any data that were collected before we receive your letter will continue to be used for the study. Taking away your permission to use your

health information will not affect your relationship with West China Hospital.

We are collecting only the personal health information that we need for the specific purpose of this study. Your personal health information cannot be used for additional research purpose.

The West China hospital may be required to provide copies of your personal information to government agencies as required by law.

Your permission to use your identifiable health information when the study is complete.

Signatures:

By signing this consent form, it means the following:

- I know my rights have not been waived by signing.
- I have had all of my questions answered and I know whom to ask if I have more questions.
- I have read this form and understand it.
- I want to join the study.
- I know I can leave the study at any time and do not have to give a reason.

_____ _____

Signature of Participant Date

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 17-18
	2b	All items from the World Health Organization Trial Registration Data Set	nil
Protocol version	3	Date and version identifier	nil
Funding	4	Sources and types of financial, material, and other support	20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page, 20
	5b	Name and contact information for the trial sponsor	Title page
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	20
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	nil
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5-6

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-16
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5-6, Fig.2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	16
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	16
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	16
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	16
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16-17
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	16
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15-16
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16-18
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17-18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	nil
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16-18

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	nil
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17-18
	31b	Authorship eligibility guidelines and any intended use of professional writers	nil
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	nil
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary material
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.