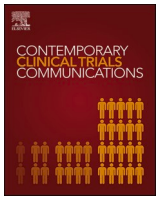
Contemporary Clinical Trials Communications 39 (2024) 101317

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: www.elsevier.com/locate/conctc



The mechanism of Sangdantongluo granule in treating post-stroke spasticity based on multimodal fMRI combined with TMS: Study protocol

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ARTICLE INFO

Keywords:
Post-stroke spasticity
Sangdantongluo granule
fMRI
TMS
Neuralplasticity

ABSTRACT

Introduction: Post-stroke spasticity (PSS) is among the prevalent complications of stroke, greatly affecting motor function recovery and reducing patients' quality of life without timely treatment. Sangdantongluo granule, a modern traditional Chinese patent medicine, has significant clinical efficacy in treating PSS. However, the mechanism of Sangdantongluo granule in treating PSS is still unknown. We designed this study to explore the mechanism of Sangdantongluo granule in treating PSS through multimodal functional magnetic resonance imaging (fMRI) combined with transcranial magnetic stimulation (TMS).

Methods and analysis: In a single-center, randomized, double-blind, parallel placebo-controlled study, 60 PSS patients will be recruited in China and randomly assigned to either the experimental or control groups at a ratio of 1:1. For eight weeks, Sangdantongluo granule or placebo will be utilized for intervention. The main outcome is the Modified Ashworth Scale (MAS), the secondary outcome includes the Fugl-Meyer Assessment Scale-upper Extremity (FMA-UE), National Institute of Health Stroke Scale (NIHSS), and Modified Rankin Scale (mRS), the mechanism measure is the changes in cortical excitability and multimodal fMRI at baseline and after eight weeks.

Ethics and dissemination: This study was approved by the Ethics Committee of the Affiliated Hospital of Hunan Academy of Traditional Chinese Medicine (approval number: [202364]).

Clinical trial registration: Chinese Clinical Trial Registry, identifier: ChiCTR2300074793. Registered on 16 August 2023.

1. Introduction

Chinese lifelong stroke risk is the highest worldwide [1]. Stroke has become the biggest cause of adult death in China, with up to two million patients each year and increasing yearly [2,3]. Post-stroke spasticity (PSS) is among the common complications after stroke, which is caused by the increased reflexes of spinal motor neurons after the injury of the higher motor center. Research shows that spasms occur in the early stages of stroke at a rate of 4–40 % [4–8]. Inadequate treatment often leads to limb muscle contracture pain and joint deformation, obstructing the recovery of affected limb function and further reducing the patient's quality of life [9,10].

PSS is treated with drugs, acupuncture [11], Tui Na [12,13], surgery, and rehabilitation. Drug therapy is the most widely used in clinical practice, including botulinum toxin type A, Baclofen, benzodiazepines, Gabapentin, dantrolene, and tizanidine [14–16], which somewhat improves the degree of limb spasms. However, the drugs also have many side effects, leading to muscle fatigue and detrimental to movement disorder recovery. Traditional Chinese Medicine (TCM) has unique advantages in treating PSS. Yin deficit and blood stasis are the basic Traditional Chinese Medicine pathogenesis of PSS, which affects the tendons and liver. Based on this theory, Sangdantongluo Tang is used to treat this disease.

Preliminary clinical studies have confirmed that Sangdantongluo Tang alleviated limb spasms and improved limb motor function in PSS patients. Moreover, animal experiments have found that Sangdantongluo Tang reduces neuronal apoptosis and infarct area, protects damaged neurons, and promotes the recovery of neural function in rats with cerebral infarction. This prescription has been transformed into

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https://doi.org/10.1016/j.conctc.2024.101317
Received 3 April 2024; Received in revised form 24 May 2024; Accepted 27 May 2024
Available online 1 June 2024

Abbreviations

PSS	Post-stroke spasticity
fMRI	functional magnetic resonance imaging
TMS	transcranial magnetic stimulation
MAS	Modified Ashworth Scale
FMA-UE	Fugl-Meyer Assessment Scale-upper Extremity
NHISS	National Institute of Health Stroke Scale
mRS	Modified Rankin Scale
TCM	Traditional Chinese Medicine
IHI	interhemispheric inhibition
ECG	electrocardiogram
GCS	Glasgow Coma Scale
RMT	resting motor threshold
MEP	motor evoked potentials
CMCT	central motor conduction time
TR	repetition time
TE	the echo time
FOV	field of view
FA	fractional anisotropy
ROI	region of interest
MD	mean diffusivity
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
Cr	Creatinine.

Chinese patent medicine Sangdantongluo granule (Z20210481000) and is widely utilized in clinical practice due to its clinical efficacy. Sangdantongluo granule are composed of ten herbs, with the composition and function are shown in Table 1. However, further research is needed on the mechanism of Sangdantongluo granule in treating PSS.

After a stroke, brain tissue begins to repair its structure and function spontaneously, and this ability to self-repair is called neural plasticity. Previous studies have shown that changes in neural plasticity promote the recovery of motor dysfunction after stroke [17–19]. Besides the spontaneous neural plasticity, exogenous learning-dependent neural repair plays an undeniable role in motor function recovery [20]. Neurological rehabilitation treatment measures have been developed based on the above mechanisms [21]. However, not all neural plasticity helps motor function recovery. Hemispheric inhibitory imbalance, a negative adaptive plasticity alteration, hinders motor function recovery and contributes to motor dysfunction. This has been confirmed in previous animal experiments. After a stroke, the excitability of the primary cortical motor area (M1) in the affected hemisphere is decreased, weakening the inhibitory effect on M1 in the contralateral hemisphere. Therefore, the excitability of M1 in the healthy hemisphere increased abnormally, which increased the inhibitory effect on M1 in the affected hemisphere, causing an imbalance in interhemispheric inhibition (IHI) [22]. This imbalance may be related to spasms after a stroke. We found that PSS rats also exhibit poor neural plasticity and an imbalance of interhemispheric inhibition. From this, we speculate that contralateral overexcitation caused by poor cortical neural plasticity on the affected side of cerebral infarction may be the core cause of PSS, and IHI theory-based treatments for IHI imbalance may be effective.

The brain's self-repair process often presents a natural logarithmic curve pattern. In the early stages of stroke, the rate of changes in neural plasticity is the fastest, often lasting until about ten weeks after stroke, followed by a gradual slowing down and entering a plateau period of around three months [23]. This change is consistent with the patient's motor function recovery characteristics observed in clinical practice. Based on this characteristic, early intervention in neural plasticity is crucial for motor function recovery. Most current research focuses on stroke recovery; thus, brain recovery has stabilized, and clinical guidance is minimal. We plan to select patients with spasms within 90 days after stroke as the observation subjects for early intervention to observe its impact on cortical excitability mediated by neural plasticity in PSS patients and to explore the potential mechanisms of PSS.

Transcranial magnetic stimulation (TMS) is a non-invasive neurophysiological detection technique that can evaluate motor cortex excitability and inhibitory neuronal network function by measuring neuronal cell membrane excitability, synaptic excitability, and neuronal and axonal plasticity, reflecting the level of cortical excitability. TMS can provide objective neuro-electrophysiological information by detecting resting motor threshold (RMT), motor evoked potentials (MEP), and central motor conduction time (CMCT) [24]. FMRI has high spatial resolution and utilizes blood oxygen level-dependent signals as alternative indicators of neural activity. It can detect brain functional network connectivity, quantitatively detect damage to white matter

Table 1
Composition, effects and pharmaceutical action of the Chinese herbal medicines that constitute Sangdantongluo granule.

Chinese name	Latin name	Plant part	Effect (TCM)	Pharmaceutical action	Doses (g)
Sangshen	Mori Fructus	Fruits	Nourishes yin and blood, and promotes fluid production for moistening dryness	Immunoregulation and antioxidation	15
Gouqizi	Lycii Fructus	Fruits	Nourishes liver and kidney	Immunoregulation, anti-inflammatory, and liver protection	15
Danshen	Salviae Miltiorrhizae Radix Et Rhizoma	Root	Promotes blood circulation for removing blood stasis and obstruction in collaterals	Neuroprotection, antioxidation, and improves lipid metabolism	30
Dilong	Pheretima	Dry body	Promotes blood circulation for removing blood stasis and obstruction in collaterals	Anticoagulant, and antithrombosis	6
Baishao	Paeoniae Radix Alba	Root	Nourishes yin for softening liver	Antioxidation, anti-inflammatory, antiapoptosis and neuroprotection	10
Tianma	Gastrodiae Rhizoma	Tuber	Suppresses hyperactive liver and subsiding yang, and relieves spasm by calming endogenous wind	Antioxidation, anti-inflammatory, inhibits synaptic remodeling and lowers blood pressure	10
Xixiancao	Siegesbeckiae Herba	Aerial part	Relieves rigidity of muscles and activates collaterals	Anti-inflammatory, antithrombosis and eases pain	9
Dashenjin	Smilax nipponica	Root	Relieves rigidity of muscles and activates collaterals	Antioxidation and anti-inflammatory	9
Chantui	Cicadae Periostracum	Carapacehard outer shell	Dispels pathogenic wind for resolving convulsion	Anti-inflammation, spasmolysis, anticoagulant, sedation and analgesis	3
Shanzha	Crataegi Fructus	Fruits	Harmonize the stomach and aid digestion	Neuroprotection	15

TCM, Traditional Chinese Medicine.

fibers [25,26], and reflect local neural activity during task execution by task-state fMRI. Multimodal fMRI can complement each other's benefits from many perspectives and better depict the central nervous system structure and function. Multimodal fMRI with TMS is used in neurology to study motor function recovery neurobiological pathways [27,28]. They can evaluate stroke-related damage to brain structure and function and explore imaging markers that affect the outcome of motor function by predicting the prognosis of motor function after stroke. This can provide objective evidence for brain remodeling for early rehabilitation treatment of stroke patients [19]. This study will use multimodal fMRI combined with TMS to clarify the role of cortical overexcitation caused by poor neuroplasticity in PSS pathogenesis, provide a new target for PSS prevention and treatment, reveal Sangdantongluo granule's mechanism in treating PSS, and provide imaging basis for its promotion and use.

2. Methods

2.1. Study setting

This is a single-center, randomized, double-blind, parallel placebo-controlled study. We will recruit 60 PSS patients with yin deficiency and blood stasis syndrome from Hunan Provincial Hospital of Integrated Traditional Chinese and Western Medicine. Eligible subjects will be randomly divided into two groups and receive intervention with Sangdantongluo granule or placebo for eight weeks, respectively. Multimodal fMRI combined with TMS will reveal the role of cortical overexcitement caused by poor neuroplasticity in PSS, providing a novel target for preventing and treating PSS. By revealing the mechanism of Sangdantongluo granule in treating PSS and providing imaging evidence for its promotion and application. The trial's flow chart is presented in Fig. 1. The schedule of enrollment and assessments is presented in Table 2.

2.2. Subjects

This study focuses on PSS patients with TCM syndrome of yin deficiency and blood stasis treated in the outpatient and inpatient departments of Hunan Provincial Hospital of Integrated Traditional Chinese and Western Medicine (Hunan Academy of Chinese Medicine Affiliated Hospital).

Table 2
Schedule of enrollment and assessments.

Time	Screening (D-5-D0)	Baseline (D1)	Treatment (8 weeks)
Eligibility screen	✓		
Informed consent	✓		
Demographic	✓		
Medical history	✓		
physical examination	✓		✓
ECG	✓		✓
Lab examination	✓		✓
MAS		✓	✓
GCS		✓	✓
NIHSS		✓	✓
FMA-UE		✓	✓
mRs		✓	✓
TMS		✓	✓
fMRI		✓	✓
Randomization		✓	
Adverse events		Record at any time	
Concomitant medication		✓	✓

Lab examination including blood routine, liver and kidney function, cardiac enzyme, blood glucose, blood lipid, urine routine. ECG, electrocardiogram; MAS, Modified Ashworth Scale; GCS, Glasgow Coma Scale; NIHSS, National Institute of Health Stroke; FMA-UE, Fugl-Meyer assessment for the upper extremity; mRS, Modified Rankin Scale; TMS, Transcranial Magnetic Stimulation; fMRI, Functional Magnetic Resonance Imaging.

2.3. Inclusion criteria

(1) Western medicine diagnosis meets the diagnostic criteria for cerebral infarction.
(2) Traditional Chinese Medicine syndrome meets Yin deficiency and blood stasis syndrome criteria (Diagnostic Scale of Syndrome

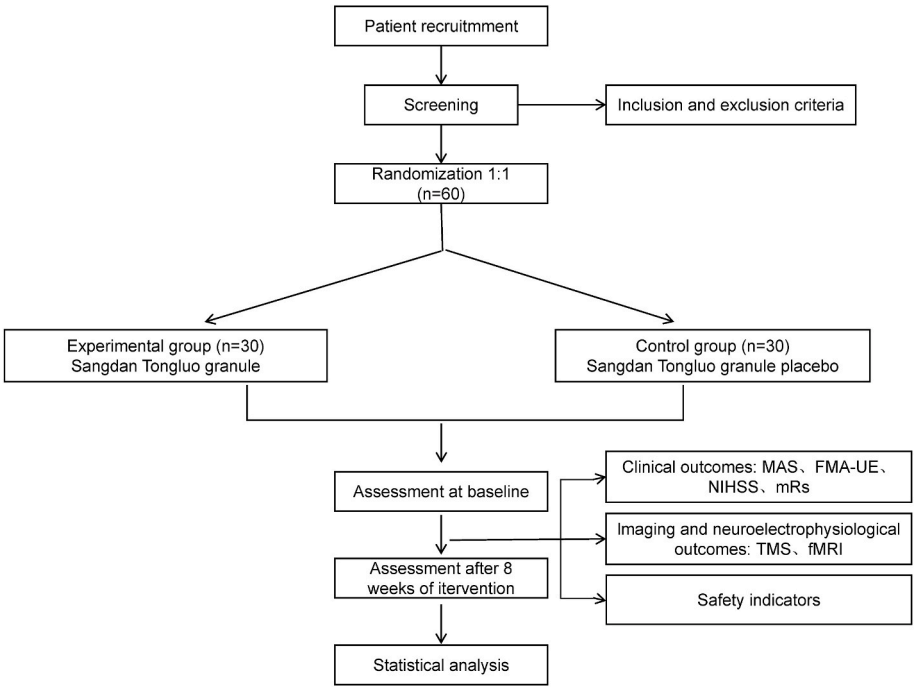

Fig. 1. Trial flow chart. MAS, Modified Ashworth Scale; NIHSS, National Institute of Health Stroke; FMA-UE, Fugl-Meyer assessment for the upper extremity; mRS, Modified Rankin Scale; TMS, Transcranial Magnetic Stimulation; fMRI Functional Magnetic Resonance Imaging.

Factors of Ischemic Stroke is used for syndrome judgment, and the syndrome is established when the score is $\geq$ 10. The rating details is shown in Supplementary Materials 2).

(3) First onset, within 15–90 days.
(4) Age $\geq$18 years and $\leq$80 years old.
(5) Individuals with unilateral upper limb hemiplegia and spasms: Modified Ashworth Spasticity Score $\geq$1 and $\leq$ 3 levels, without symptoms of neurological deficits like aphasia, dysarthria, dysphagia, facial paralysis, and cognitive impairment.
(6) Conscious patients (GCS score = 15) who participate in consultation, physical examination, instructions, and treatment.
(7) Patients who have been determined as right-handed by the Chinese Handedness Scale.
(8) Patients who have not participated in other clinical trials in the past three months.
(9) Patients or their family member agrees and signs an informed consent form.

2.4. Exclusion criteria

(1) Previous motor dysfunction, like rheumatoid arthritis, multiple sclerosis, spinal cord injury, or neuromuscular disease which, affects limb activities.
(2) Patients with a history of stroke and limb spasms.
(3) Patients with mental disorders, cognitive or emotional disorders who cannot understand or obey the research procedure and follow-up.
(4) Previous history of long-term alcoholism or consumption of central nervous system active drugs.
(5) Patients with severe liver and kidney dysfunction (ALT >2 times normal upper limit or AST >2 times normal upper limit; Cr > 1.5 times normal upper limit).
(6) Complicated with serious heart, liver, kidney, endocrine disease and other life-threatening serious diseases, and the expected survival time is less than three months.
(7) Patients who have received antispasmodic treatment within two weeks before enrollment, like antispasmodic drugs.
(8) Allergic to the ingredients of Sangdantongluo granule.
(9) Pregnant or lactating women.
(10) Ischemic stroke is caused by intracranial tumors, heart disease, blood disease, brain trauma and other no arteriosclerosis.
(11) Have MRI or TMS contraindication, like claustrophobia and a history of metal implantation.

2.5. Recruitment of participants

All subjects will be recruited through posters from inpatients and outpatients of Hunan Provincial Hospital of Integrated Traditional Chinese and Western Medicine (Hunan Academy of Chinese Medicine Affiliated Hospital).

2.6. Interventions

All subjects will be randomly divided into an experimental and control group, with 30 cases in each group. Standardized Western medicine treatment will be given to all subjects, including risk factor control, antiplatelet therapy, and rehabilitation. Therefore, the control group will receive Sangdantongluo granule placebo twice a day for eight weeks, while the experimental group will receive Sangdantongluo granule twice a day for eight weeks.

2.7. Outcomes

2.7.1. Clinical outcomes

(1) Primary outcome

MAS: Evaluate the degree of limb spasms at baseline and after eight weeks of intervention.

(2) Secondary outcome

FMA-UE: Evaluate upper limb motor function at baseline and after eight weeks of intervention.

NIHSS:Evaluate the degree of neurological impairment at baseline and after eight weeks of intervention.

mRS:Evaluate the degree of disability at baseline and after eight weeks of intervention.

2.7.2. Imaging and neuro-electrophysiological outcomes

(1) Cortical excitability test

Detect motor evoked potential (MEP), MEP amplitude and MEP latency of the resting motor threshold (RMT) by TMS to evaluate the cerebral cortex's excitability at baseline and after eight weeks of intervention.

Use Magpro X100 transcranial magnetic stimulator to send a single pulse, and electromyography receives MEP signal. The contralateral abductor pollicis brevis motor representative area continuously leads to the stable maximum MEP site, the primary motor cortex area (M1 area). To measure the RMT of MEP, gradually reduce the stimulus intensity and adjust the maximum MEP elicited by the stimulus intensity; the spectrum with the shortest latency and highest amplitude recorded is MEP latency and amplitude. According to whether TMS can induce MEP in the affected M1 area, patients are divided into MEP (+) and MEP (−) to measure cortical excitability.

(2) Multimodal fMRI

Routine MRI, DTI, Resting-state fMRI and task-state fMRI will be performed at baseline and after eight weeks of intervention.

The scanning parameters are as follows: 3D T1-BRAVO sequence: the repetition time (TR) = 8.14 ms, the echo time (TE) = 3.17 ms, the field of view (FOV) = 240 × 240 mm, matrix size = 96 × 96, slice thickness = 1 mm, slice gap = 1 mm, flip angle = 12°. DTI:TR = 5000 ms, TE = 98.8 ms, FOV = 220 × 220 mm, matrix size = 256 × 256, lice thickness = 1 mm, 30 axial slices, flip angle = 90°, B = 1000 s/mm 2, 25 direction.rs-fMRI: TR = 2000 ms, TE = 30 ms, FOV = 240 × 240 mm, matrix size = 64 × 64, lice thickness = 3.2 mm, 43 axial slices, flip angle = 90°. Instruct patients to keep their eyes closed and body motionless and not engage in specific thinking activities during the scanning process. After the resting state scan, the task state will be scanned with the same parameters. Participants will be instructed to perform finger-to-thumb opposition movement during the task state scanning. The stimulation task will be arranged in a block pattern: hemiplegic side finger-to-thumb opposition movement for 30 s, rest for 30 s, and healthy side finger-to-thumb opposition movement for 30 s, repeated thrice for 6 min. Those who cannot complete active movements will be assisted by the operator to complete passive movements.

2.8. Image data processing

The image data processing is as follows: DTI will be preprocessed using the Diffusion Toolkit software to obtain fractional anisotropy (FA) graphs. Based on previous research, region of interest (ROI) will be selected and outlined, and quantitatively, the structural integrity of bilateral corticospinal tracts by calculating the average FA value and mean diffusivity (MD) value of ROI. Two imaging physicians will perform the above surgeries, and a third will assess those with significant differences.

Rs-fMRI: The data will be processed using DPARSFA and SPM software, including removing the first 10-time point data, flipping the image

to ensure that the lesions are all located on the left side, time correction, head movement correction, spatial standardization, spatial smoothing, de linear drift, low-frequency filtering (0.01–0.1 Hz), and removing physiological interference factors (head movement, whole brain signal, white matter signal, and cerebrospinal fluid). The ROI-wise FC analysis method will calculate the functional connectivity between ROIs. Based on previous research, motor function regions will be identified, centered on the MNI coordinate with a radius of 6 mm, and the average time series of all voxels in each ROI will be extracted. The correlation coefficient between each ROI will be calculated, and the correlation coefficient will be subjected to a Fisher Z transformation to approach a normal distribution. Then, the cortical motor network will be presented using BrainNet Viewer.

Ts-fMRI: SPM software will be used for data preprocessing and analysis, flipping the image to ensure the lesions are all located on the left side performing time correction, head movement correction, spatial standardization, and spatial smoothing. Paired t-tests will be used to analyze brain activation at baseline, and after eight weeks of intervention, average activation values will be extracted.

2.9. Safety evaluation and adverse events

Safety indicators include electrocardiogram, blood routine, liver function, kidney function, myocardial enzymes, blood sugar, blood lipids, and urine routine. Adverse events will be detailed in the case report form throughout the study. Serious adverse events, like causing disability, affecting workability, and endangering life or death, should be immediately notified to the researchers and the ethics committee. The research team will provide advice and treatment guidance to the subject and decide whether they can continue participating in the study.

2.10. Sample size

The goal of this trial is to investigate how Sangdantongluo granule treats PSS. Imaging study sample size calculation requires 25 patients per group for more reliable results [29]. Considering the case dropout and unclear imaging collection, we plan to recruit 30 patients per group, totaling 60.

2.11. Randomization and blinding

A block randomization method will be used in this study. A random number grouping table will be generated using SAS statistical software to generate a random grouping plan, which will be sealed in an opaque envelope. We will open the envelopes in the order of subject enrollment to include patients and distribute medication.

Blinding will include drugs and packaging. The research and blinding units will keep the blind bottom in an opaque envelope to keep subjects and researchers blind until the trial ends. After the study, we will conduct a first-level unblinding to separate groups and conduct statistical analysis. After statistical analysis, Secondary unblinding will clarify the experimental and control groups. During the research, if there is an urgent need to break the blind, like severe adverse reactions, the researcher will decide whether to break the blind and record the reasons for the break in detail.

2.12. Combination medications

During the trial, the combined drug use will be monitored, and additional traditional Chinese medicines that nourish Yin and promote blood circulation will be prohibited.

2.13. Data management

Researchers will collect data and accurately, timely, complete, and standardized record the data in a paper case report form. The database will be entered and verified by two staff members. Inconsistencies must be checked individually, and the causes must be determined. After the data administrator verifies the data and writes a data audit report, the database will be locked, and unauthorized modifications will be prohibited. Research institutions, statisticians, and sponsors will conduct data statistical analysis after approving the data management report.

2.14. Statistical analysis

2.14.1. Baseline data, laboratory indicators, and scale scores

These data will be analyzed using SPSS software (version 25.0). Measurement data will be described by mean ± standard deviation ($x \pm s$). Those that conform to normal distribution and homogeneity of variance will be compared between groups using a *t*-test, otherwise rank sum test will be used. The counting data will be described using frequency tables, percentages, or composition ratios; the Chi-square test, Fisher's exact probability method, or rank sum test will be used for inter-group comparison. It will be considered statistically significant when the *P*-value is less than 0.05.

2.15. Neuro-electrophysiological indicators

Paired t-tests will be used to compare the differences between the healthy and affected hemispheres and the changes in neuro-electrophysiological indicators baseline and after eight weeks intervention. The Least Significant Difference (LSD) method will be used for inter-group comparison. The Pearson correlation test will be used for correlation analysis between neuro-electrophysiological indicators and clinical scale scores. It will be considered statistically significant when the *P*-value is less than 0.05.

2.16. Multimodal fMRI data

DTI: Paired t-tests will be used to analyze FA and MD values at baseline, and after eight weeks of intervention, the LSD method will be used for inter-group comparison. Pearson correlation test will examine the correlation between FA, MD values, and scale scores.

Rs-fMRI: Paired t-tests will be used to analyze FC values at baseline, and after eight weeks of intervention, the LSD method will be used for inter-group comparison. Pearson correlation analysis will test the correlation between FC and motor function changes.

Ts-fMRI: Paired t-tests will be used to analyze brain activation at baseline and after eight weeks of intervention. The activation value will be extracted, and the Pearson correlation test will be used to analyze its correlation with clinical scale scores. The LSD method will be used for inter-group comparison.

It will be considered statistically significant when the *P*-value is less than 0.05.

2.17. Quality control

To ensure the quality of the experiment, the participants will be carefully informed of the instructions for filling out the diary card, including the content, filling method, recycling method of the diary card, and the recording and handling methods of adverse drug reactions. We will improve subject follow-up to ensure medication compliance. Reasons for midway withdrawals will be documented. To assure data reliability, increase researchers' uniform training, master intervention procedures, objectively record subject symptoms, and truly and thoroughly fill out the case report form before the experiment. A three-level quality assurance system will be established to control and supervise the quality of the entire research process. Regular verification of research data records and review of test progress, authenticity, and safety will be conducted.

3. Discussion

Stroke is among the main causes of long-term disability worldwide [30]. Despite active rehabilitation treatment, many stroke patients still have varying degrees of motor disorders [31,32]. Motor dysfunction is often manifested as limb disharmony, mainly due to spasms, which hinder patients' motor function recovery and increase their economic burden [33]. Data shows that PSS increases patients' medical expenses fourfold [34]. Currently, there are no particularly effective treatment measures for PSS. Drug therapy has negative effects, whereas physical therapy provides few short-term benefits, lowering patient confidence and compliance. Thus, economical, effective, and convenient treatment is of paramount importance. Traditional Chinese Medicine has unique advantages in treating PSS, as it can promote the improvement of spasms to a certain extent with minimal side effects [35–37]. In clinical applications, we have found that Sangdantongluo granule is safe and effective in treating PSS, but currently, there is a lack of high-quality research results to support it.

The pathogenesis of PSS is unknown, but neural plasticity is involved in spasm occurrence and relief [21]. After a stroke, the cortical structure and function immediately begin reorganizing, which is the basis for recovering motor dysfunction. However, maladaptive plasticity is the cause of spasms, and IHI imbalance is one of its types. Stroke disrupts the balance of mutual inhibition between the cerebral hemispheres, resulting in an enhanced inhibitory effect of the healthy hemisphere on the affected side. Spasms may be alleviated by reducing the healthy hemisphere's excitability or increasing the affected one [38]. The excitability of the reticular spinal tract, caused by maladaptive plasticity, is gradually recognized for its role in spasms and is the most likely mechanism. It was proven in animal and clinical trials. Spasticity and motor recovery require maladaptive plasticity regulation. Low-frequency rTMS is a significant tool for inducing neural plasticity. The study showed that low-frequency rTMS treatment of the contralateral hemisphere can improve upper limb spasticity in patients with severe hemiplegia [39]. Using static functional magnetic resonance imaging, Gottlieb found that low-frequency rTMS reduces spasticity by stimulating neural plasticity and increasing functional connections between the cerebral cortex [40]. Peripheral repetitive magnetic stimulation may improve spasms by increasing affected cortex excitability and motor cortex functional reorganization [41]. The main mechanism of botulinum toxin A in treating PSS is regulating maladaptive plasticity [42], which may also be the focus of acupuncture, moxibustion, Tui Na, and other therapies [43]. As mentioned above, we speculate that abnormal cortical excitability caused by poor neural plasticity is the core pathological mechanism of PSS, and the mechanism of Sangdantongluo granule in treating PSS may be to regulate neural plasticity.

TMS combined with multimodal fMRI can better observe changes in neural plasticity. Few studies use electrophysiology combined with neuroimaging to explore the neuro-electrophysiological mechanisms of motor function recovery, specifically spasm improvement [44,45]. Neuro electrophysiological detection using TMS can survey the excitability of the cerebral cortex, and multimodal functional magnetic resonance imaging can better observe the characteristics of neural plasticity after stroke from different perspectives. DTI detects the integrity and directionality of the white matter fiber bundle in the brain, thereby evaluating the degree of secondary neurodegeneration and white matter fiber bundle injury after stroke. Previous studies have shown that the integrity of the corticospinal tract affects the prediction of motor function recovery [46]. Task state functional magnetic resonance imaging can reflect the correlation between neural plasticity and motor function recovery, intuitively displaying neurons' activity in specific brain functional areas during task execution [47]. There is, however, a degree of data error due to variations in task execution and synchronization produced by varied degrees of post-stroke motor disorders. Resting-state functional magnetic resonance imaging requires the patient to perform in a fully conscious, eye-closed, and quiet state, which, to some extent, avoids the impact of patient compliance on data analysis. Resting-state functional resonance shows alterations in motor area functional connectivity following stroke, indicating a correlation with motor recovery [48]. TMS combined with multimodal fMRI provides a more comprehensive understanding of neural plasticity mechanisms in the pathogenesis and improvement of PSS. This is why we chose multimodal functional magnetic resonance imaging with TMS to study the mechanism of Sangdantongluo granule in PSS treatment and improve PSS treatment regimens.

Ethics and dissemination

The study has been registered in the Chinese Clinical Trials Register (registration number: ChiCTR2300074793) and has been approved by the Ethics Committee of the Affiliated Hospital of Hunan Academy of Traditional Chinese Medicine (approval number: [202364]). All participants will sign a written informed consent form (The Informed Consent is shown in Supplementary Materials 1). We will strictly abide by the Declaration of Helsinki. The findings of the study will be published in a peer-reviewed journal and will be presented at national or international academic conferences.

Trial status

The trial is in progress and recruiting pose-stroke spasticity patients.

Funding

This study was supported by the Hunan Province Clinical Medical Technology Innovation Guidance Project (Grant No. 2021SK51005), and the science and technology innovation Program of Hunan Province (Grant No. 2023RC3215).

Data availability

Currently, no data has been generated. Relevant data will be available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Jie Tang: Writing – original draft, Methodology, Investigation. **Yao Xie:** Methodology, Investigation. **Rui Fang:** Methodology. **Huizhong Tan:** Investigation. **Shanshan Zeng:** Investigation. **Zan Wen:** Investigation. **Xiongxing Sun:** Investigation. **Ting Yao:** Investigation. **Shiliang Wang:** Investigation. **Le Xie:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Dahua Wu:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2024.101317.

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