Research Article

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# Effects of paired associative magnetic stimulation between nerve root and cortex on motor function of lower limbs after spinal cord injury: study protocol for a randomized controlled trial

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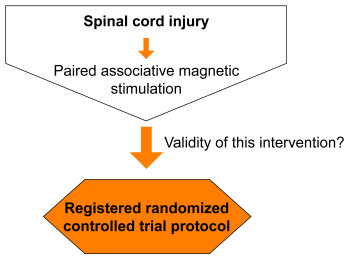
**Graphical Abstract** *Paired associative magnetic stimulation to treat spinal cord injury*




## Abstract

Classic paired associative stimulation can improve synaptic plasticity, as demonstrated by animal experiments and human clinical trials in spinal cord injury patients. Paired associative magnetic stimulation (dual-target peripheral and central magnetic stimulation) has been shown to promote neurologic recovery after stroke. However, it remains unclear whether paired associative magnetic stimulation can promote recovery of lower limb motor dysfunction after spinal cord injury. We hypothesize that the current caused by central and peripheral magnetic stimulation will converge at the synapse, which will promote synapse function and improve the motor function of the relevant muscles. Therefore, this study aimed to examine the effects of paired associative magnetic stimulation on neural circuit activation by measuring changes in motor evoked and somatosensory evoked potentials, motor and sensory function of the lower limbs, functional health and activities of daily living, and depression in patients with spinal cord injury. We will recruit 110 thoracic spinal trauma patients treated in the Department of Spinal Cord Injury, China Rehabilitation Hospital and randomly assign them to experimental and control groups in a 1:1 ratio. The trial group ($n$ = 55) will be treated with paired associative magnetic stimulation and conventional rehabilitation treatment. The control group ($n$ = 55) will be treated with sham stimulation and conventional rehabilitation treatment. Outcomes will be measured at four time points: baseline and 4, 12, and 24 weeks after the start of intervention (active or sham paired associative magnetic stimulation). The primary outcome measure of this trial is change in lower limb American Spinal Injury Association Impairment Scale motor function score from baseline to last follow-up. Secondary outcome measures include changes in lower limb American Spinal Injury Association sensory function score, motor evoked potentials, sensory evoked potentials, modified Ashworth scale score, Maslach Burnout Inventory score, and Hamilton Depression Scale score over time. Motor evoked potential latency reflects corticospinal tract transmission time, while amplitude reflects recruitment ability; both measures can help elucidate the mechanism underlying the effect of paired associative magnetic stimulation on synaptic efficiency. Adverse events will be recorded. Findings from this trial will help to indicate whether paired associative magnetic stimulation (1) promotes recovery of lower limb sensory and motor function, reduces spasticity, and improves quality of life; (2) promotes neurologic recovery by increasing excitability of spinal cord motor neurons and stimulating synaptic plasticity; and (3) improves rehabilitation outcome in patients with spinal cord injury. Recruitment for this trial began in April 2021 and is currently ongoing. It was approved by the Ethics Committee of Yangzhi Affiliated Rehabilitation Hospital of Tongji University, China (approval No. YZ2020-018) on May 18, 2020. The study protocol was registered in the Chinese Clinical Trial Registry (registration number: ChiCTR2100044794) on March 27, 2021 (protocol version 1.0). This trial will be completed in April 2022.

**Key Words:** interstimulus interval; motor-evoked potentials; Modified Ashworth Scale; Maslach Burnout Inventory; paired-associative magnetic stimulation; plasticity; repetitive transcranial magnetic stimulation; sensory-evoked potential; spinal cord injury; spike timing-dependent plasticity

## Introduction

### Background and rationale

Targeted functional exercise and neural regulation technology have been shown to effectively improve the limb dysfunction caused by spinal cord injury (SCI). However, it remains unclear whether paired magnetic stimulation can improve neural circuit reconstruction in patients with SCI.

Causes of SCI include trauma, infection, and degenerative processes; however, most severe SCIs are traumatic (Calabró et al., 2017). Traumatic SCI typically results from vertebral fracture and consequent spinal cord compression, which causes varying degrees of permanent neurological dysfunction. SCI is

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associated with high morbidity, high cost, and life-long disability. It severely limits activities of daily living and can induce mental illness in affected individuals. Overall, SCI is a large burden on the patient, family, and society. Reported global incidence rates of SCI range between 236 and 1009 per one million (Hill et al., 2010). Many SCI patients are young and had previously employed before injury; therefore, their permanent disability imposes great psychological and economic pressures. The need to develop effective SCI treatment is urgent (Herrmann et al., 2011).

Limb paralysis is one of the most catastrophic consequences of SCI (Kuppuswamy et al., 2011). SCI disrupts neural circuit connectivity, which results in long-term neurological disability. However, recovery of function depends on augmenting neuroplasticity. Therefore, it is necessary to promote nerve cell sprouting and regeneration and expand the strength of remaining neural connections in order to promote neural circuit reconstruction (Raineteau et al., 2001). Previous studies have reported that various rehabilitation modalities can improve motor function. Most therapeutic approaches focus on kinesiotherapy and physical therapy. Despite recent advances in SCI treatment with stem cells and brain-computer interfaces, no treatment directed at neural circuit reconstruction has yet been explored (Yousefifard et al., 2016).

Rapid progress has been made in neuromodulation over the past two decades. Electrical and magnetic stimulation of the central and peripheral nervous system has been shown to elicit neural plasticity and enhance nerve conduction (Tazoe et al., 2015). Transcranial magnetic stimulation (TMS) is a form of neuromodulation that improves neural plasticity and is regarded as a non-invasive rehabilitation modality (Cortes et al., 2017). TMS acts on various zones and pathways within the central nervous system, including the primary motor cortex and corticospinal tract. However, formation and reconstruction of functional neural circuits probably rely on neuromodulation combined with rehabilitation, such as exercise training (Leszczyńska et al., 2020).

Paired associative magnetic stimulation (PAMS) is an innovative neural network-based treatment modality that has potential to induce neural plasticity by enhancing activation of residual motor circuits and may have promise as an effective enhancer of neurologic recovery after incomplete SCI. This study aims to explore the effect of PAMS on motor function after SCI and determine its effects on corticospinal transmission.

### Objective

The purpose of this trial is to verify the effects of PAMS on neural circuit activation by measuring changes in motor evoked and somatosensory evoked potentials, motor and sensory function of the lower limbs, functional health and activities of daily living, and depression.

## Methods/Design

### Study design

This trial is a prospective, single-center, randomized, controlled, blinded study with parallel design (**Figure 1**). A total of 110 patients will be randomly assigned to undergo either active PAMS (experimental group) or sham PAMS (control group) as the intervention in conjunction with conventional rehabilitation treatment. Four study time points will be used: baseline and 4, 12, and 24 weeks after initiation of treatment. Interventions will be performed 5 times a week for 4 weeks (a total of 20 sessions). The protocol was registered with Chinese Clinical Trial Registry (ChiCTR2100044794, http://www.chictr.org.cn/index.aspx) on March 27, 2021.

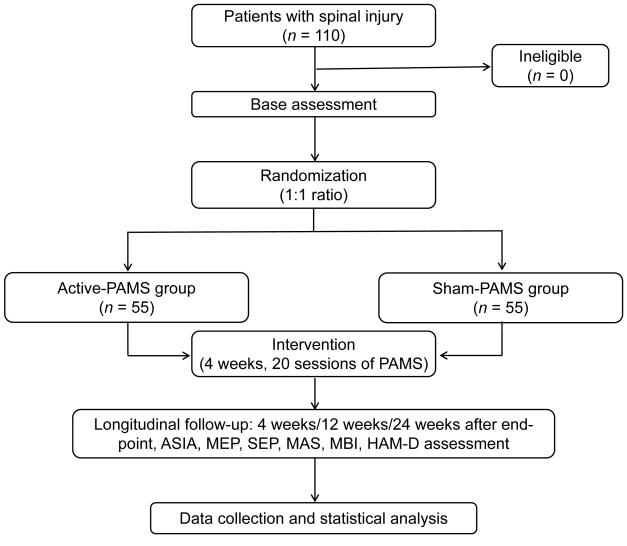


**Figure 1** | **Study design.**
ASIA: American Spinal Injury Association; HAM-D: Hamilton Rating Scale for Depression; MAS: Modified Ashworth Scale; MBI: Maslach Burnout Inventory; MEP: Motor Evoked Potentials; PAMS: Paired associative magnetic stimulation; SEP: Sensory Evoked Potential.

This trial will follow the Standard Protocol Items: Recommendations for Interventional Trial (SPIRIT) guidelines (Chan et al., 2013) (**Additional file 1**). Each participant will sign an informed consent form before participation (**Additional file 2**). All participants will be informed of the nature of the trial, the purpose and procedures involved, the expected completion time, potential adverse reactions, and possible benefits. The trial was approved by the Ethics Committee of Yangzhi Affiliated Rehabilitation Hospital of Tongji University, China (approval No. YZ2020-018) on May 18, 2020 (**Additional file 3**).

### Recruitment

Patients with SCI who receive rehabilitation treatment at the Yangzhi Affiliated Rehabilitation Hospital of Tongji University from April 2021 to April 2022 will be screened for eligibility. Specific treatment plans and contact information will be provided to eligible participants and those interested will contact the researchers directly. Possible risks of trial participation will be discussed as part of the informed consent process. Those who decide to participate will be included in the trial for randomization. If a participant withdraws from the study, the researcher will carefully record the reason for withdrawal. To strengthen participant compliance, we will conduct timely education and communicate with participants regularly.

### Eligibility criteria

#### *Inclusion criteria*

Participants who meet all of the following conditions will be considered for inclusion: (1) age 18–70 years; (2) incomplete SCI as defined by American Spinal Injury Association (ASIA) C–D (Kalsi-Ryan et al., 2014); (3) traumatic and non-progressive lesions (clinical diagnosis of SCI with non-progressive etiology with the characteristics of spinal, vascular, and infectious trauma) (de Araújo et al., 2017); (4) SCI has been present for more than 6 months (de Araújo et al., 2017); and (5) ability to provide informed consent.

Included patients will be classified according to cognitive function. All patients with mini-mental state exam (MMSE) score ≤ 17 points will be considered to have cognitive dysfunction. Patients with score ≤ 20 points and less than 6 years of education and those with score ≤ 24 points and more than 6 years of education will also be considered to have cognitive dysfunction. All others will be considered to have normal cognitive function (Brucki et al., 2003).

#### *Exclusion criteria*

Patients with any of the following conditions will be excluded: (1) severe systemic disease; (2) osteoporosis with high risk of pathological fracture; (3) joint contractures; (4) heart failure; (5) confirmed diagnosis of mental illness or epilepsy; (6) SCI caused by myelitis, multiple sclerosis, spinal hemangioma, or spinal tumor; (7) multiple traumatic injuries; (8) inability to tolerate TMS; and (9) presence of metal prosthesis within the body (e.g., orthopedic plate, screw, cardiac stent, spinal cord stimulator, etc.).

### Sample size calculation

Sample size was calculated based on a set of previous research data of SCI patients who received repetitive TMS (rTMS) to the vertex (Benito Penalva et al., 2010). This study reported that rTMS intervention was associated with improvement in clinical motor score after 8 weeks of rehabilitation. In addition, we found that lower limb ASIA motor score could be improved by 6 points after magnetic stimulation treatment, compared to 1 point without stimulation. Two groups (experimental and control) will be designated. Two -sample mean comparison estimation formula will be as follows:

$$n_t = n_c = \frac{(Z_{1-\alpha}+Z_{1-\beta})^2\sigma^2(1+\frac{1}{K})}{(\mu_t-\mu_c-\Delta)^2}$$

Where, $n_t$ and $n_c$ are the number of patients in the experimental group and the control group; $Z$ is the standard normal deviation boundary value ($Z_{1-\alpha}$ and $Z_{1-\beta}$ represent the corresponding one-sided boundary values of 1–α and 1–β, respectively), = Mean score of experimental group, = Mean score of control group, Δ = optimality bounds; σ = standard deviation; $\alpha$ = type I error, $\beta$ = type II error, K = ratio of the number of subjects in the experimental group to the number of subjects in the control group. Sample size: $\mu_t$ = 6, $\mu_c$ = 1, Δ = 3, σ = 3 (assuming that the standard deviations of the two groups are the same), K = 1; $\alpha$ = 0.025; and $\beta$ = 0.02; $n$ = 45.562. Assuming a 20% dropout rate, a recruitment target of 55 participants in each group was determined, for a total of 110 participants.

### Recruitment strategies

Qualified patients will be recruited from the Yangzhi Affiliated Rehabilitation Hospital of Tongji University in strict accordance with the inclusion and exclusion criteria mentioned above. The source of outpatients and inpatients is very stable in this hospital because it has a special ward for SCI rehabilitation. The hospital will advertise the trial online (https://www.shygkf.org.cn/) and offline (poster). During the recruitment process, potential participants will be introduced to the intervention methods, research schedule, and study procedures. The SPIRIT diagram of enrollment, interventions, and assessments is shown in **Figure 2**. Travel expenses related to study participation will be reimbursed at the end of the trial.

### Research groups

(1) Experimental group: active PAMS + conventional rehabilitation treatment. In addition to routine rehabilitation treatment to promote motor function, patients will receive PAMS to the cortex and lumbar nerve roots five times a week for 4 weeks.

(2) Control group: sham PAMS + conventional rehabilitation treatment. In

| Assessment | $-t_2$ | $-t_1$ | 0 | 4 wk | 12 wk | 24 wk |
|---|---|---|---|---|---|---|
| Enrollment | | | | | | |
| Informed consent | × | | | | | |
| Demographic information | × | | | | | |
| Vital sign | × | | | | | |
| Medical history | × | | | | | |
| MMSE | × | | | | | |
| Eligibility assessment | × | | | | | |
| Random allocation | | × | | | | |
| Interventions | | | | | | |
| *PAMS* | | | | | | |
| *Sham-PAMS* | | | — | — | | |
| ASSESSMENTS | | | — | — | | |
| ASIA-motor | | × | | × | × | × |
| ASIA-sensory | | × | | × | × | × |
| MEP | | × | | × | × | × |
| SEP | | × | | × | × | × |
| MAS | | × | | × | × | × |
| MBI | | × | | × | × | × |
| Hamilton Rating Scale for Depression | | × | | × | × | × |
| Blinding index | | | × | × | | |
| Adverse events | | | × | × | × | × |

**Figure 2 | Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Figure.**
0: Time of the start of treatment; –t1: baseline evaluation; –t2: screening; 4, 12, 24 wk: 4, 12, 24 weeks after treatment and evaluation. The blue line represents the treatment cycle in the chart, for a total of 4 weeks of treatment. ASIA: American Spinal Injury Association; MAS: Modified Ashworth Scale; MBI: Maslach Burnout Inventory; MEP: Motor Evoked Potentials; MMSE: Mini-Mental State Examination; PAMS: Paired associated Magnetic Stimulation; SEP: Sensory Evoked Potential.

addition to routine rehabilitation treatment, sham PAMS will be performed. Dummy coils rather than treatment coils will be used in sham PAMS.

**Randomization and blinding**
A simple stratified (computer-generated) randomization protocol will be used. Randomization will be performed according to inpatient/outpatient status. A rehabilitation doctor will be responsible for generating the allocation sequence and the assignment, as well as distribution of the intervention for the entire study. Randomization will be performed following a check of the participant's compliance. All researchers and subjects will remain blinded to the allocation of interventions throughout the study. The subjects will be randomly assigned to groups during the study by personnel unrelated to the trial.

Serially numbered opaque closed envelopes will be used for allocation concealment. An opaque envelope will be identified with different numbers. After sequence generation, sheets of paper containing the information of the corresponding group will be placed in the envelope. The envelopes will be placed in a safe place in numerical order until intervention. Sequence generation and envelope making will be carried out by rehabilitation doctors who are not involved in this study.

An experienced blinded therapist will perform the initial electrophysiology assessment. Emergency unblinding will be performed if a serious adverse event occurs. In the event of unblinding during the study, the involved subject will be removed from the study protocol. After trial completion, participant grouping will be revealed and data analysis will commence. Once the analysis is complete, a summary report will be completed. First, the statistician will obtain two sets of data without knowing which one is the experimental group. Next, the treatment received by each group will be announced after data analysis. The biostatistician will open the blinded group management information.

**Intervention**
(1) During treatment, rTMS will be given prior to lumbar magnetic stimulation (LMS). All subjects will engage the assigned treatment plan for 20 sessions over 4 weeks. Active or sham PAMS will be applied for 15 minutes in each session.

(2) TMS intervention: For TMS (MagVenture® MagPro R30, Denmark), circular coils will be applied over the primary motor cortex area and the angulated figure-eight-shaped coil over the waist. rTMS and root magnetic stimulation will be acquired with a frequency of 10 Hz (Ellaway et al., 2014; Kumru et al., 2017). The same stimulation parameters will be used during the treatment. Participants will be seated during interventions in a comfortable recliner with the arms and hands relaxed, feet placed on a platform, and the eyes kept open to stay awake. The circular coils will be placed on the motor cortex of the lower limb and be held with a custom coil holder. The most accurate location for inducing a motor evoked potential (MEP) in the tibialis anterior (TA) muscle (hot spot) will be performed by moving the coil in small steps along the lower limb representation of the motor cortex. The hot spot refers to the region where the largest MEP in the TA can be induced with lowest strength. The intensity of cortical stimulation will be 100% of the resting motor threshold intensity for induction of a motor-evoked potential at the lowest muscle threshold in the lower limb. Resting motor threshold will be determined as the minimum intensity of TMS that induces an MEP higher than 50 μV in peak-to-peak amplitude in the resting target muscle in no more than 5 of 10 successive trials (Rothwell et al., 1999).

(3) LMS will be performed with the participant comfortably seated, the back straight, and legs extended (Macdonell et al., 1992). Lumbosacral nerve root responses will be elicited with a figure-eight magnetic coil, which will be held perpendicular to the spinal cord with the handle at a right angle to the vertebral column. The coil will be placed in a plane parallel to the L3/4 level. Lumbosacral root intensity of stimulation will be considered as the lowest stimulation intensity that can trigger muscle contraction. Synaptic plasticity in the spinal cord occurring in neuromodulation is called spike time-dependent plasticity (**Figure 3**).

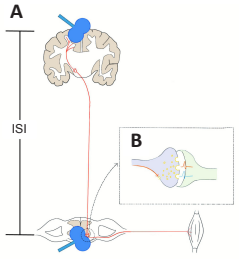


**Figure 3 | Schematic diagram of synaptic plasticity regulation in the spinal cord.**
The red line in A represents the corticospinal tract. B shows the synaptic structure. The yellow waveform on the postsynaptic membrane represents the potential from the central source and the blue waveform represents the potential from the peripheral source; they reach the postsynaptic membrane at the same time. ISI: Interstimulus interval.

(4) Routine rehabilitation treatment: All patients will receive conventional rehabilitation treatment, including physical therapy and lower limb functional training. Once the intervention has begun, patients will not be able to change conventional or drug treatment plans at will. If it is necessary to change the conventional treatment plan during the intervention process, the investigator needs to evaluate whether the intervention can be continued and record the treatment results truthfully.

**Outcome measures**
Outcome measures will be evaluated at four time points: baseline and 4, 12, and 24 weeks after the start of intervention. All evaluations will be performed by blinded therapists. Any negligence of the assessor will be reported. In addition, during the evaluation process, the evaluator will remain blinded to the intervention.

***Primary outcome***
The primary outcome measure is lower limb ASIA motor score. Changes in score over time will be determined. The ASIA motor score is derived from the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSI) and is a 100-point score based on the muscle grade of five key muscle groups in each limb. Muscle grade ranges between 0 (no contraction) and 5 (normal resistance). The highest score for each limb is 25 points (Kirshblum et al., 2011).

***Secondary outcomes***
ASIA sensory score is a secondary outcome measure and is also derived from the ISNCSI. It evaluates the ability to detect pinprick and light touch on the skin and is evaluated on a 3-point scale (0, 1, and 2). Complete inability to distinguish between sharp and dull sensation is scored as zero. The highest total score is 224; the higher the score, the better the sensory function. In the needle pricking test of sensory function, the examiner must determine whether the patient can correctly distinguish between sharp and dull at each needle pricking point. If the patient is uncertain, it is recommended to take 8 of the 10 correct answers as the accuracy standard because this reduces the probability of correct guessing to less than 5% (Kirshblum et al., 2011).

Modified Ashworth Scale (MAS) score is another secondary outcome. It is a reliable method to evaluate spasticity. When a muscle is stretched passively, the resistance encountered by the muscle is graded (Bohannon and Smith, 1986; Ghotbi et al., 2011). The degree of spasm is scored 0–5 (Baunsgaard et al., 2016).

MEPs evoked by TMS equipment will be used to evaluate changes in motor cortex excitability and corticospinal and intracortical excitability. The subjects will be seated in a comfortable chair with their body relaxed and their hands on their sides. TMS (MagVenture® MagPro R30 Denmark) will be performed through a batwing coil. The coil will be held tangentially to the corresponding motor cortex of the lower extremity at the most appropriate stimulation point. Resting motor threshold will be considered as the minimum intension of TMS that elicits an MEP greater than 50 μV in peak-to-peak amplitude in the resting target muscle in not less than 5 of 10 trials. If an MEP is not induced, it will be documented as zero (Nojima and Iramina, 2018; Tazoe and Perez, 2015).

Sensory evoked potentials (SEPs) will also be measured and used to evaluate sensory function of the injured spinal cord. Electrophysiological examination of paravertebral SEPs can evaluate the degree of sensory impairment in patients with SCI (Linden and Berlit et al., 1994).

Maslach Burnout Inventory (MBI) will be assessed as a general measure of functional health and activities of daily living (Leung et al., 2007). The inventory relates to 10 items and is scored on a scale from 0 to 100 with a higher score expressing greater independence.

The 17-item Hamilton Rating Scale for Depression will be assessed as a measure of depression severity. Severe depression is defined as more than 25 points, moderate depression as 18-24 points, and mild depression as 7–17 points (Williams, 2001).

**Safety and adverse effects of rTMS**
High-frequency rTMS is non-traumatic but can cause headaches and fatigue. Patients will be clinically evaluated before and after each intervention. Those with headache and/or fatigue will be undergo evaluations using the Visual Analog Scale (VAS) and Fatigue Self-Assessment Scale (FSAS), respectively.

Adverse events will be addressed as follows: (1) The investigator will determine before the intervention whether the patient is suitable to proceed and instruct the patient to communicate any discomfort during treatment. (2) If discomfort is communicated, the investigator will immediately stop the treatment, evaluate the patient's vital signs and type and degree of discomfort, and then administer appropriate treatment. (3) All adverse events will be recorded and reported to both the primary investigator and ethics committee, who will determine together the patient's suitability for continued participation.

**Statistical analysis**
Statistical analyses will be conducted using SPSS software version 20.0 (IBM, Armonk, NY, USA). Efficacy will be evaluated using per-protocol analysis.

***Baseline analysis***
Categorical patient characteristic variables will be analyzed between the experimental and control groups using the chi-square test or Fisher's exact test as appropriate Graded data will be analyzed using the rank sum test. Data with an abnormal distribution or uneven variance measurement data will compared using the Wilcoxon rank sum test. If an indicator is different between the two groups, that indicator will be used as a covariate and included in subsequent data analysis..

***Efficacy analysis***
The primary and secondary outcome measures will be expressed as the mean ± standard deviation. Data will be tested for normality of distribution. Before and after treatment, the homogeneity of variance data between the two groups will be analyzed using the *t*-test. If data are in a skewed distribution, they will be converted to a normal distribution according to the data distribution type. If data do not conform to any distribution law, the rank sum test will be used to conduct hypothesis testing on the data. Data with an abnormal distribution or uneven variance will be analyzed using the Wilcoxon rank sum test.

***Safety analysis***
Adverse events and will be compared between groups using the chi-square or Fisher's exact test.

**Data integrity and management**
All study data and records will be stored and managed in an electronic database. Paper files will be scanned and stored on an encrypted password-protected network. Only researchers and statisticians involved in the study will have database/network access.

***Original data collection plan and data entry***
The original data will be directly collected using paper forms or evaluation equipment. Each form will be entered into the database by two independent personnel. Data collected by the evaluation equipment will be sorted and entered by two independent personnel. The data entered by the two persons will be compared using software. Any inconsistencies will be investigated and corrected.

***Data verification***
The data manager will check the data in the database according to the plan requirements (time check, logic check, selection/exclusion condition check, evaluation result check, and missing log check). Based on verification results, the data manager will list the answering form for the questions in the case report form and make inquiries to the investigator through the inspector. The investigator will respond as required.

***Data sharing statement***
Relevant data will be reported after deidentification (text, tables, figures, and appendices). All relevant data will be uploaded immediately after publication. The research results will be disseminated in the form of reports at scientific conferences or published in authoritative journals. The anonymized data will be available on www.figshare.com indefinitely. The data generated and analyzed in the course of this study will not be disclosed at this time, as it is currently underway; however, it can be obtained from the corresponding authors upon reasonable request.

***Auditing***
The database will be backed up after auditing. The primary investigators, statisticians and supervisors will lock the data to ensure data security. Any changes to the database after auditing will only be carried out with the consent of all parties.

***Withdrawals***
Participants can withdraw from the study owing to severe adverse events (e.g., having a seizure or cerebrovascular accident) or other personal factors (inability to contact the participant, refusal of the participant to continue, etc.).

**Monitoring**
The independent data monitoring committee (IDMC) is composed of a statistician and two rehabilitation investigators. The primary responsibilities include safety supervision, trial quality supervision, and periodic review of accumulated data. The IDMC will go to every experimental site to examine trial procedures to ensure data reliability and evaluate participant compliance. Adverse events will be defined as any adverse medical event, regardless of causality. The IDMC will record all adverse events from admission to discharge and report them to the local institutional review committee. An interim analysis of the primary outcome measure will be performed when 50% of patients have been randomized and have completed 24 weeks of follow-up. The interim analysis will be conducted by a statistician blinded to patient grouping and reported to the IDMC. The IDMC will disclose all data and discuss the interim analysis results with the steering committee, who will decide whether to continue, stop, or modify the trial.

**Ethics and dissemination**
The study protocol and associated documents will be reviewed and approved by the ethics committee of Yangzhi Affiliated Rehabilitation Hospital of Tongji University. Any required changes in the protocol or documents that become apparent during the trial will be reviewed by the ethics committee. In addition, the research team will regularly report project progress and other relevant items to the ethics committee every year during the trial. The ethics committee will review all trial data. After approval, any protocol modifications proposed by the primary investigators will be submitted and reviewed by the ethics committee before proceeding.

**Consent**
The members of the research team responsible for recruiting patients will explain to patients in detail the main content of the study and all items in the informed consent form. Any questions posed by potential recruits will be answered. All study documents will be in Chinese, as only Chinese participants will be recruited. Subjects who agree to take part in the study will sign the informed consent form to indicate their participation. Biological specimens will not be collected from participants so there is no need to sign related documents.

**Confidentiality and data access permissions**
We will make every effort to protect the personal privacy of patients within the scope permitted by law. Any public reporting of the results of this study will not disclose any personal patient information. Identifying information will not be disclosed to individuals outside of the research team without patient permission. All study members will be required to keep patient identities and associated personal data confidential. Patient files will be stored in a locked filing cabinet for investigator access as needed. To ensure compliance with regulations, members of the government management department or the ethics review committee will have access to patient personal data.

**Post-trial care**
If a patient experiences an adverse event during the trial, the patient will contact the investigator in charge of the study and receive timely treatment. For any injury that is causally related to the study, the primary investigator and affiliated hospital will pay for any related medical expenses and provide corresponding financial compensation in accordance with relevant national laws and regulations. Subjects who are included in the control group will receive the conventional rehabilitation treatment to ensure effective SCI rehabilitation during the study.

**Dissemination policy**
The research team will report all results to the ethics committee and transfer the data to the Chinese Clinical Trial Registry within six months of trial completion. Investigators who have made substantial contributions to conception of study design, trial implementation and analysis, and writing associated manuscripts and reports will be recognized as authors in the research manuscripts and reports.

## Discussion

Electromagnetic neuromodulation technology is an important frontier in rehabilitation research. TMS has been extensively studied in a variety of neurological diseases including stroke, Alzheimer's disease, and pain (Soler et al., 2010; Cortes et al., 2017; Hutson and Giovanni et al., 2019;). After SCI, neural circuitry is severely disrupted because of interruption of both afferent input and efferent output. Neural circuit reconstruction aims to promote functional recovery after nervous system damage (Angeli et al., 2014). From a theoretical standpoint, the corticospinal tract, which arises from the cerebral cortex and terminates in the spinal cord, is essential for motor output in humans. However, restoring the functional connections of the corticospinal tract after injury is challenging. Research has demonstrated that the functional effects of exercise can be enhanced by neural stimulation, which is thought to activate spared neural pathways (McPherson et al., 2015; Gad et

al., 2018). TMS is a noninvasive technique that can elicit excitability in certain electrically conductive tissues (Wagner et al., 2007). Repetitive peripheral magnetic stimulation has been shown to induce local nerve excitation (Zschorlich et al., 2019). However, it does not induce long-term neuroplastic effects. Another study indicated that short-term rTMS can reduce cortical inhibition and improve motor and sensory function recovery in patients with incomplete SCI (Awad et al., 2015). Although these therapies facilitate exercise-mediated recovery, the overall problem of limb paralysis after SCI is still unresolved. The central nervous system can recover after SCI, owing to plasticity mechanisms and remodeling of residual neural pathways (Okada et al., 2018); however, recovery is limited. Nevertheless, the neural circuit is considered to play an important role in functional recovery (Welniarz et al., 2017). Recovery of neural circuits can be achieved by axonal sprouting and local reconnection of neurons above and below the injury level (Wang et al., 2020). Therefore, if remnant circuits can be adjusted appropriately, structural remodeling and functional recovery are possible. According to Hebbian plasticity theory, "when an axon of cell A is near enough to excite cell B and repeatedly or continuously takes part in firing it, a series of metabolic changes take place in one or both cells such that A's efficiency, as one of the cells firing B, is increased" (Welniarz et al., 2017; Brown, 2020). In the 1990s, Markram indicated that amplitude of synaptic strength, which changes according to Hebbian theory, is relevant to the timing of presynaptic and postsynaptic peaks (Mikaitis et al., 2018). The connection between the magnitude of these changes and the relative time of presynaptic and postsynaptic peaks is called spike-timing-dependent plasticity (STDP). Most prominently, PAMS-caused changes in neuronal connectivity symbolize a pattern of STDP (Sowman et al., 2014; Brzosko et al., 2019). In addition, post-PAMS excitability has been shown to be a long-term potentiation-like effect (Gao et al., 2020). STDP of residual corticospinal tract synapses has been proposed as the mechanism responsible for changes in the gain of the synapse (Lisman, 2017).

SCI affects both descending circuits and proprioceptive input, which affects plasticity of remaining neural circuits. This study aims to demonstrate that PAMS-induced reconstruction of functional connections between the cerebral cortex and spinal cord is feasible and can result in convergence of residual supraspinal circuits and proprioceptive input (van den Brand et al., 2015). It is possible that PAMS enhances corticospinal transmission or activates motor neuron pools in patients with SCI.

Magnetic stimulation has several advantages over peripheral electrical stimulation. Although magnetic stimulation can activate afferent fibers, it does not provide greater benefit than conventional methods. However, high-frequency magnetic stimulation has a stronger and more constant impact on excitability of the cerebral cortex-spinal circuit (Krause et al., 2005). In addition, magnetic stimulation is relatively non-invasive and less painful than electrical stimulation.

In this protocol, we perform PAMS over the cerebral cortex and lumbar nerve roots based on the Hebbian concept of STDP. TMS produces descending volleys in corticospinal neurons, with the first stimulus originating from the lower motor cortex, and the second from spinal L3–L4. Then, we calculate the conduction time from the motor cortex to the lumbar nerve root. We also induce functional and structural plasticity in the corticospinal tract, with the purpose of promoting functional recovery. Findings from this trial will help indicate whether PAMS has potential as a treatment for SCI.

This study protocol is limited by its small sample size and single-center design. In addition, the follow-up time is short (≤ 3 months).

This study protocol compares active and sham PAMS to determine the effect of PAMS on neurologic recovery after SCI and uses ASIA score, MEPs, SEPs, MAS, MBI, Hamilton Depression score, and other subjective and objective indicators for evaluation. To our knowledge, this study is the first to examine efficacy of PAMS in the treatment of SCI.

## Trial status

Patient recruitment for this trial began in April 2021 and is currently underway. The study is scheduled to be completed in April 2022.

**Author contributions:** *Protocol conception: DSX, XYH; protocol design: TTS, DSX; ethical review: TTS; ethical approval: GMS, GYZ; statistical analysis: DZ, QY; establishment of study database: GYZ; clinical population recruitment: QLH, YRM, RX; manuscript drafting: TTS, YZ, YRM. All authors approved the final version of this manuscript.*
**Conflicts of interest:** *None declared.*
**Availability of data and materials:** *All data generated or analyzed during this study are included in this published article and its supplementary information files.*

**Additional files:**
***Additional file 1:*** *SPIRIT checklist.*
***Additional file 2:*** *Informed consent form (Chinese).*
***Additional file 3:*** *Ethics approval document (Chinese).*

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