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Effects of cortical intermittent theta burst stimulation combined with precise root stimulation on motor function after spinal cord injury: a case series study

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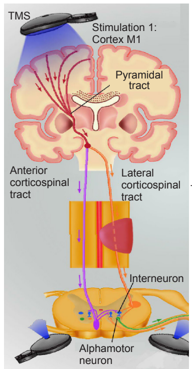
Graphical Abstract *Intermittent theta burst stimulation combined with root stimulation as a targeted treatment for improving motor function after spinal cord injury*



Intermittent theta burst stimulation combined with precise root stimulation improved nerve conduction of the corticospinal tract and lower limb motor function recovery in patients with chronic spinal cord injury

Abstract

Activation and reconstruction of the spinal cord circuitry is important for improving motor function following spinal cord injury. We conducted a case series study to investigate motor function improvement in 14 patients with chronic spinal cord injury treated with 4 weeks of unilateral (right only) cortical intermittent theta burst stimulation combined with bilateral magnetic stimulation of L3–L4 nerve roots, five times a week. Bilateral resting motor evoked potential amplitude was increased, central motor conduction time on the side receiving cortical stimulation was significantly decreased, and lower extremity motor score, Berg balance score, spinal cord independence measure-III score, and 10 m-walking speed were all increased after treatment. Right resting motor evoked potential amplitude was positively correlated with lower extremity motor score after 4 weeks of treatment. These findings suggest that cortical intermittent theta burst stimulation combined with precise root stimulation can improve nerve conduction of the corticospinal tract and lower limb motor function recovery in patients with chronic spinal cord injury.

Key Words: central motor conduction time; intermittent theta burst; lower extremity motor score; motor evoked potential stimulation; neuromodulation; neuronal plasticity; spinal cord injury; transcranial magnetic stimulation

Introduction

Spinal cord injury (SCI) can be caused by injury to the spinal bones, nerve roots, ligaments, and other structures, and has high morbidity and mortality. SCI is mainly treated by surgical repair, neuro-nutrition, hyperbaric oxygen therapy, stem cell transplantation, and rehabilitation interventions, such as body weight-supported gait training (Zheng et al., 2020). However, there is residual innervation in the lesioned area of motor neurons after SCI (Tazoe and Perez, 2015), and an analysis of early autopsies of patients with clinically diagnosed complete SCI found that 75% of patients still had cross-regional connectivity in central nervous system tissue at the site of injury (Long et al., 2017).

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The spinal cord circuitry is composed of central nerve conduction tracts, peripheral nerves, and the cerebral cortex. Activation and reconstruction of the spinal cord circuitry is an important process for improving motor function following SCI. The clinical goal for patients in the bottleneck stage following SCI involves finding a safe and reliable method for promoting the repair and reactivation of residual nerve connections, as well as realizing the reconstruction of motor control, motor execution, superficial sensation, and autonomic nerve functions (Bunday and Perez, 2012). Physical factors (magnetic or electrical stimulation) can play a role in nerve repair by improving neuronal excitability, expanding recruitment of the neuron pool, and increasing the secretion of neurotransmitters (Ellaway et al., 2014).

Transcranial magnetic stimulation (TMS) has been widely used in clinical practice because of its safe and non-invasive nature (Kobayashi and Pascual-Leone, 2003). Repetitive TMS (rTMS), in which hundreds of TMS pulses are applied in sequence, is based on the principle that repeated stimulation of the same set of synapses results in long-term changes in the excitability of the corticospinal tract, rarely lasting more than 30 minutes (Hoogendam et al., 2010; Xie et al., 2021; Yuan et al., 2021). Compared with traditional rTMS, intermittent theta burst stimulation (iTBS) modes were found to have a greater stimulus effect with acceptable inter-individual variability. iTBS produces consistent long-term potentiation effects (Gharooni et al., 2018). Compared with traditional rTMS, this leads to prolonged increases in motor cortical excitability and can produce consistent, rapid, and controllable electrophysiological and behavioral changes in the function of the human motor system (Huang et al., 2005). Huang et al. (2005) demonstrated that the use of extremely short, low-intensity (80% active motor threshold) iTBS in the motor cortex had strong influences on physiology and behavior, lasting more than 1 hour.

iTBS has demonstrated efficacy in patients with conditions including stroke, brain injury, and mental disorders (Chen et al., 2008), and has also recently shown efficacy in dystonia and other fields (Korzhova et al., 2018). However, iTBS has not been widely used for SCI, and comparative studies on the effects of TMS protocols for treating chronic SCI are lacking. Our current study was based on the principle that neuromodulation of SCI should focus not only on the cortex, but also on the spinal cord itself. We therefore explored motor function improvements in patients with chronic SCI treated with cortical iTBS magnetic stimulation combined with 15 Hz root magnetic stimulation, to determine the benefit of cortical stimulation combined with root stimulation as a targeted treatment for motor function recovery after SCI.

Subjects and Methods

Subjects

We enrolled 14 patients with grade C or D chronic SCI between March and October 2020, classified according to the American Spinal Cord Injury Association Impairment Scale (Harvey and Graves, 2011), who were in the bottleneck stage after receiving traditional rehabilitation treatment at Shanghai Yangzhi Rehabilitation Hospital. All the patients completed the trial, and none developed epilepsy or other adverse reactions during TMS treatment.

The inclusion criteria were: age 18–70 years; chronic SCI with American Spinal Cord Injury Association Impairment Scale grade C/D; no neurological diseases or tumor history; disease course less than 10 years; and discontinued gamma aminobutyric acid/benzodiazepines and baclofen (which interfere with cortical excitability) 2 weeks prior to the study.

The exclusion criteria were: concomitant neurological diseases, including epilepsy or multiple neurological disorders; contraindication to magnetic resonance imaging, electrophysiology, and TMS, e.g., because of metal intracranial or extracranial implants; failure to cooperate with basic treatment; reluctance to accept assessments or follow-up reassessment; cognitive impairment or any substantial disease; and advanced liver, kidney, heart, or lung disease.

The patients' characteristics, including demographic characteristics, were collected before treatment. This study was conducted in accordance with the research protocol and the Declaration of Helsinki. All patients were fully informed about the trial and signed written informed consent (**Additional file 1**) before participating. This study was approved by the Shanghai Tongji Hospital Ethics Committee before the trial, with ethical batch No. 2019-053 on September 4, 2019 (**Additional file 2**), and registered in the Chinese Clinical Trial Registry (Registration No. ChiCTR2000031095) on March 22, 2020. This study followed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.

iTBS protocol

We performed a self-controlled case series study in patients treated with unilateral cortical iTBS magnetic stimulation combined with bilateral 15 Hz root magnetic stimulation (non-simultaneous). In the iTBS protocol, the stimulus point was located in the M1 region of the right hemisphere (Gomes-Osman and Field-Fote, 2015). Electromyography (EMG) was evaluated in conjunction with TMS. Subjects were asked to wear a positioning cap as per standard and sit comfortably on a semi-retractable bed or chair.

EMG signals were recorded using Ag-AgCl surface electrodes (Alpine BioMed ApS Co., Copenhagen, Denmark) on the tibialis anterior muscles of bilateral lower extremities. Resting motor evoked potentials (rMEPs) were recorded by EMG in the tibialis anterior muscles of the lower extremities to evaluate the elicited motor evoked potentials (MEPs). Data were analyzed using Dantec Keypoint (9033A07, Alpine BioMed ApS Co.) The locus that triggered the maximum MEP of the tibialis anterior was detected as the motor hotspot (Alexeeva et al., 1998). We used a Magventure X100 transcranial magnetic stimulator with model MMC-140 circular coil (Magventure Co., Farum, Denmark). When TMS stimulation was applied, the coil center was aligned with the lower extremity motion hotspots, and the coil handle was pointed vertically to the occipital. The stimulation was focused on the right motor M1 and the stimulus intensity was correlated with the active motor threshold of each machine, with a minimum monopulse intensity higher than 200 µV generated over 10 trials on the contralateral side, while the subject maintained about 20% of the maximum muscle contraction through visual feedback. The cortical magnetic stimulus was iTBS with 80% active motor threshold (Kim et al., 2015). After finishing iTBS cortical magnetic stimulation 10 minutes, the subjects continued to receive nerve root magnetic stimulation.

SCIs require lower extremity extensor strength training, including the quadriceps femoris and tibialis anterior muscle, which are innervated by the L3–L4 nerve. We therefore applied magnetic stimulation of the L3–L4 nerve roots using a Magventure transcranial cerebral magnetic stimulation model X100 and MMC-90 small circular coils. A small circular coil can stimulate a narrow field with centimeter-level precision. The location of the L3–L4 nerve root from the outlet of the spinal canal (foraminal) could be accurately located under EMG guidance, and was selected and marked with a sticker. Accurate root stimulation was performed with reference to this marker at each treatment. The root stimulus protocol for 15 Hz consisted of 40 sequences of 20 pulses each, with 3 seconds between each sequence, for a total of 800 pulses, with a rest motor threshold of 100%. Subjects received treatments five times a week for 4 weeks (**Additional Figure 1**).

Outcome measurements

The patients' motor function assessment scale and neuro-electrophysiological indicators were evaluated before treatment and after 4 weeks of treatment. The rMEP amplitude was the main observation measurement.

Neuro-electrophysiological assessment

The rMEP amplitude refers to the amplitude between negative troughs and positive peaks (Stefan et al., 2000). The latency of cortical MEP and spinal cord MEP was determined by placing the MMC-90 magnetic stimulation coils (Magventure Co., Farum, Denmark) on the M1 motor cortex and the T12 thoracic spinous processes, respectively. We collected 10 single-pulse trials using a TMS intensity of 120% of the resting motor threshold, and obtained the average amplitude of the 10 waveforms with good repeatability and large peaks. The central motor conduction time (CMCT) was defined as the difference in MEP latency between the cortical motor area and the spinal cord induced by TMS.

Assessment of motor function

The total lower extremity motor score (LEMS), maximum value 50, represented the sum of the five key muscle forces of both lower extremities measured by manual muscle test (Morgan and Solinsky, 2021), with a higher score indicating greater muscle strength of the lower limbs. The Berg balance scale was used to measure the patient's balance ability, with a maximum score of 56 (Handelzalts et al., 2021), with a higher score indicating better balance. The Spinal Cord Independence Measure-III (SCIM-III) scale was used to evaluate the independent living ability of patients with SCI, with a maximum score of 100 (Levasseur et al., 2021) and a higher score indicating greater independence. Gait analysis included a 10-m walking speed test, in which the subject walked 10 m unaided. The speed was measured over the middle 6 m, and timing started when the front foot crossed the 2-m mark and ended when the toe crossed the 8-m mark. The experiment was repeated three times, and the average value was taken as the result.

Statistical analysis

Statistical analysis was performed using SPSS version 22.0 (IBM, Armonk, NY, USA). The data conformed to a normal distribution, as determined by the Shapiro-Wilk. Data before and after the intervention were compared using paired *t*-tests. The difference in the data before and after comparison was referred to as the D-value, and D-values between the left and right sides were calculated and tested using inter-group *t*-tests. Resting MEP and motor function data were analyzed by Pearson's correlation analysis. $P < 0.05$ was considered significant. The statistical methods of this study were reviewed by Professor Jue Li of Tongji Universtity.

Results

Clinical and demographic characteristics

The characteristics of the 14 patients with chronic incomplete SCI are shown in **Table 1**. The mean age was 40.57 ± 13.20 years and the mean disease course was 15.14 ± 12.55 months. Falls were the most common cause of injury (36%, 5/14) and trauma was less common (21%, 3/14). Before treatment, the 14 patients had a wide range of lower extremity motor functions based on LEMS (range 6–42, 21.43 ± 12.51), Berg balance score (3–37, 15.07 ± 11.55), and 10-m walking speed (0–0.45, 0.13 ± 0.13 m/s).

Safety and adverse reactions

In the iTBS protocol, short and low-intensity burst stimulation of 50 Hz TMS have been shown to be safe and produce consistent, rapid, and controllable electrophysiological and behavioral changes targeted at specific groups of neurons in the motor cortex (Hausmann et al., 2004). No serious adverse reactions were recorded in previous studies (Nardone et al., 2017) or in the current study. The only TMS-related complication was a self-limited mild headache in one patient (1–3 days).

Neurophysiological results

Left rMEP and right rMEP amplitudes were significantly increased after 4 weeks compared with before treatment ($P < 0.01$; **Table 2** and **Figure 1A**). Meanwhile, right CMCT was significantly changed after 4 weeks of treatment compared with pre-intervention data ($P < 0.01$; **Table 2** and **Figure 1B**). There was no significant difference in rMEP amplitudes between the left and right sides before the intervention ($P = 0.051$; **Table 3**), and no significant difference in the D-value of rMEP amplitudes between the left and right sides after the intervention ($P = 0.940$; **Table 3**).

Compared with before treatment, the LEMS and Berg balance scores and SCIM were significantly increased after 4 weeks of magnetic stimulation ($P < 0.01$; **Table 4** and **Figure 1C–E**), and the 10-m walking speed was also significantly increased after treatment ($P = 0.022$; **Table 4** and **Figure 1F**).

Correlation analysis

The lower limb muscle strength based on LEMS was weakly correlated with the rMEP amplitude for both sides before the intervention ($r = 0.314$ & $r = 0.366$, $P > 0.05$; **Table 5** and **Figure 2**). However, after right cortical and bilateral root stimulation, there was a tight correlation between the right rMEP amplitude data and post-intervention LEMS data ($r = 0.640$, $P < 0.05$; **Table 5** and **Figure 2**), compared with a weak correlation between the left rMEP amplitude without cortical stimulation and the LEMS data ($r = 0.086$, $P > 0.05$; **Table 5** and **Figure 2**). There was also a significant correlation between the right rMEP amplitude and the Berg balance score after the intervention ($r = 0.533$, $P < 0.05$; **Table 5** and **Figure 2**).

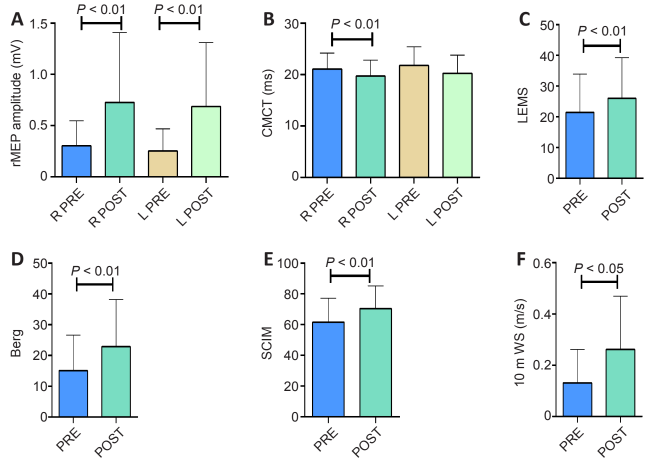

Figure 1 | Comparison of rMEP amplitude, CMCT, and motor functional assessment before and after treatment.

(A) rMEP amplitude. (B) CMCT. (C) LEMS. The maximum LEMS was 50, with a higher score indicating greater muscle strength of the lower limbs. (D) Berg balance score. The maximum score was 56, with a higher score indicating better balance. (E) SCIM. The maximum SCIM-III score was 100, with a higher score indicating greater independence in patients with spinal cord injury. (F) 10-m walking speed. 10 m WS: 10-m walking speed; CMCT: central motor conduction time; L POST: left side posttreatment; L PRE: left side pretreatment; LEMS: lower extremity motor score; POST: posttreatment; PRE: pretreatment; R POST: right side posttreatment; R PRE: right side pretreatment; rMEP: resting motor evoked potential; SCIM-III: Spinal Cord Independence Measure-III.

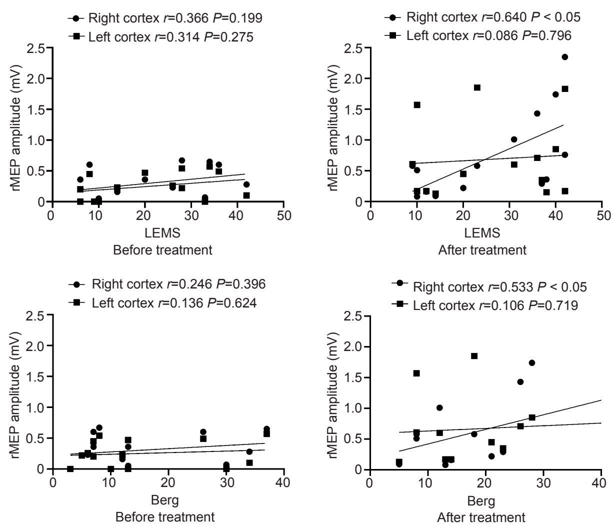

Figure 2 | Pearson's correlation analysis of motor functional assessment and rMEP amplitude before and after treatment.

Berg: Berg balance scale; LEMS: lower extremity motor score; rMEP: resting motor evoked potential.

Discussion

The combination of iTBS magnetic stimulation and precise root stimulation may be a valuable treatment for patients with SCI. Axonal loss and demyelination after SCI may lead to transient dispersion of the descending nerves, which may affect the recruitment of the spinal motor itself. Because of its noninvasive nature, TMS is the most widely used clinical noninvasive brain stimulation technique. However, studies of TMS for SCI rehabilitation have tended to ignore root stimulation, and have mainly focused on cortical stimulation (Macdonell and Donnan, 1995). Most doctors use rTMS protocols to treat SCIs, involving hundreds of TMS pulses applied in sequence (Kuppuswamy et al., 2011). Belci et al. (2004) first applied 10 Hz rTMS to the left motor area of the upper extremity in patients with SCI, and observed the total sensory and motor function assessment scales after 5 days of treatment. Gomes-Osman and Field-Fote (2015) performed 20 Hz TMS stimulation in the M1 area of the hand

Table 1 | **Baseline clinical and demographic characteristics of patients with chronic spinal cord injury**

No.	Age (yr)	Sex	Cause of injury	Course of disease (mon)	Level	ASIA	LEMS	Berg balance score	10-m walking speed (m/s)	SCIM-III
1	67	Male	Cervical spinal stenosis	6	C7	D	33	30	0	44
2	43	Male	Trauma	6	T12	C	28	8	0	55
3	29	Male	Traffic accident	13	T12	C	20	13	0.31	76
4	44	Female	Cervical spinal stenosis	6	T10	C	26	6	0.05	56
5	53	Female	Spinal arteriovenous tumor	12	T12	D	34	37	0.12	78
6	53	Male	Traffic accident	20	C3	C	28	5	0.19	42
7	46	Male	Fall	51	T12	C	6	10	0.03	61
8	45	Male	Trauma	11	C7	C	9	3	0	26
9	19	Male	Fall	11	L1	C	6	7	0.12	73
10	40	Male	Fall	33	T12	C	10	13	0.09	63
11	18	Male	Fall	12	L1	C	8	7	0.18	73
12	42	Male	Fall	10	T12	C	36	26	0.22	67
13	33	Male	Sports injury	6	T12	C	14	12	0.07	68
14	36	Male	Trauma	15	T12	C	42	34	0.45	80

The total LEMS is 50. The higher the score, the stronger the muscle strength of the lower limbs. The total score of Berg balance scale 56. A higher score means better balance. The total score of SCIM-III is 100. A higher score indicates greater independence in patients with spinal cord injury. ASIA: American Spinal Cord Injury Association Impairment Scale; LEMS: lower extremity motor Score; SCI: spinal cord injury; SCIM: Spinal Cord Independence Measure.

Table 2 | **Comparison of rMEP amplitude (mV) and CMCT (ms) before and after treatment**

Variable	PRE	POST	*P*-value
rMEP amplitude			
Left	0.25±0.22	0.69±0.62	0.004
Right	0.30±0.24	0.73±0.68	0.008
CMCT			
Left	21.77±3.64	20.22±3.57	0.051
Right	21.06±3.13	19.70±3.11	0.004

Data are expressed as mean ± SD (*n* = 14), and were analyzed by paired *t*-test. CMCT: Central motor conduction time; POST: posttreatment after 4 weeks; PRE: pretreatment; rMEP: resting motor evoked potential.

Table 3 | **Comparison of rMEP amplitude (mV) and D-value between left and right sides**

	PRE	POST	D-value
Left	0.25±0.22	0.69±0.62	0.43±0.46
Right	0.30±0.24	0.73±0.68	0.42±0.51
P-value	0.051	0.814	0.940

Data are expressed as mean ± SD (*n* = 14), and were analyzed by paired *t*-test. D-value: Difference value; POST: posttreatment after 4 weeks; PRE: pretreatment; rMEP: resting Motor evoked potential.

Table 4 | **Comparison of motor functional assessment before and after treatment**

Variable	PRE	POST	*P*-value
Lower extremity motor score	21.43±12.51	26.00±13.26	0.001
Berg balance	15.07±11.55	22.86±15.33	0.001
Spinal Cord Independence Measure-III score	61.57±15.65	70.35±14.83	0.001
10-m walking speed (m/s)	0.13±0.13	0.26±0.21	0.022

Data are expressed as mean ± SD (*n* = 14), and were analyzed by paired *t*-test. POST: Posttreatment after 4 weeks; PRE: pretreatment.

Table 5 | **Pearson's correlation between motor functional assessment and rMEP amplitude**

	Left side rMEP amplitude		Right side rMEP amplitude	
	r-value	*P*-value	*r*-value	*P*-value
Before				
LEMS	0.314	0.275	0.366	0.199
berg balance	0.136	0.624	0.246	0.396
SCIM-III	0.460	0.098	0.507	0.064
10m WS	0.222	0.446	0.271	0.345
After				
LEMS	0.086	0.796	0.640	0.014
berg balance	0.106	0.719	0.533	0.050
SCIM-III	0.486	0.078	0.428	0.127
10m WS	0.098	0.739	0.127	0.665

Data are expressed as mean ± SD (*n* = 14). 10m WS: 10-m walking speed; LEMS: Lower extremity motor score; rMEP: resting Motor evoked potential; SCIM-III: Spinal Cord Independence Measure-III.

motor cortex in patients with incomplete cervical SCI, combined with hand function training, and showed that the total upper limb muscle strength score was significantly improved compared with the sham-stimulation group. Nardone et al. (2017) used iTBS for the first time in patients with SCI. Ten patients with incomplete cervical or thoracic SCI received iTBS for 10 days, resulting in a significantly increased resting MEP amplitude and a significantly reduced H/M amplitude ratio (Nardone et al., 2017). The Modified Ashworth Scale and Spinal Cord Injury Assessment Tool for Spasticity scores were also significantly reduced in these patients after treatment. Huang et al. (2005) proposed that the iTBS protocol was safe and produced consistent, rapid, and controllable electrophysiological and behavioral changes in the function of human motor systems with a duration of more than 60 minutes. Our current study also demonstrated that iTBS cortical stimulation combined with precise root stimulation was effective for the treatment of chronic SCI.

Nardone et al. (2017) showed that iTBS cortical stimulation increased the rMEP amplitude, indicating that rMEP was a meaningful neurological measure for comparing motor function. The present data also suggested that cortical stimulation combined with precise root stimulation increased the rMEP amplitude, and suggested that root stimulation was a non-inferior treatment. In addition, other studies only reported improvements in upper limb muscle strength (Gomes-Osman and Field-Fote, 2015) or reductions in spasticity (Nardone et al., 2017), while our study further demonstrated that iTBS combined with precise root stimulation could improve lower extremity motor function, muscle strength, balance, and independence, and thus represented an effective choice for TMS stimulus protocols.

This study aimed to investigate the precise stimulation location and effective treatment for patients with chronic SCI in the bottleneck stage. The main stimulation hotspot in clinical studies is currently the motor cortex M1, with no TMS applied directly to the spinal cord. Savulescu et al. (2021) demonstrated the use of repetitive peripheral magnetic stimulation for treating lumbar radiculopathy. In their study, the root localization was a fuzzy nerve localization at the lower edge of the internal fixation, with low accuracy and reproducibility, and TMS could not be achieved because of the anatomical structure and plate shielding. Nerve root stimulation may be the best hotspot for spinal cord stimulation; however information on the effect of root stimulation on recovery from SCI is lacking. Maccabee et al. (1998) proposed that a small circular coil was a suitable candidate for magnetic stimulation of the spinal nerves, allowing localization of the nerve roots with centimeter-level precision by EMG. Stimulation via the nerve root can travel upwards to stimulate the spinal cord thalamic tract, as well as downwards to stimulate the peripheral nerves. In our experiment, root TMS stimulation was achieved with centimeter-level precision using MMC-90 small circular coils guided by EMG.

For patients with SCI, we used unilateral cortical stimulation (right only) and bilateral root stimulation, applying different stimuli to the left and right sides, and measuring the left and right CMCTs before and after treatment. There was a significant difference in the right CMCT, but not in the left CMCT, which had no cortical stimulation. CMCT is the nerve conduction time of cortical excited impulses to the anterior horn of the spinal cord, and thus more directly reflects the central nerve conduction velocity after SCI (Groppa et al., 2012). Shortening of the CMCT indicated improved spinal cord conduction. It is suggested that the side receiving iTBS combined with root stimulation (right) showed improved spinal cord conduction compared with the side receiving root stimulation alone (left). iTBS is a non-invasive and painless protocol that modulates cortical excitability in motor areas and strengthens the descending projections with a segmental effect of spinal interneurons (Valero-Cabré et al., 2001), while root stimulation promotes the activity of ascending pathways from the nerve root to the cortex. The combination therapy should thus be effective for managing SCI.

To further optimize the TMS protocol, it is necessary to compare root stimulation with cortical combined with root magnetic stimulation to find a better protocol. The current study used unilateral cortical stimulation (right only) and bilateral root stimulation, resulting in significantly increased motor function parameters and rMEP amplitudes on both sides, indicating that both neural function and motor function were significantly improved by the intervention. Consideration of the left and right sides of the same patient was selected for comparison, the results may be interfered with by the etiology of spinal cord injury. However, rMEP amplitudes between the left and right sides before the intervention were tested by an inter-group *t*-test, which showed no significant difference between the two sides

Before the intervention, the correlation between the LEMS data and rMEP amplitude was consistent. After the intervention, there was a significant correlation between the rMEP amplitude and the LEMS on the cortical stimulation side (right side), and a significant correlation between the right rMEP amplitude and the Berg score for balance. This indicated that the neurological response following the combined stimulation was more highly correlated with lower extremity motor function than that following root stimulation alone.

TMS has been the most commonly used non-invasive neuromodulation technique in recent years and has been applied for the clinical treatment of SCI. After 4 weeks of treatment, patients with cervical SCI showed decreased spasticity, and LEMS increased in patients with thoracic lumbar vertebra SCI. This study found that subjects with chronic SCI with a disease course of 6 months to 1 year increased their 10-m walking speed by 110% compared with pre-treatment, while subjects with disease course longer than 1 year only increased their 10-m walking speed by 58%. This suggests that patients with chronic incomplete SCI should receive this treatment within 1 year after their injury. The size of the nervous system lesion will inevitably affect the patient's prognosis. Although the lesion size cannot be controlled in a clinical study, we selected patients at Shanghai Yangzhi Rehabilitation Hospital who had no motor functional recovery 6 months after their SCI, to exclude recovery of the disease itself as much as possible. We initially considered measuring the size of the defect in the patients to determine if the defect size was related to the SCI; however, interference in the images due to titanium alloy after surgery meant that the defect size could not be measured by magnetic resonance imaging at the time of enrollment. Among the included patients, patient 8 with a C7 cervical SCI had severe neuropathic pain and postural hypotension, with a visual analog scale of 8, self-reported severe sleep disturbance, and accompanying depression. The lower limb motor function was improved after treatment, but the neuropathic pain showed no improvement.

The neuromodulation of cortical stimulation combined with precise root stimulation may effectively reconstruct the residual neural network of the injured nerve. It improves the excitability of the nerve fibers, enhances the synaptic plasticity of the anterior horn of the spinal cord, and upregulates the secretion of neurotransmitters. Electrophysiological data can reflect changes in neurotransmitter plasticity. According to Hebb's theory, synapses repeatedly synchronize activities, strengthen synaptic connections, and form neuronal associations, causing calcium ion influx (Wayman et al., 2008). NMDA receptors showed long-term synaptic potentiation after stimulation (McDonnell et al., 2007).

Accurate L3–L4 nerve root stimulation under the guidance of EMG meets the rehabilitation needs for the quadriceps femoris and tibial anterior muscles. Selection of back stimulation with a small circular coil can narrow the stimulation range and achieve nerve root stimulation with centimeter-level accuracy. We analyzed the changes in spinal cord conduction velocity and synaptic plasticity using objective electrophysiological data (calculated by EMG keypoint software). Meanwhile, we found significant improvements in rehabilitation, and concluded that patients with chronic SCI should ideally receive the treatment within 1 year after their injury. The experimental validity and non-invasive nature of TMS suggest that it is a suitable option for the treatment of chronic SCI.

Because of the limited clinical conditions including the small sample size, short observation time, and small number of patients inducing lower limb rMEP, no control group was established, which limited the ability of the study to conclude that iTBS combined with precise root stimulation was more effective than root magnetic stimulation for managing chronic SCI.

This study initially observed the function of the sensorimotor neuron circuit activated by cortical magnetic stimulation and precise root stimulation, reflecting the promotion of motor function recovery. This study included three patients with cervical segmental injury (quadriplegia) and 11 patients with thoracolumbar injury (paraplegia). However, this case series only focused on lower limb motor scores, and the upper limbs were not evaluated. In addition, the lesion size and location varied among the patients, and the root stimulation points remained at the level of L3–L4 in all patients, which may be a possible confounding factor. Further studies are needed to determine if the beneficial effect derives from the cortical stimulation or root stimulation, whether the neural circuit is reconstructed, and if it is indirectly supported by long-term potentiation. This study was an original spinal cord injury TMS stimulation protocol. Considering the difficulty in recruiting American Spinal Cord Injury Association Impairment Scale grade C/D patients, it was not possible to compare the current patients with a historical control. However, we analyzed the electrophysiological indicators for the left and right sides of the subjects before treatment and found no significant difference between the sides in terms of the electrophysiological indicators of SCI. Our group recently demonstrated that nerve root magnetic stimulation promoted the recovery of motor function in a rat model of SCI. We also aim to conduct further animal experiments to compare the effects of combined cortical/root stimulation with root or cortical stimulation alone.

In conclusion, we investigated the neuromodulation of cortical stimulation combined with precise root stimulation, as a potentially better method of achieving motor function recovery in patients with chronic SCI. The experimental validity and non-invasive nature of TMS suggest that it provides a clinical solution for the treatment of chronic SCI. The current results suggest that iTBS combined with precise root stimulation improves nerve conduction of the corticospinal tract and lower limb motor function recovery in patients with chronic SCI, although further case-control studies are needed to support these findings.

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Additional files:
Additional file 1: *Informed consent form (Chinese).*
Additional file 2: *Hospital ethics approval (Chinese).*
Additional file 3: *Open peer review reports 1 and 2.*
Additional Figure 1: *Schematic diagram of unilateral cortical iTBS magnetic stimulation combined with bilateral 15 Hz root magnetic stimulation (non-simultaneous).*

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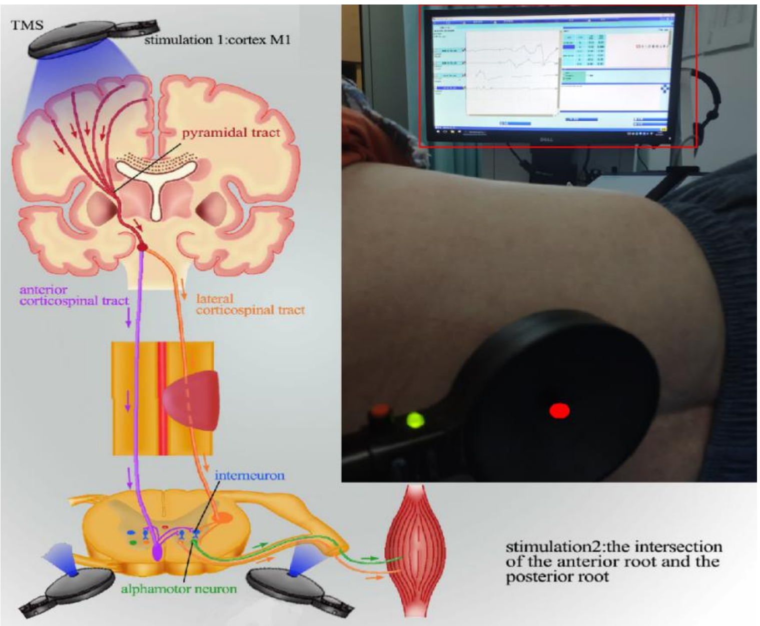

Additional Figure 1 Schematic diagram of unilateral cortical iTBS magnetic stimulation combined with bilateral 15 Hz root magnetic stimulation (non-simultaneous).

iTBS: Intermittent theta burst stimulation; M1: primary motor cortex; TMS: transcranial magnetic stimulation.