Effectiveness of Repetitive Transcranial Magnetic Stimulation Combined With Transspinal Electrical Stimulation on Corticospinal Excitability for Individuals With Incomplete Spinal Cord Injury: A Pilot Study

Bor-Shing Lin, *Senior Member, IEEE*, Zhao Zhang, Chih-Wei Peng,
Shih-Hsuan Chen, Wing P. Chan, and Chien-Hung Lai

Abstract*— Repetitive Transcranial Magnetic Stimulation (rTMS) and transspinal electrical stimulation (tsES) have been proposed as a novel neurostimulation modality for individuals with incomplete spinal cord injury (iSCI). In this study, we integrated magnetic and electrical stimulators to provide neuromodulation therapy to individuals with incomplete spinal cord injury (iSCI). We designed a clinical trial comprising an 8-week treatment period and a 4-week treatment-free observation period. Cortical excitability, clinical features, inertial measurement unit and surface electromyography were assessed every 4 weeks. Twelve individuals with iSCI were recruited and randomly divided into a combined therapy group, a magnetic stimulation group, an electrical stimulation group, or a sham stimulation group. The magnetic and electric stimulations provided in this study were intermittent theta-burst stimulation (iTBS) and 2.5-mA direct current (DC) stimulation, respectively. Combined therapy, which involves iTBS and transspinal DC stimulation (tsDCS), was more effective than was iTBS alone or tsDCS alone in terms of increasing corticospinal excitability. In conclusion, the effectiveness of 8-week combined therapy in increasing corticospinal excitability faded 4 weeks after the cessation of treatment. According to the results, combination of iTBS rTMS and tsDCS treatment was more effective than was iTBS rTMS alone or tsDCS alone in enhancing corticospinal excitability. Although promising, the results of this study must be validated by studies with longer interventions and larger sample sizes.

***Index Terms*— Spinal cord injury, repetitive transcranial magnetic stimulation, transspinal electrical stimulation, corticospinal excitability, surface electromyography.**

I. INTRODUCTION

SPINAL cord injury (SCI) is a serious disease of the central nervous system and a major health problem worldwide [1]. The nerve damage caused by SCI affects the muscles and causes them to degenerate rapidly, which makes it difficult for an affected individual to walk and seriously affects the individual's performance of activities of daily living [2].

Manuscript received 11 June 2023; revised 20 September 2023 and 19 November 2023; accepted 27 November 2023. Date of publication 30 November 2023; date of current version 7 December 2023. This work was supported in part by the Ministry of Science and Technology in Taiwan under Grant MOST 110-2314-B-038-005, Grant MOST 108-2314-B-305-001, Grant MOST 110-2221-E-A49-096-MY3, Grant MOST 110-2314-B-305-001, and Grant MOST 111-2221-E-038-008; in part by the National Science and Technology Council in Taiwan under Grant NSTC 112-2221-E-305-001-MY3, Grant NSTC 112-2811-E-038-002, Grant NSTC 112-2221-E-038-004-MY3, and Grant NSTC 112-2221-E-038-005-MY3; in part by the University System of Taipei Joint Research Program under Grant USTP-NTPU-NTOU-112-01; in part by the Faculty Group Research Funding Sponsorship by National Taipei University under Grant 2023-NTPU-ORD-01; in part by the Higher Education Sprout Project by the Ministry of Education (MOE) in Taiwan under Grant DP2-TMU-112-N-02 and Grant DP2-TMU-112-N-06; and in part by the Taipei Medical University Hospital, Taiwan, under Grant 111TMUH-MOST-04. *(Corresponding author: Chien-Hung Lai.)*

This work involved human subjects or animals in its research. Approval of all ethical and experimental procedures and protocols was granted by the Ethics Committee of Taipei Medical University under IRB No. 201905031.

Bor-Shing Lin and Shih-Hsuan Chen are with the Department of Computer Science and Information Engineering, National Taipei University, New Taipei City 237303, Taiwan (e-mail: bslin@mail.ntpu.edu.tw; nakaharamisakinya@gmail.com).

Zhao Zhang is with the School of Mechanical and Electrical Engineering, Wuyi University, Wuyishan, Fujian 354300, China, and also with the Department of Computer Science and Information Engineering, and the College of Electrical Engineering and Computer Science, National Taipei University, New Taipei City 237303, Taiwan (e-mail: 18259956201@163.com).

Chih-Wei Peng is with the School of Biomedical Engineering, College of Biomedical Engineering, Taipei Medical University, Taipei 11031, Taiwan, and also with the School of Gerontology and Long-term Care, College of Nursing, Taipei Medical University, Taipei 11031, Taiwan (e-mail: cwpeng@tmu.edu.tw).

Wing P. Chan is with the Department of Radiology, School of Medicine, College of Medicine, Taipei Medical University, Taipei 11031, Taiwan, and also with the Department of Radiology, Wan Fang Hospital, Taipei Medical University, Taipei 11696, Taiwan (e-mail: wingchan@tmu.edu.tw).

Chien-Hung Lai is with the Department of Physical Medicine and Rehabilitation, School of Medicine, College of Medicine, Taipei Medical University, Taipei 11031, Taiwan, and also with the Department of Physical Medicine and Rehabilitation, Taipei Medical University Hospital, Taipei 11031, Taiwan (e-mail: chlai@tmu.edu.tw).

Digital Object Identifier 10.1109/TNSRE.2023.3338226

Currently, the main clinical rehabilitation method for patients with SCI is exercise rehabilitation. Studies have indicated that treadmill training is helpful for recovery from SCI; however, the rehabilitation effect of this therapy is limited [3], [4]. Therefore, other rehabilitation methods have been developed in recent years, and nerve regeneration and nerve remodeling are key methods that can restore the function of patients with SCI [5]. Brain remodeling and motor neuronal connection from the brain to the spinal cord play crucial roles in the recovery and rehabilitation of sensory and motor dysfunctions of distal limbs [6]. For patients with incomplete SCI (iSCI), walking ability can be partially restored through neural remodeling [7]. However, enhancing the plasticity of the brain and spinal cord to restore motor function in patients with iSCI remains a clinical challenge [8].

Transspinal electrical stimulation (tsES) and repetitive transcranial magnetic stimulation (rTMS) are safe nerve rehabilitation methods in which changes are induced in spinal cord and cortical excitability through the application of electric and magnetic fields [9], [10]. tsES is a noninvasive electrical stimulation method that involves placing electrodes on the skin on the spinal cord of patients with iSCI to modulate the excitability of their cortical, corticospinal, and spinal neurons [11]. Albuquerque et al. observed that direct current (DC) can be used to regulate spinal cord excitability [12]. rTMS is a noninvasive and painless method for regulating the excitability of the motor cortex and inducing long-term changes in corticospinal transmission [13]. Leszczy et al. noted that rTMS can reduce the tension of the upper limbs and improve the neurotransmission function of the spinal cord in patients with iSCI [14]. rTMS produces different effects depending on its frequency. Studies have indicated that high-frequency magnetic stimulation (>5 Hz) increases cortical motor excitability, whereas low-frequency magnetic stimulation (1 Hz) decreases cortical motor excitability [12]. Benito et al. demonstrated that high-frequency rTMS can improve the motor function and gait of patients with iSCI [15]. Nardone et al. observed that theta-burst stimulation (TBS) modulates motor cortex excitability [16].

Combined rTMS and tsES treatment is a novel nerve stimulation rehabilitation method that promotes the continuous enhancement of the corticospinal circuit through simultaneous tsES and rTMS [17], [18]. Rodionov et al. explored the rehabilitation effects of combined rTMS and ES treatment on the hand and leg functions of patients with iSCI. They found that the group that received combined rTMS and ES therapy exhibited better rehabilitation effects than did the sham stimulation group [19], [20]. Shulga et al. demonstrated that long-term combined rTMS and ES therapy can restore muscle control in patients with iSCI [21]. Zhang et al. explored the changes caused in patients with iSCI by different combinations of combined rTMS and ES treatment. Their results indicated that the four groups subjected to combined rTMS and ES treatment exhibited superior rehabilitation effects relative to the sham stimulation group [22]. However, the rehabilitation effects of these combined therapies are affected by age, severity of injury, and initial muscle strength [19]. Few studies have compared the therapeutic effects of combined rTMS and ES treatment, magnetic stimulation alone, and ES treatment alone, and few settings are available for conducting such a comparison [11], [17]. Moreover, few studies have examined the rehabilitation effects of theta burst stimulation TMS (non-high frequency) combined tDCS for patients with iSCI because of the lack of available device on the market that provides the parameters of multiple functions. Therefore, suitable settings must be developed to conduct combined rTMS and ES therapy for individuals with iSCI.

Our previous study has assessed the immediately therapeutic effects of intermittent theta-burst stimulation (iTBS) rTMS and transspinal DC stimulation (tsDCS) treatments in patients with iSCI [22]. However, this previous study didn't have particular stimulation strategy and didn't examine cumulative effects of combination of iTBS rTMS and tsDCS intervention in patients with iSCI. In this study, therefore, we developed a system that integrates magnetic and electrical stimulators to provide tsDCS, iTBS rTMS, and combined iTBS rTMS and tsDCS therapies to patients with iSCI. This system contains an inertial measurement unit (IMU) and surface electromyography (sEMG) devices, which can be used to measure the cumulatively therapeutic effectiveness of tsDCS, iTBS rTMS, and combined iTBS rTMS and tsDCS treatments. In addition, by using the aforementioned system and the clinical trials proposed in this paper, one can compare the cumulatively therapeutic effects of combined iTBS rTMS and tsDCS therapy, iTBS rTMS alone, and tsDCS alone for patients with iSCI. The results of this study can be used as a reference for future research.

II. METHODS

A. System Overview

The rehabilitation system developed in this study contains five major blocks; these blocks contained an electrical stimulator and control device (ESCD), a rTMS device, IMU devices, sEMG devices, and a host. The overall system architecture is illustrated in Fig. 1. The ESCD and rTMS device are used to provide nerve stimulation to treat individuals with iSCI. The sEMG and IMU devices are used to collect sEMG signals and motion data, respectively, for evaluating the effectiveness of therapies. The host controls the ESCD and rTMS device through a program installed on the host computer and collects data from the sEMG and IMU devices. The ESCD, sEMG devices, and IMU devices communicate with the host computer wirelessly through Bluetooth, and the rTMS device communicates with the host computer through the RS-232 interface. The developed system can be easily operated through a graphical user interface (GUI) on the host computer. To validate the proposed system, a short-term clinical trial was conducted at the Department of Physical Medicine and Rehabilitation, Taipei Medical University Hospital, Taipei, Taiwan.

B. ESCD and rTMS Device

The ESCD used in this study is a modified version of the ESCD used in the study of Li et al. [23]. A photograph of the exterior of the ESCD is depicted in Fig. 2(a). The dimensions

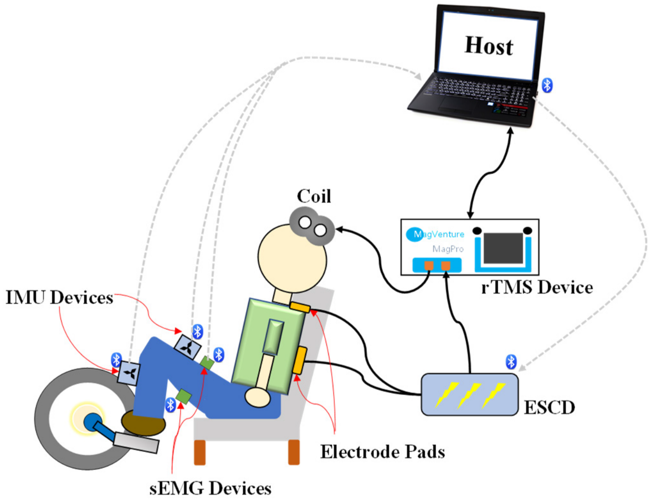
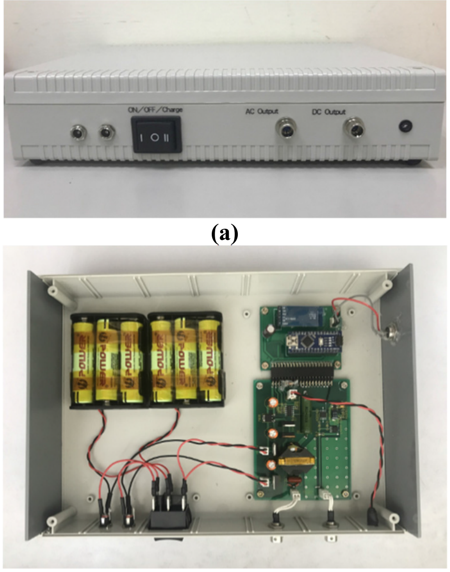


Fig. 1. Overall system architecture.



(a)

(b)

Fig. 2. Photographs of the (a) exterior and (b) interior of the ESCD.

of this device are 24.5 cm × 17.5 cm × 5 cm. The layout of the internal circuit of the ESCD is shown in Fig. 2(b). This device consists of a microprocessor, an optocoupler isolator, two digital-to-analog converters (DACs), an alternating current pulse and DC generator, a stimulus current detector, a DC–DC converter, a Bluetooth module, and lithium-ion batteries. The block diagram of the entire ESCD is displayed in Fig. 3. This device is powered by six 3.6-V lithium-ion batteries (NCR18650, Panasonic Corporation, Osaka, Japan), which ensures its high safety performance during use.

The DACs (TLC5618, Texas Instruments, Dallas, TX, USA) are controlled by the microprocessor (ATmega328, Microchip Technology, Chandler, AZ, USA) in an Arduino NANO board to generate DC, and the intensity of the output current was adjusted to meet the 2.5-mA requirement in the clinical experiments. A crucial feature of the electrical stimulator adopted in this study is that it can be wirelessly controlled through Bluetooth by using the computer program developed in this study to improve the safety of electrical stimulation for rehabilitation [24]. In addition, combination of iTBS rTMS and tsDCS therapy can be generated by connecting a commercially available rTMS device with a trigger signal generated by the ESCD. The current strength and waveforms of the adopted ESCD were determined in [22].

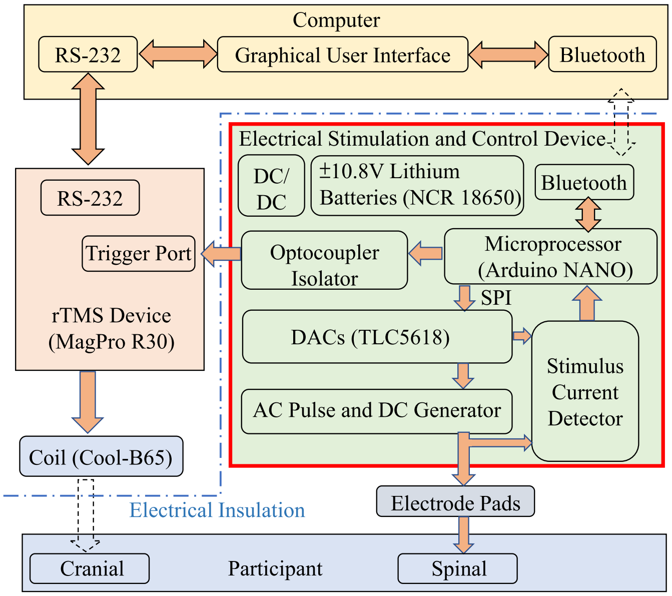


Fig. 3. Overall block diagrams of the ESCD and its peripheral equipment.

The rTMS device used in this study (MagPro R30, MagVenture, Farum, Denmark) can generate a maximum magnetic field of 2.2 T at the center of the coil. A water-cooled coil (Cool-B65, MagVenture) was used to ensure that prolonged magnetic stimulation did not cause the coil of the rTMS device to overheat and crash during the clinical procedure, thereby interrupting the experiment [25]. The host computer communicates with the electrical stimulator used in this study through the RS-232 communication interface. Users can adjust the magnetic stimulation parameters through the developed computer program. When the rTMS device is in the external trigger mode, precise triggering can be achieved through the ESCD, and magnetic pulses can be sent according to the timing of the microprocessor.

C. sEMG and IMU Devices

The sEMG device (Desktop DTS, Noraxon Inc., Scottsdale, AZ, USA) was used in this study, which have high reliability for short- and medium-term exercise assessment [26]. In this study, the sampling frequency of the aforementioned devices was set at 1500 Hz. Through Bluetooth, the data of the sEMG devices are transmitted to the receiving program in the host, the EMG signal waveform during rehabilitation can be displayed in real time, and EMG data can be stored for subsequent analysis.

The IMU devices used in this study contain a circuit board that we developed. This board includes an IMU chip (MPU-9250, TDK InvenSense Inc., San Jose, CA, USA), a 3.7-V Lithium-ion battery, and a Bluetooth module (Ct-BT02,

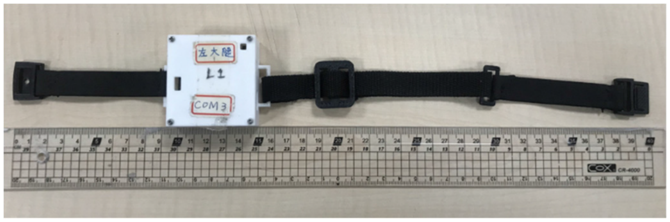
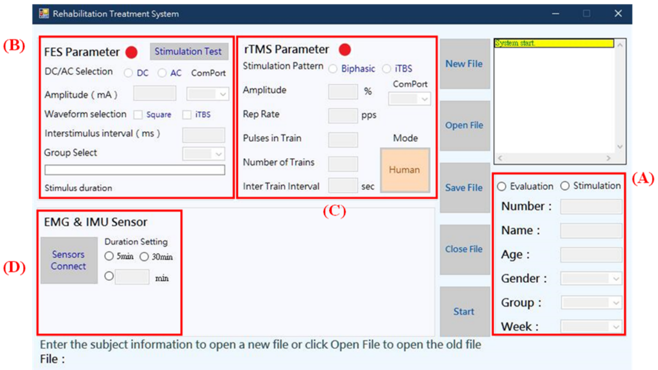


Fig. 4. Photograph of an IMU device.



Enter the subject information to open a new file or click Open File to open the old file
File :

Fig. 5. GUI for the main form, which comprises areas depicting the subject's information (area A), FES parameters (area B), rTMS parameters (area C), and evaluation time setting (area D).

Connectec Electronics, Taiwan). The accuracy and stability of the IMU motherboard developed by us were verified in [27]. We placed the circuit board in a three-dimensional-printed shell and connected a Velcro strap to the shell to form a wearable device that can be tied to the thigh or calf (Fig. 4). An MPU-9250 IMU provides data obtained from a three-axis accelerometer, three-axis gyroscope, and three-axis magnetometer. In this study, these data indicated an individual's performance in a cycling-based rehabilitation exercise. The sampling rate of the IMU devices was set as 50 Hz. The data collected by these devices was transmitted through Bluetooth to the host program to be saved and displayed.

D. Graphical User Interface

The GUI used in this study was developed in C# language and runs on the Windows 10 operating system. This GUI contains two parts: the main form (Fig. 5) and sensor connection form (Fig. 6). The main form comprises four areas, namely those depicting subject information, electrical stimulation parameters, magnetic stimulation parameters, and evaluation time settings. The sensor connection form also comprises four blocks, namely those depicting the connection status of the IMU devices, the calibration settings of the IMU devices, real-time knee joint angle and evaluation time, and sEMG waveform.

The operation flowchart of the developed GUI is displayed in Fig. 7. After opening the GUI, the operator must first select the evaluation or stimulation mode in area A of Fig. 5 and then enter the subject number. For the first assessment, complete subject information must be entered. In subsequent assessments and stimulation treatments, the stored subject information is automatically loaded. In the evaluation mode, the operator can input the electrical stimulation and magnetic stimulation parameters to be used for the patient in areas B and C of Fig. 5, respectively. The evaluation time is entered in area D of Fig. 5, and the "Sensors Connect" button is clicked to switch to the sensor connection form. In the stimulation mode, the electrical stimulation and magnetic stimulation parameters used for the subject are automatically loaded. The "Start" button in the main form is clicked to begin the stimulation therapy, which automatically stops when the stimulation therapy time expires.

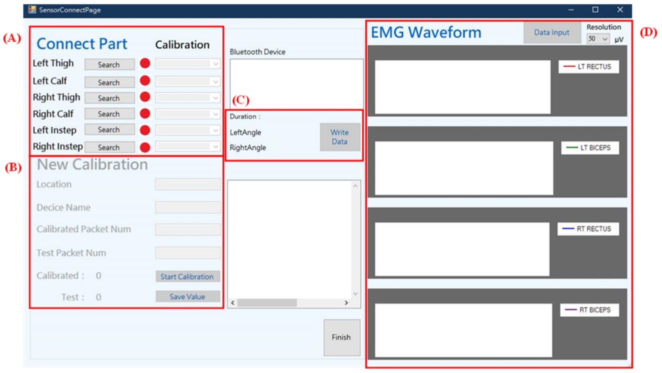


Fig. 6. GUI of the sensor connection form, which comprises areas depicting the connection status of the IMU devices (area A), IMU calibration parameters (area B), cycling information (area C), and sEMG waveform (area D).

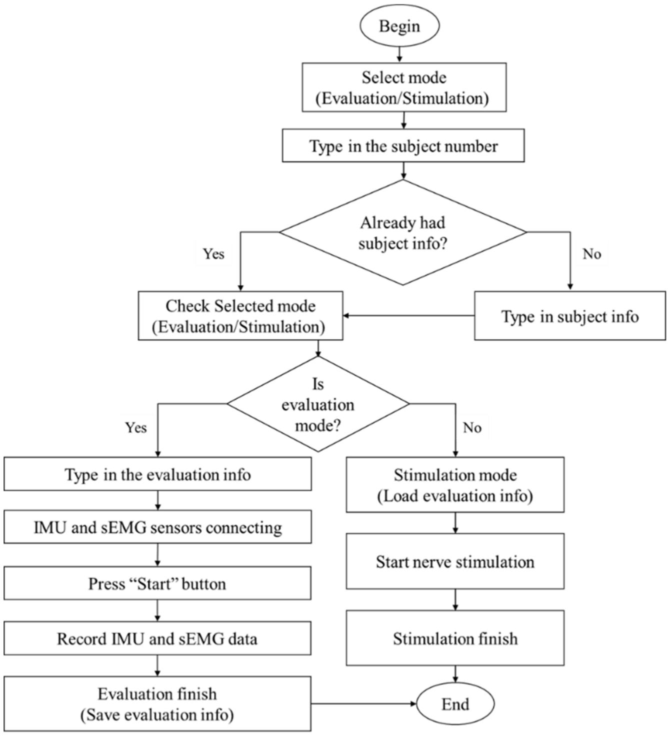


Fig. 7. Operation flowchart of the GUI.

When operating the sensor connection form (Fig. 6), the operator can connect or disconnect the IMU devices in area A in Fig. 6. The wearable IMU devices provide three-axis magnetometer data, which may be disturbed by the current environment. To avoid this problem, the operator can calibrate

TABLE I
DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE PARTICIPANTS

ID	Gender	Age	AIS	Injury part	Years post injury	Group
N01	Male	64	D	C5	2	A
N02	Male	42	D	T2	7	A
N03	Male	58	C	C6	10	A
N04	Female	62	C	C5	9	B
N05	Male	64	D	C5	7	B
N06	Male	65	D	C6	7	B
N07	Female	55	C	T6	4	C
N08	Male	53	C	C5	1	C
N09	Male	48	D	C4	1	C
N10	Male	65	D	C5	7	D
N11	Male	62	C	C6	4	D
N12	Male	59	C	C5	4	D

the magnetometer in area B in Fig. 6. After a sensor is connected and calibrated, the "Write Data" button in area C in Fig. 6 is clicked to begin saving the accelerometer, gyroscope, magnetometer, and sEMG data of the subject's cycling rehabilitation. The real-time knee joint angle of the subject during cycling and the elapsed time of the rehabilitation treatment are displayed in area C of Fig. 6. The real-time sEMG waveform of the subject is depicted in area D of Fig. 6, and six voltage resolutions can be selected: 50, 100, 150, 200, 250, and 300 μV. Data collection stops automatically when the evaluation period has passed.

III. CLINICAL TRIAL

A. Participants

A total of 12 patients with iSCI (nine men and three women; aged 56.18 ± 12.58 years) were recruited in this study. Prospective participants were included if they (i) were aged 20–65 years with an injury at American Spinal Injury Association Impairment Scale (AIS) Grade C or D, (ii) had an injury site above the 10th thoracic vertebra, (iii) were injured for more than 1 year, (iv) had unlimited range of motion, and (v) had a stable medical status. Prospective participants were excluded if they had (i) metal implants, including heart rate regulators; (ii) a history of epilepsy; or (iii) other neurological, psychiatric, or serious medical conditions. Table I lists the demographic and clinical characteristics of the participants.

B. Experimental Procedure

The clinical trial of this study was performed at Taipei Medical University Hospital, Taipei, Taiwan. This research was reviewed and approved by the Ethics Committee of Taipei Medical University (IRB No. 201905031), and the participants gave their written informed consent. The process of the clinical trial is illustrated in Fig. 8. The 12 participants were randomly assigned to four groups: Group A was provided 2.5-mA tsDCS combined with iTBS rTMS, Group B was provided sham tsDCS combined with iTBS rTMS, Group C was provided 2.5-mA tsDCS combined with sham iTBS rTMS, and Group D was provided sham tsDCS combined with sham iTBS rTMS. To evaluate the therapeutic effects of the aforementioned stimulation pairs, baseline data were gathered for each participant through electrophysiological measurements and in clinical assessments [including lower extremity muscle strength (LEMS), sEMG, and 5-min cycling assessments] prior to treatment. Both patients and evaluators don't know what is being test. Each participant then received electromagnetic or sham stimulation rehabilitation, followed by 30 min of cycling rehabilitation three times a week for 8 weeks. An electrophysiological measurement and set of clinical assessments were performed at 1 day before the beginning of the intervention, and 4 (1day after the end of 4-week intervention), 8 (1 day after the end of the intervention), as well as 12 (four weeks after the end of the intervention) weeks since the beginning of the intervention. The aim of evaluating the electrophysiological and clinical functions 4 weeks after the end of the intervention was to determine whether the efficacy of the treatments persisted.

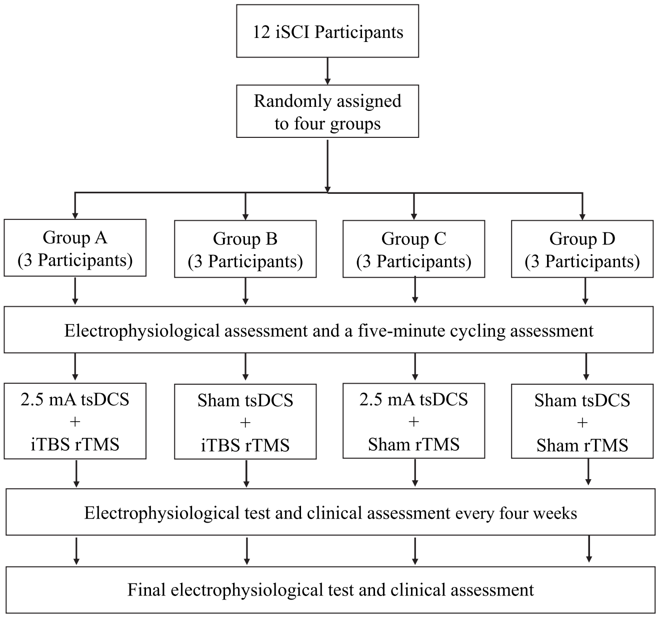


Fig. 8. Flowchart of the clinical process.

C. Applications of iTBS rTMS, and tsDCS

rTMS was applied to the hot spot of the vertex area on the top of the participant's head by using the rTMS device with a water-cooled coil. The hot spot area was determined by slowly moving the coil backward and forward along the Cz (10–20 electroencephalogram system) area where transcranial magnetic stimulation (TMS) generated the largest motor evoked potential (MEP). The stimulation intensity was set at 90% of the resting motor threshold (RMT) intensity for inducing MEPs at the lowest muscle threshold of tibialis anterior muscles. The RMT is defined as the minimum stimulus intensity that produces a minimal motor-evoked response (at least five evoked peak-to-peak amplitudes that are $> 50\ \mu$V in 10 consecutive stimulations) at rest [18]. The magnetic stimulation exhibited the iTBS waveform, which contained 2-s (5-Hz) theta pulses (10 bursts, each of which contained three stimulations at 50 Hz). An iTBS wave was delivered every 10 s till 200s were delivered, and these waves comprised a total of 600 stimulations [16], [28].

Anodal electrode of tsDCS was applied to the participants' 11th and 12th thoracic vertebra through a rectangular self-adhesive electrode patch (5 cm × 5 cm) with a thickness of 5 mm, and the reference electrode was placed on the left shoulder [29]. The intensity of tsDCS was set at 2.5 mA, and the stimulation time was set at 200 s to match the iTBS treatment in the combined therapy group. Nevertheless, tsDCS was applied for 20 min with intensity 2.5 mA in the tsDCS only group. Sham stimulation followed the same montage of real tDCS but after 30 seconds, the stimulator was turned off as previous study [12].

D. Outcome Measurements

1) Electrophysiological Test for Corticospinal Excitability: Motor corticospinal excitability was assessed in terms of the latency and amplitude of MEPs. Bestmann et al. demonstrated that MEPs can be used to quantify the corticospinal excitability during stimulation [30]. In this study, MEPs were measured using the magnetic stimulator. The amplitude and latency of the MEPs were examined at baseline (before intervention) and at 4, 8, and 12 weeks since the beginning of the intervention. These parameters were assessed in terms of the period (ms) and peak-to-peak voltage (μV), respectively. In the evaluation of MEPs, the optimal single TMS was adjusted to achieve the largest MEP by setting the stimulation intensity at 120% of the RMT [31] of initial assessment. This stimulation intensity could be consistently induced over the motor representation of contralateral tibialis muscles in both legs. Hence, the same MEP intensity was used before and after intervention in this study. Each MEP was measured thrice, and the data were averaged for further analysis, as in [22].

2) Lower Extremity Muscle Strength: LEMS was determined in terms of the sum of the strength scores obtained for bilateral hip flexors, knee extensors, ankle dorsiflexors, long toe extensors, and ankle plantar flexors on a 6-point ordinal scale ranging from 0 (lowest strength) to 5 (highest strength). Therefore, the maximum LEMS score was 25 for each leg [32]. LEMS has been used to examine muscular strength in people with chronic SCI [33], [34]. LEMS was executed by physical the same physical therapist in this study.

3) IMU Data: The IMU devices were tied to the rectus femoris and tibialis anterior muscles of the participants' feet. The revolutions per minute (RPM) achieved in cycling can be used as a parameter for assessing patients with neurological diseases [35]. The RPM in cycling was determined from the three-axis accelerometer, three-axis gyroscope, and three-axis magnetometer data collected by the IMU devices. The Madgwick algorithm was used to obtain the angle between the thigh and the calf of the participants when cycling. The waveform of the angle change was drawn according to the stored data, and the RPM in cycling was calculated using the angle change [36]. The participants' cycling speed reflected the transmission speed of their lower limb muscle fibers [37].

4) sEMG Signals: EMG signals were collected using the sEMG devices. The recording electrodes were placed on the biceps femoris and rectus femoris muscles of both feet. Four channels of signals were used in this study, and the EMG signal (μV) was analyzed using the time-domain root mean square (RMS) value [38]. The RMS value is related to the contractile force of the muscle; thus, this value can reflect the change in the amplitude of the EMG signal to a certain extent. The characteristics of the change in RMS value depend on the muscle load and the physiological factors of the muscle; thus, the RMS value is a reliable parameter for sEMG analysis [39].

E. Data Analysis

This study used LEMS scores, MEP, the RPM in cycling, and RMS values of sEMG signals as indicators of the effectiveness of the treatments provided. The data were illustrated using GraphPad Prism 8.0 (GraphPad Software, San Diego, CA, USA). Statistically significant differences among groups were determined using a Linear mixed model following post-hoc Bonferroni test statistical assessments were two-tailed, and $p < 0.05$ was considered significant. All statistical analyses were carried out using IBM SPSS statistical software version 25 for Windows (IBM Corp., Armonk, New York, USA).

IV. RESULTS

In this study, a combination of rTMS and tsES treatment for patients with iSCI and an evaluation system for this treatment were developed. The developed system comprises an ESCD and rTMS device for neuromodulation treatment, IMU and sEMG devices for therapy evaluation, and a computer program for system control. The safety and reliability of the devices used in the clinical trial of this study have been verified in previous studies [22], [23], and no major side effects of the adopted treatments were observed among the participants. The clinical trial was conducted to evaluate the efficacy of neurostimulation treatment and rehabilitation.

The therapeutic protocol for each participant group is displayed in Fig. 8. The linear mixed model was used to compare the four groups with respect to MEP amplitude, MEP latency, LEMS score, EMG RMS value, and cycling speed assessed every 4 weeks.

The results indicated that, the MEP amplitudes of Group A was higher after intervention than that in Groups B, C and D (all $p < 0.05$, Table II). The MEP amplitude of Group A at week 4, 8 and 12 were approximately 40%, 85% and 48% higher than that in the zeroth week, respectively (Fig. 9a). While the MEP amplitude of Group D at week 4, 8 and 12 were only approximately 1%, 1% and 0% higher than that in the zeroth week, respectively [Fig. 9(a)]. A trend toward higher rate of increase in MEP amplitudes at week 4 and 8 were found in Groups B (week 4 and 8: 19% and 33%) and C (week 4 vs. 8: 39% and 74%) than that in Group D, although it was not significantly different between Groups B, C and D (all $p > 0.05$, Table II and Fig. 9a). However, by the 12th week, these rates in Groups B and C nearly decreased to their levels in the zeroth week. The rate of increase in the MEP amplitude during the 8-week follow up period had the following order: Group A > Group C > Group B > Group D.

In addition, compared to Group D, the MEP latencies of Groups A, B, and C significantly decreased during the 8-week treatment (all $p < 0.05$, Table II). The MEP latency of Group A at week 4, 8 and 12 were approximately 17%, 21% and 16%

TABLE II

LINEAR MIXED REGRESSION MODEL OF THE RELATIONSHIP BETWEEN THE GROUPS DURING THE 12-WEEKS INTERVENTION

Variables	Week 0	Week 4	Week 8	Week 12	*p*-value#
MEP amplitude (*μ*V), mean ± SD					<0.001*
Group A	143.6±53.5	193.8±53.2	246.2±35.6	196.5±34.3	P_1<0.001*; P_2<0.001*;
Group B	76.3±4.6	91.2±15.2	100.9±6.4	70.0±14.0	P_3<0.001*; P_4=0.670;
Group C	45.4±12.2	66.8±29.9	80.3±25.1	45.4±0.1	P_5=0.610; P_6=1.000;
Group D	55.2±3.2	54.9±3.8	55.8±3.2	55.1±3.6	
MEP latency (ms), mean ± SD					<0.001*
Group A	43.9±12.3	35.5±6.6	33.6±5.5	35.4±4.7	P_1=1.000; P_2=1.000;
Group B	40.1±4.6	36.2±1.9	35.8±3.6	41.3±4.4	P_3<0.001*; P_4=1.000;
Group C	40.2±6.2	36.5±4.2	36.8±2.0	37.2±3.6	P_5<0.001*; P_6<0.001;
Group D	59.6±2.9	58.9±3.6	58.1±3.1	59.6±2.9	
LEMS score, mean ± SD					0.262
Group A	40.3±5.7	39.7±7.7	40.7±7.5	41.3±6.6	P_1=1.000; P_2=0.923;
Group B	36.5±8.5	38.5±6.5	38.0±6.0	38.5±6.5	P_3=0.923; P_4=1.000;
Group C	34.0±12.0	34.0±13.0	33.0±13.0	32.5±13.5	P_5=1.000; P_6=1.000;
Group D	42.5±6.5	42.5±6.5	41.0±7.0	40.5±3.5	
Cycling speed (rpm), mean ± SD					0.014*
Group A	34.7±10.7	34.3±9.4	39.7±9.9	42.3±7.4	P_1=1.000; P_2=0.032*;
Group B	43.0±7.0	40.0±12.0	46.0±18.0	48.5±6.5	P_3=0.047*; P_4=0.026*;
Group C	32.5±11.5	35.0±14.0	30.0±9.0	25.0±4.0	P_5=0.034*; P_6=1.000;
Group D	32.0±11.0	32.5±11.5	30.5±9.5	28.0±7.0	
sEMG amplitude (*μ*V), mean ± SD					0.033*
Group A	35.0±6.4	54.0±18.9	82.9±26.4	65.6±17.5	P_1=1.000; P_2=0.019*;
Group B	43.3±13.3	53.3±27.5	74.7±48.9	79.7±35.8	P_3=0.042*; P_4=0.011*;
Group C	20.2±13.1	26.0±17.7	28.8±23.3	15.7±12.1	P_5=0.034*; P_6=1.000;
Group D	29.6±25.3	25.1±20.6	25.8±21.4	28.4±25.0	

MEP, corticospinal excitability; LEMS, lower extremity muscle strength; sEMG, surface electromyography. #*P*-value: *P*1 (Group A vs. Group B); *P*2 (Group A vs. Group C); *P*3 (Group A vs. Group D); *P*4 (Group B vs. Group C); *P*5 (Group B vs. Group D); *P*6 (Group C vs. Group D).

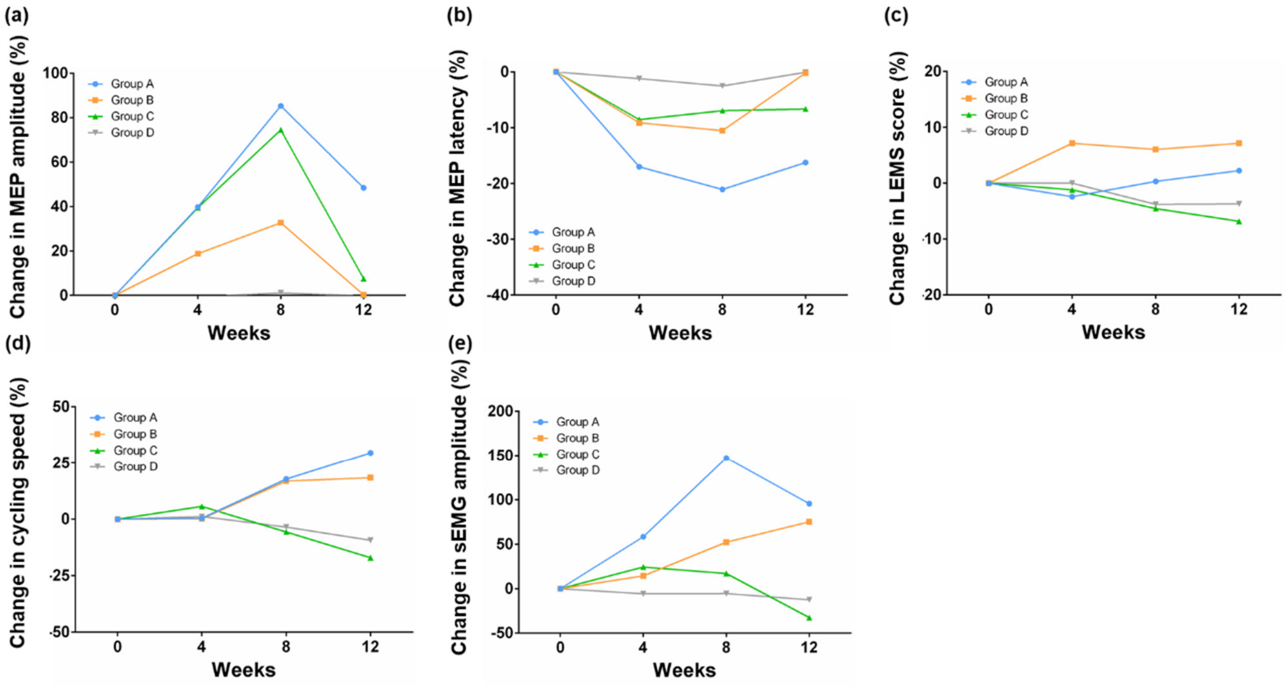


Fig. 9. Rates of MEP change in (a) EMP amplitude, (b) MEP latencies, (c) LEMS scores, (d) cycling speed, and (e) sEMG amplitude for the four groups during the 12-week trial.

lower than that in the zeroth week, respectively [Fig. 9(b)]. The MEP latency of Group B at week 4, 8 and 12 were approximately 9%, 11% and 0% lower than that in the zeroth week, respectively (Fig. 9b). The MEP latency of Group C at week 4, 8 and 12 were approximately 9%, 7% and 7% lower than that in the zeroth week, respectively (Fig. 9b).

While the MEP latency of Group D at week 4, 8 and 12 were only approximately 1%, 3% and 0% higher than that in the zeroth week, respectively (Fig. 9b). The rates of MEP latency reduction of the four groups had the following order during the 8-week treatment period: Group A > Group B > Group C > Group D; however, the rates of decrease at week 12 in Groups B nearly decreased to their levels in the zeroth week (Fig. 9b).

The results obtained for the LEMS scores indicated that no significant changes were observed in the LEMS scores of Groups A, B, C, and D ($p = 0.262$, Table II). Fig. 9(c) displays the changes in the LEMS scores of the four groups during the entire clinical trial. The LEMS score of Group B marginally increased during the first 4 weeks before reaching a plateau. A similar result was obtained for the rate of LEMS score change for Group B [Fig. 9(c)].

The results obtained for the cycling speed indicated that, compared to Group C or D, the cycling speeds of Groups A and B significantly increased during the 8-week treatment (all $p < 0.05$, Table II). In particular, the cycling speed of Group A and B increased by 14.41% and 6.98% after 8-week treatment, respectively [Fig. 9(d)]. In contrast to Groups A and B, Groups C and D did not exhibit significant changes in pedaling speed at the end of the treatment period [Fig. 9(d)]. The increases in the cycling speeds of Groups A and B were maintained 4 weeks after the intervention ended. Fig. 9(d) indicates that the rate of cycling speed change increased for Groups A and B during the treatment period. The aforementioned results imply that the rehabilitation effects related to the pedaling speed might be persistent for Groups A and B.

The results obtained for the sEMG amplitude indicated that, compared to Group C or D, the RMS values of the EMG signals in lower extremities increased during the 8 weeks of treatment for Groups A and B (all $p < 0.05$, Table II). The results obtained for the sEMG amplitude indicated that the RMS values of the sEMG signals in the lower extremities increased by approximately 147%, 52%, and 17% for Groups A, B, and C, respectively, after the 8-week treatment [Fig. 9(e)]. However, the RMS values of the EMG signals in the lower extremity exhibited no increase at 8th and 12th weeks for Groups C and D while compared to week 0. In general, the rate of change in the RMS value of the EMG signal in the lower extremity had the following order for the four groups: Group A > Group B > Group C > Group D.

V. DISCUSSION

We developed a sophisticated setting that can provide combination of iTBS rTMS and tsDCS therapy to individuals with iSCI and assess the effectiveness of this therapy for them. Therapeutic designs involving combination of iTBS rTMS and tsDCS therapy, iTBS rTMS, and tsDCS interventions were compared in this study.

To verify the feasibility and effectiveness of the developed treatment method and treatment evaluation system, a 12-week clinical trial was conducted among 12 individuals with iSCI. These individuals were randomly divided into four groups with different stimulation protocols. Patients with SCI for more than 1 year are less likely to recover naturally than are those with SCI for less than 1 year [40], and patients with more recent injuries have better recovery [41]. Therefore, to reduce the influence of natural recovery on the results of this study, all the individuals enrolled in the conducted clinical trial were patients who had iSCI for more than 1 year. To explore the persistence of the efficacy of the four adopted treatment protocols, electrophysiological and clinical outcomes were assessed 4 weeks after stopping interventions.

MEPs, which are generated through the application of TMS to the human motor cortex, quantify corticospinal excitability during stimulation [30], [42]. In the present study, the latency and amplitude of MEPs were used to evaluate the change in corticospinal excitability after combination of iTBS rTMS and tsDCS therapy, iTBS rTMS, tsDCS, and sham stimulation. After 8-week neuromodulation therapy, the MEP amplitudes of those who received the combination of iTBS rTMS and tsDCS therapy, iTBS rTMS, and tsDCS treatments increased by approximately 137%, 87%, and 76%, respectively. Moreover, the MEP latencies of these patients decreased by approximately 17%, 15%, and 13%, respectively. By contrast, no significant changes were observed in the MEP latency and amplitude in the sham stimulation. The MEP amplitude in the 12th week since the beginning of combination of iTBS rTMS and tsDCS therapy (4 weeks after the end of the intervention) was approximately 6% higher than that in the zeroth week. Moreover, the MEP latencies of Groups A, B, and C were 15%, 12%, and 7% lower, respectively, in the 12th week than in the zeroth week. By contrast, no significant improvement was noted in the control group. This result implied that the improvement caused in corticospinal excitability because of 8-week neuromodulation may not be maintained over a longer period. Increases in the MEP amplitude might be associated with changes in the excitability of the motor cortex or corticospinal tract. MEP induces motor control but is not always related to motor ability [30]. The MEP data collected in this study indicate that combination of iTBS rTMS and tsDCS therapy might be more effective than iTBS rTMS alone or tsDCS alone in neuromodulation for patients with iSCI.

The exact mechanisms underlying the plastic changes in corticospinal circuits elicited by combination of iTBS rTMS and tsDCS therapy, iTBS rTMS, and tsDCS are not completely clear. Nardone et al. found that TBS modulates motor cortex excitability [16]. tsDCS may involve long-term potentiation and long-term depression mechanisms and mediates changes in glutamatergic neurotransmission at the spinal level [12]. Studies have suggested that the continual provision of tsDCS on the spinal cord results in increases in the intensity of the magnetic pulse of the motor cortex after combination of iTBS rTMS and tsDCS therapy, and then increases corticospinal excitability, and the MEP during stimulation [17], [43]. The LEMS scores of the four groups did not exhibit significant changes during the trial because LEMS score is stepwise scale (0, 1, 2, 3, 4, 5). Hence, it mayn't detect differences between a small amount of change of muscle strength. MEP and EMG signals are continuous score. Therefore, they may be easy to detect a small amount of change. Other reason may be as follows. First, patients with iSCI may experience spasms due to changes in neuronal excitability, and spasm-induced tension may have affected the LEMS data [44]. Second, the sample size of the current study was relatively small, which may not have allowed significant changes in LEMS scores to be observed. Finally, an 8-week intervention may be insufficient for improving LEMS. Therefore, future studies should enroll additional individuals and conduct longer interventions to obtain more reliable results. The cycling speed was determined from IMU data. After 8-week of combined iTBS rTMS and tsDCS treatment and iTBS rTMS only, the cycling speed increased by approximately 10%, and 6%, respectively, compared with that before the treatments. Moreover, these effects persisted 4 weeks after the discontinuation of the treatments. However, no significant changes in cycling speed were observed for the tsDCS and sham stimulation groups. Cycling speed data show that the combination therapy of iTBS rTMS and tsDCS is able to improve the conduction velocity of muscle fibers in the lower limbs of iSCI patients to a greater extent than magnetic stimulation or electrical stimulation alone [37]. For Groups, A, B, and C, the RMS value of the EMG signal in the eighth week was approximately 112%, 72%, and 42% higher than that in the zeroth week, respectively. Moreover, for these groups, the aforementioned value in the 12th week was approximately 71%, 84%, and 8% higher than that in the zeroth week, respectively. An increase in the RMS value of the EMG signal implies that neuromodulation might effectively enhance the discharge signal intensity from the brain to the muscles of the lower extremities in patients with iSCI. The aforementioned enhanced effect was stronger for combination of iTBS rTMS and tsDCS therapy than for rTMS alone or tsDCS alone. No significant difference was noted in the RMS value of the EMG signal of the sham stimulation group in the entire study.

The results obtained for the MEP amplitude and the RMS value of the EMG signal indicate that combination of iTBS rTMS and tsDCS therapy can activate neural pathways to a greater extent than can iTBS rTMS alone or tsDCS alone [45]. The results of this study indicated that the effects of neuromodulation treatment declined within 4 weeks of treatment cessation. The activation of neural pathways for 8 weeks does not always result in long-term improvements in exercise capacity. The rehabilitation effect of combination of iTBS rTMS and tsDCS treatment is affected by age, years post injury, and residual muscle strength, and this effect may vary from patient to patient [19]. The results of this study indicate that combination of iTBS rTMS and tsDCS therapy may be more effective for treating patients with iSCI than is magnetic or electrical stimulation alone.

This study has several limitations. Although we included participants with an injury site above the 10th thoracic and randomly divided into four groups, further investigation should be determined the effect of lesions' heterogeneity on the outcomes. Due to small sample size, the results should be regarded as preliminary finding. Further larger sample sizes study is suggested for validation. Moreover, baseline MEP amplitude of combined therapy group was higher than other groups. This may affect the results during comparison among the four groups. Previous study suggested that SCI had substantial functional improvement are not able to get further improvement after intervention due to a ceiling effect [46]. However, it's necessary to further verify if there is ceiling effects or other effects that affect MEP amplitude of SCI patients in the future. In addition, the 200 seconds of tsDCS treatment in combined treatment group of this study may or may not be long enough to influence underlying neuronal tissues. Nevertheless, iTBS rTMS combined with tsDCS was more effective than iTBS rTMS alone for enhancing MEP amplitude. Therefore, these results are pilot findings and further investigation (longer tDCS therapy time or other rTMS parameters) is warranted to get more solid results. Despite these limitations, this study is one of the few that investigated the effects of combining iTBS rTMS and tsDCS therapy to individuals with iSCI and examined the efficacy using electrophysiology results, LEMS score, EMG RMS value, and cycling speed data.

VI. Conclusion

In this pilot study, we developed a combination of iTBS rTMS and tsDCS treatment for individuals with iSCI and an assessment system for this treatment. The developed system comprises an ESCD and rTMS device for neuromodulation treatment, IMU and sEMG devices for evaluating treatment effects, and a computer program for operating the entire system. By using this system, we collected data for muscle strength parameters and electrophysiological MEPs during exercise for comprehensively evaluating the effect of neurostimulation therapy on patients with iSCI. We recruited 12 patients with iSCI, who were randomly allocated to four groups: a combination of iTBS rTMS and tsDCS treatment group, single iTBS rTMS group, single tsDCS group, and sham stimulation group. The rTMS involved iTBS rTMS, and the ES involved tsDCS. During a 12-week clinical trial, we explored the difference in neuromodulation effects among combination of iTBS rTMS and tsDCS therapy, iTBS rTMS alone, and tsDCS alone. The data of this study indicated that combination of iTBS rTMS and tsDCS treatment was more effective than was iTBS rTMS alone or tsDCS alone in enhancing corticospinal excitability and the sEMG signal of the lower extremities. In addition, the effectiveness of 8-week combination of iTBS rTMS and tsDCS therapy in enhancing corticospinal excitability faded 4 weeks after the cessation of treatment. Finally, we observed no major side effects of combination of iTBS rTMS and tsDCS therapy among the participants. Although promising, the results of this study should be validated in future studies with larger sample sizes or longer clinical trials.

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