Non-invasive brain stimulation to promote motor and functional recovery following spinal cord injury

Aysegul Gunduz1, John Rothwell2, Joan Vidal3,4,5, Hatice Kumru3,4,5,*
1 Department of Neurology, Cerrahpasa School of Medicine, Istanbul University, Istanbul, Turkey
2 Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, Queen Square, University College London, London, UK
3 Institut Guttmann, Institut Universitari de Neurorehabilitacio adscrit a la UAB, Badalona–Barcelona, Spain
4 Universidad Autonoma de Barcelona, Bellaterra (Gerdanyola del Vallés), Spain
5 Fundació Institut d’Investigació en Ciències de la Salut Germans Trias i Pujol, Badalona, Barcelona, Spain


Abstract

We conducted a systematic review of studies using non-invasive brain stimulation (NIBS: repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS)) as a research and clinical tool aimed at improving motor and functional recovery or spasticity in patients following spinal cord injury (SCI) under the assumption that if the residual corticospinal circuits could be stimulated appropriately, the changes might be accompanied by functional recovery or an improvement in spasticity. This review summarizes the literature on the changes induced by NIBS in the motor and functional recovery and spasticity control of the upper and lower extremities following SCI.

Key Words: spinal cord injury; non-invasive brain stimulation; transcranial magnetic stimulation; transcranial direct current stimulation; functional improvement; spasticity; neuropathic pain

Introduction

Spinal cord injury (SCI) is a traumatic or non-traumatic event that results in altered sensory, motor, or autonomic function and ultimately affects a patient’s physical, psychological, and social well-being (Pickett et al., 2003). The management of SCI requires many healthcare resources and can place a substantial financial burden on patients, their families, and the community (Pickett et al., 2003). Because SCI mainly affects young people and lacks curative treatment, the functional changes caused by severe SCI persist throughout the patient’s life, and are an important cause of physical disability (McKinley et al., 1999; Singh et al., 2014). SCI has been considered totally irreversible for many years; however, research performed in the last decade is opening new paths that, until recently, were impossible to imagine. Our increased understanding of the pathophysiological mechanisms involved in SCI have made it evident that strategies to promote functional recovery have to proceed gradually, focusing on different goals at different intervals after injury and using multiple approaches rooted in various fields (Fawcett and Curt, 2009).

Since SCI is incomplete in most of the cases one way to promote recovery of motor function is to increase the effectiveness of connections of spared descending corticospinal pathways (Martin, 2016). In studies of animals with unilateral damage to the corticospinal tract, direct activation of the remaining corticospinal tract through electrical stimulation of motor cortex has been shown to increase axon outgrowth of corticospinal tract terminals within spinal cord, and promote formation of new synaptic connections in the denervated side of the cord (Carmel et al., 2010, 2014). In humans, non-invasive brain stimulation (NIBS) can potentially be used to increase the activity of corticospinal connections, with the intention of promoting sprouting of new connections from remaining axons to denervated regions of the cord.

Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are well-known, commonly used, NIBS techniques. TMS uses a rapidly changing magnetic field to induce brief electric current pulses in the brain that can trigger action potentials in cortical neurons, especially in superficial parts of the cerebral cortex (Rossini et al., 2015). Most rehabilitation methods make use of repetitive TMS (rTMS) in which many (maybe several hundred) TMS pulses are applied sequentially in order to induce long term changes in the excitability of the corticospinal connection. The principle follows that used to produce long term potentiation/depression of synapses in animal experiments. Each single pulse of TMS evokes activity in cortical synapses. Repeated activation of the same set of synapses then leads to long term changes in efficiency that can be expressed as suppression or facilitation, depending on the number, frequency and intensity of the stimulation.

In the human motor cortex, low-frequency (≤ 1 Hz) rTMS tends to reduce excitability, whereas high-frequency rTMS (≥ 5 Hz) increases excitability. More complex forms of rTMS exist. In theta burst stimulation (TBS), three 50-Hz stimuli are sequentially in order to induce long term changes in the excitability of the corticospinal connection. The principle follows that used to produce long term potentiation/depression of synapses in animal experiments. Each single pulse of TMS evokes activity in cortical synapses. Repeated activation of the same set of synapses then leads to long term changes in efficiency that can be expressed as suppression or facilitation, depending on the number, frequency and intensity of the stimulation.
Data Source and Methodology

We performed a literature search using the terms "non-invasive brain stimulation," "repetitive transcranial magnetic stimulation [rTMS]," "theta burst stimulation," "transcranial direct current stimulation [tDCS]," "paired associative stimulation," "spinal cord injury," "upper extremity muscle strength," "hand motor function," "lower extremity muscle strength," "gait," and "spasticity." The search included all articles published in English in the PubMed, Cochrane Library, Google Scholar, and MEDLINE databases until July 2017 that analyzed motor recovery after NIBS with or without amelioration in spasticity in adult or pediatric patients with SCI.

The exclusion criteria were: 1) non-invasive such as spinal cord and/or peripheral nerve stimulation; 2) studies done in animals; 3) studies investigating pain or solely sensory function.

This review examined the clinical and demographic characteristics of the patient population (age, number of subjects, time since SCI, clinical criteria for NIBS), their clinical data and assessment, the study design, outcome measures, neurophysiological assessment if included, details of intervention methods (NIBS), other nonpharmacological treatments, outcomes, and follow-up details.

The clinical outcome assessments in these articles included one or more of the following measures:

- Upper limb function: the American Spinal Injury Association (ASIA) upper extremity motor scale (UEMS), the action research arm test (ARAT), pinch strength, grasp strength, and fine motor performance (nine-hole peg test, Purdue pegboard test, and Minnesota dexterity test).
- Lower limb function: the ASIA lower extremity motor scale (LEMS) for muscle strength. To evaluate gait function, the timed up-and-go test, 10-meter walk test (10MWT: velocity, step length, and cadence), walking index for spinal cord injury (WISCI), and 2-minute treadmill walking.
- Sensory function: ASIA sensory scale, numerical rating scale (NRS), or VAS for neuropathic pain.
- Autonomic function: Heart rate and blood pressure.
- Activities of daily living (ADL).

The neurophysiological measures were:

- Transcranial magnetic stimulation: The amplitude or area under the curve of the motor evoked potential (MEP), recruitment curve (RC), motor threshold (MT), cortical silent period (CSP), intracortical facilitation (ICF), short intracortical facilitation (SICF), and short intracortical inhibition (SICI) to examine changes in the integrity and excitability of the corticospinal tract.
- Electromyography: The amplitude and persistence (%) of the F wave, H-maximum and M-maximum amplitude ratio (Hmax/Mmax), T reflex and withdrawal reflex (nociceptive or flexor withdrawal reflex to study the integrity and excitability of the spinal cord).
- Sensory function: electrical perception threshold to study changes in peripheral sensory function.
- Autonomic function (C and A delta fibers): Sympathetic skin response, heart rate, blood pressure, sphincter, and erectile function.

One study used robotic kinematics to assess the effects of tDCS for upper extremity recovery following SCI. This robotic device provided kinematic measurements for mean and peak speed, duration and displacement of movement for hand and shoulder–elbow components (Cortes et al., 2017).

In some studies, findings were compared with sham stim-
ulation. Sham TMS was applied by using a sham coil (Kuppuswamy et al., 2011), by stimulation of another part of cortex (such as occipital cortex) (Belci et al., 2004), by tilting the angle of the coil to 90° (Nardone et al., 2017) or by placing a coil which is not connected to TMS machine on the scalp and then producing the familiar “clicking” sound of stimulation by discharging a second coil away from the head (Kumru et al., 2010; Nardone et al., 2014). For sham tDCS, the electrical current was slowly ramped up to 1 or 2 mA and then immediately turned slowly off. This mimics the initial tingling sensation of tDCS and is an excellent sham procedure.

The results were organized according to the type of NIBS (TMS or tDCS) and the clinical indications for NIBS, such as effects on motor function (of the upper or lower extremities) and gait or spasticity with or without effects on sensory or autonomic dysfunction.

Results
We found 22 studies of the effects of TMS or tDCS following SCI that met the inclusion criteria: i.e., analyzing the role of NIBS in motor and functional changes in the upper or lower extremities or the changes in spasticity with or without sensory disturbance/dysautonomia after SCI in adult or pediatric patients. Fifteen of the 22 articles were about TMS following SCI and 7 assessed the effects of tDCS (all about motor function).

TMS
Fifteen articles studied the effect of different TMS modalities following SCI: high-frequency rTMS in 8 articles, paired-associated stimulation in 3, and paired-pulse TMS coupled with I-wave rhythmicity (I-wave protocol), QuadroPulse TMS (QPS), iTBS, and spike time-dependent plasticity (STDP) in 1 each (Additional Tables 1 and 2).

Effects on motor function
Upper extremity: Belci et al. (2004) were the first to apply rTMS in patients following SCI. Applying it at 10 Hz with a circular coil over the left motor area of the upper extremity for 5 days in four cervical, incomplete SCI patients, they reported improvement in the total motor and sensory scores and in upper extremity function. Kuppuswamy et al. (2011) used rTMS at 5 Hz and a figure-of-eight coil over the hand motor area for 5 consecutive days without additional physical therapy in nine participants and reported modest functional gains, as measured by ARAT. This increase in the ARAT after rTMS compared with baseline (pre-treatment) was evident at 1 hour, whereas the mean rectified EMG activity was increased in both hands than the PNS-treated hands and was maintained for at least 1 month (Tolmacheva et al., 2017).

Alexeeva and Calancie (2016) applied QuadroPulse TMS to the motor cortex hand/leg area in three SCI patients. Single-day QPS application had no clear effect in the two whose hand function was targeted, whereas it improved the walking speed of the person targeted for walking; the latter was accompanied by increased cortical excitability and reduced spinal excitability. Functional improvement was reported following the 5-day QPS intervention, the effect being even more pronounced after the 5-day combined QPS + exercise sessions (Alexeeva and Calancie, 2016).

Bunday and Perez (2012) applied one session of 100 paired-pulse stimulations of the spike time-dependent plasticity (STDP) protocol for hand function; specifically, TMS was delivered over the hand representation in the motor cortex, and spinal motoneurons were activated antidromically by PNS over the ulnar nerve at the wrist. STDP induced an improvement in manual dexterity measured by the nine-hole peg test and increased the magnitude of force exerted by the index finger, whereas the mean rectified EMG activity was increased in both groups (Bunday and Perez, 2012).

Long et al. (2017) studied the effect of 180 pairs of TMS for ~30 minutes over the hand representation of the motor cortex at an interstimulus interval mimicking the rhythmicity of descending late indirect (I) waves in corticospinal neurons (4.3 ms; I-wave protocol) or at an interstimulus interval between I-waves (3.5 ms; control protocol) on separate days in a randomized order in 15 patients with chronic incomplete cervical SCI and 17 uninjured participants. They reported that the hand motor output and hand dexterity increased in the SCI patients after the I-wave protocol. The MEP size increased, intracortical inhibition decreased, and the F-wave amplitude and persistence increased after the I-wave but not the control protocol (Long et al., 2017).
Lower extremity and gait function: Roy et al. (2010) used 120 PAS stimuli "pairing afferent ascending sensory inputs from the homonymous common peroneal nerve and TMS inputs over TA motor cortex" randomly delivered every 5–6 seconds, at ~0.2 Hz. PAS produced appreciable (>20%) facilitation of the MEP following the intervention in 7 of 13 SCI subjects. The increase in corticospinal tract excitability with PAS was transient (<20 minutes) and tended to be more prevalent in SCI subjects with stronger functional ascending sensory pathways.

Using rTMS at 20 Hz (1,600 pulses), with a double-cone coil over the vertex for 15 days combined with over-ground gait training, Benito et al. (2012) reported significant improvement in motor strength in the lower extremities and in gait velocities in 10 incomplete SCI patients. In another study, Kumru et al. (2016b) applied rTMS at 20 Hz for 20 days just before gait rehabilitation with a Lokomat® (the early phase of gait rehabilitation) in 15 incomplete SCI patients and reported improvement in the motor strength of the lower extremities; this improvement was significantly greater for the group who received real rTMS than the sham group. In that study, there was gait improvement (10MWT) in 71.4% of the patients after real rTMS and in 40% of the patients after sham rTMS, but there was not a significant difference between groups (Kumru et al., 2016b).

Spasticity

Spasticity is one of the most incapacitating conditions of upper motor neuron syndrome. It is usually defined as a velocity-dependent increase in muscle tone and presents with exaggerated tendon jerks, clonus, and spasms, which result from hyper-excitability of the stretch reflex (Elbasiouny et al., 2010). The effects of NIBS have been reviewed on spasticity in different neurological disorders (Gunduz et al., 2014). In SCI, we found three articles studying the effects of different TMS protocols on spasticity as a primary outcome (Kumru et al., 2010; Nardone et al., 2014, 2017). Other studies examined spasticity together with motor scores or gait (Benito et al., 2012; Kumru et al., 2016b). After using rTMS at 20 Hz for 5 days in 14 incomplete SCI patients, Kumru et al. (2010) reported a significant improvement in spasticity measured using clinical scales (MAS, SCI-SET, SCAT, and MPSFS) and a VAS; however, neurophysiological studies did not show significant changes (maximum H wave/M wave amplitude, T wave, withdrawal reflexes). The improvement in spasticity was maintained for 1 week as measured by the SCI-SET (Kumru et al., 2010). The same group also reported an improvement in spasticity measured using the MAS in the lower extremities applying rTMS at 20 Hz for 3 weeks in 10 patients (Benito et al., 2012). Nevertheless, the same group failed to show significant changes in spasticity in the early phase of rehabilitation (Kumru et al., 2016b). The authors explained their result based on the relatively short time span since SCI (changing from the hypotonic phase to the spastic phase) and the fact that the spasticity was mild or non-existent in most of the patients in that study (Kumru et al., 2016b). Nardone et al. (2014) used 20-Hz rTMS over the motor cortex for 5 days and reported an improvement in the spasticity of the lower extremity measured using both MAS and SCAT accompanied by a modification in reciprocal inhibition in 20 SCI patients. In another study, Nardone et al. (2017) applied iTBS over the leg motor cortex after 10 daily sessions in 10 incomplete SCI patients and reported an improvement in spasticity in the lower extremities as measured by the MAS and SCAT; in the neurophysiological assessment, the MEP amplitude was increased and the H/M ratio was reduced. Alexeeva and Calancie (2016) performed QPS for 5-day trials with a single-day QPS protocol in three groups: (1) QPS only; (2) exercise only (targeting hand or leg function); and (3) QPS combined with exercise. They reported no changes in spasticity following the 5-day QPS intervention.

Adverse effects of rTMS

Generally, TMS is considered safe. Adverse effects in the reviewed articles included pain or redness at the application site, discomfort because of sitting for long periods, feelings of drowsiness, musculoskeletal pain (Shulga et al., 2016; Tolmachева et al., 2017), and facial muscle twitches (Kumru et al., 2010, 2016b). There were no adverse effects associated with QPS (Alexeeva and Calancie, 2016).

tDCS following spinal cord injury

Seven articles examined tDCS following SCI: four studies evaluated the effects of tDCS on upper limb function (Gomes-Osman and Field-Fote, 2015b; Murray et al., 2015; Yozbatıran et al., 2016; Cortes et al., 2017) and three examined lower extremity function and gait (Kumru et al., 2016a; Raithatha et al., 2016; Yamaguchi et al., 2016). Additional Tables 3 and 4 show summary of studies using tDCS.

Upper extremity function

In a single session using 2 mA anodal tDCS or transcutaneous electrical nerve stimulation (TENS) for 30 minutes in 24 patients, tDCS was associated with moderate improvement in the nine-hole peg test, pinch force, and visuomotor tracking performance, suggesting potential for improvement in hand-related function: however, it was not superior to TENS (Gomes-Osman and Field-Fote, 2015b). Murray et al. (2015) administered three single-session exposures of 20 minutes of 1 mA anodal tDCS, 2 mA anodal tDCS, or sham stimulation over the hand motor cortex in nine chronic SCI patients with motor dysfunction in the wrist extensor muscles. For sham stimulation, the device was turned off after the ramp procedure. The electrode positioning comprised an anode over the extensor carpi radialis muscle representation in the left primary motor cortex and a cathode over the right supraorbital area. The stimulations were delivered at rest with at least 1 week between sessions (Murray et al., 2015). tDCS transiently raised the corticospinal excitability to the affected muscles as measured with the MEP amplitude after 2 mA stimulation, and sensory perception improved with both the 1 and 2 mA stimulations (Murray et al., 2015). Using one session of 1 mA, 2 mA, or sham anodal tDCS over the hand primary motor cortex, Cortes et al. (2017) observed a significant improvement in grasp (peak ratio speed) with 2 mA in 11 patients with chronic incomplete SCI measured by robotic kinematics, which was not observed using the functional clinical scales. Yozbatıran et al. (2016) performed 10 sessions of anodal or sham tDCS combined with robot-assisted arm training over the dominant hand motor cortex in nine incomplete cervical SCI patients. The active group showed better arm and hand performance post-treatment and at the 2-month follow-up.
Adverse effects of tDCS

There were no adverse effects in most of the studies and, when present, they were limited to a tingling sensation or redness of the skin, sleepiness, trouble concentrating, headache, and neck pain, which were also observed under the sham condition (Yozbatiran et al., 2016).

Conclusions

Of the published studies, eight used high-frequency rTMS, three used PAS, and one each used QPS, iTBS, the STDP protocol, or the I-wave protocol. All studies involved multiple sessions (between 3 and 20); four investigated upper extremity function plus sensory (Belci et al., 2004; Shulga et al., 2016; Tolmacheva et al., 2017) or autonomic function (Kuppuswamy et al., 2011), and three analyzed only upper limb strength and function (Bunday and Perez, 2012; Gomes-Osman and Field-Fote, 2015a; Long et al., 2017). In one study, the authors analyzed gait and upper extremity strength. Three studies reported results for spasticity only (Kumru et al., 2010; Nardone et al., 2014, 2017), whereas four analyzed motor score and gait (one also investigated erectile function, and two also investigated spasticity) (Roy et al., 2010; Benito et al., 2012; Kumru et al., 2016b; Calabrò et al., 2017). The clinical outcome measures in all the studies were accompanied by appropriate electrophysiological investigations.

Studies of tDCS application in spasticity or motor function are more limited than those of TMS application. All studies used anodal tDCS (n = 7); four examined only upper limb muscle strength and function (Gomes-Osman and Field-Fote, 2015b; Murray et al., 2015; Yozbatiran et al., 2016; Cortes et al., 2017), with just 1 tDCS session in three studies and 10 sessions of tDCS in one study. Their results suggested that tDCS could improve upper extremity motor function. Three studies analyzed the effects of tDCS (multiple sessions in two and one session in one) on lower extremity motor function and gait (Kumru et al., 2016a; Raithatha et al., 2016; Yamaguchi et al., 2016). Although all studies showed improvement in lower extremity motor function, there was no significant change compared with sham stimulation in one study involving 20 sessions (Kumru et al., 2016a).

The studies of noninvasive brain stimulation investigating its effect on pain or positive sensory phenomena were not included in this review. The studies investigating its effects on negative sensory phenomena were less in number and were generally investigated in studies assessing other functions. One study of high-frequency rTMS (Belci et al., 2004) and one study of anodal tDCS (Murray et al., 2015) reported sensory improvement.

Most studies of rTMS were sham-controlled, double- or single-blind studies. The major limitation of these studies was the small number of patients included (from 2 to 34 patients with SCI, most frequently 5 to 15). Of the tDCS studies, only three were double-blind (Kumru et al., 2016a; Raithatha et al., 2016; Yozbatiran et al., 2016), whereas six were sham-controlled studies. The significant changes in MEP amplitudes, the cortical silent period, a reduction in H/M amplitude, the increased magnitude of disynaptic reciprocal inhibition and long-loop presynaptic inhibition, and the improved lower extremity motor function provide evidence of the effect on cortical and subcortical structures.

The time lapse since SCI is the other important point during application of NIBS. Most of the studies of NIBS were done in the chronic phase of SCI with significant changes (Additional Tables 1 and 3), although there are studies performed in the acute-subacute phase with positive response to real rTMS (Kumru et al., 2010, 2016b). On the other hand, anodal tDCS was not superior to sham stimulation in patients with acute-subacute SCI (Kumru et al., 2016a). Much of the animal work has been performed soon after the injury, although some of the studies have waited up to 8 weeks and still found useful changes (Carmel et al., 2010, 2014). So in fact there may not be an optimal “window” of time for NIBS to promote recovery following SCI.

In conclusion, NIBS techniques, such as TMS and tDCS, are safe and easy to perform with infrequent mild side effects. The time elapsed since the SCI; the level, severity, and etiology of the SCI; the characteristics of rTMS or tDCS; and the area where they were applied and the outcome measures used may have contributed to the differences in results of different groups.

Author contributions: HK devised the study context and designed the study. AG and HK conducted the literature review, selected the papers, performed the analysis, and interpreted the data. AG, HK, and JV wrote the manuscript. All authors revised the manuscript for intellectual content.

Conflicts of interest: None declared.

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Additional file:
Additional Table 1: Demographic and clinical features and outcome mea-
sures in studies using various TMS methods.

Additional Table 2: Application protocols and outcomes in studies using various TMS methods.

Additional Table 3: Demographic and clinical features and outcome measures in studies using tDCS.

Additional Table 4: Application protocols and outcomes in studies using tDCS.

References


