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INVITED REVIEW

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

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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.

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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 given in blocks at 200-ms intervals (5 Hz) (Rossini et al., 2015). Intermittent TBS (iTBS) involves the delivery of pulses for 2 seconds followed by an 8-second rest for a total of about 3 minutes; this is hypothesized to induce long-term potentiation (LTP) (Rossini et al., 2015), whereas continuous TBS pulses for 40 seconds (continuous TBS, cTBS) generates an effect similar to long-term depression (LTD). TBS has the advantage over rTMS in that the same number of stimuli can be applied

in a much shorter period of time. QuadroPulse stimulation (rTMS(QP) or commonly known as QPS) uses a high-frequency burst of 4 stimuli repeated every 5 seconds and, depending on the interval between pulses, can increase or decrease corticospinal excitability (Hamada et al., 2007; Hamada and Ugawa, 2010; Nakamura et al., 2011). The I-wave protocol involves repetitive paired-pulse stimulation of the motor cortex at an interpulse interval of 1.5 ms in order to mimic the rhythmicity of the indirect (I) waves in corticospinal neurons (Long et al., 2017). It has been hypothesized that the I-wave protocol targets intracortical GABAergic inputs and thereby increases excitability (Long et al., 2017). Paired-associative stimulation (PAS) involves repeated pairing of a peripheral nerve stimulus with TMS over the motor cortex. If the afferent input reaches the motor cortex after the TMS pulse is applied (ISI = 25 ms: PAS25) then it can increase corticospinal excitability for the next 30min. If the afferent input arrives before the TMS pulse (*e.g.*, ISI = 10–15 ms: PAS10), then corticospinal excitability is reduced (Rossini et al., 2015). The effects of PAS are thought to be equivalent to spike timing dependent plasticity (STDP) studied in animal experiments. A modified version of this approach involves timing TMS and peripheral stimulation to evoke volleys that arrive almost simultaneously at the spinal motoneurone rather than the cortex. In this instance the intention is to increase the excitability of corticomotoneuronal synapses in spinal cord (Bunday and Perez, 2012).

tDCS delivers a continuous current (1–2 mA) over the scalp, through a paired anode and cathode (Nitsche et al., 2003, 2004). Unlike TMS, tDCS does not produce action potentials in cortical neurons: all it can do it modify the discharge rate of already active neurons. When placed over the primary motor cortex, anodal tDCS is thought to increase firing by hyperpolarizing the dendrites and depolarizing the cell body of vertically oriented pyramidal neurons by < 1 mV. Cathodal tDCS has the opposite effect. It is postulated that long term effects on corticospinal excitability that follow 10 minutes or more tDCS are a consequence of the up- or downregulation of membrane receptors (Nitsche et al., 2003, 2004) that lead to LTP- or LTD-like changes in cortical synapses. Stimulation periods longer than 10 minutes may produce effects that last for hours. In addition to the polarity of stimulation, effects are modulated by the duration, intensity and area of stimulation as well as the placement of the electrodes (Lefaucheur et al., 2017).

In this review paper, we have examined the potential of NIBS to promote motor and functional recovery and to improve spasticity following complete or incomplete spinal cord injury (cSCI or iSCI).

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.
- Spasticity evaluation: the Ashworth (AS) or modified Ashworth scale (MAS), spinal cord injury spasticity evaluation tool (SCI-SET), Spinal Cord Assessment Tool for Spastic Reflexes (SCAT), modified Penn spasm frequency scale (MPSFS), and visual analogue scale (VAS) for spasticity.
- 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 (H_{max}/M_{max}), 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 90º (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-associative 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, but it was not sustained at 72 and 120 hours. Gomes-Osman and Field-Fote (Gomes-Osman and Field-Fote, 2015a) applied rTMS with a figure-of-eight-coil over the motor cortex of the weakest hand combined with hand training and reported larger effect sizes in both the trained and untrained hands on tests of functional hand use and grasp strength in the trained hand. They compared the effects of three sessions of 10-Hz rTMS with those of three sessions of sham rTMS in 11 participants with chronic tetraplegia, asking the patients to perform a skilled motor task in the 30-second intervals between the rTMS trains. After using rTMS at 20 Hz for 20 days with a double-cone coil over the vertex in eight incomplete cervical SCI patients, Kumru et al. (2016b) reported significant improvement in the UEMS in comparison with the sham group.

Two studies assessed the effects of PAS on hand motor functions after SCI. Shulga et al. (2016) studied the effects of a combination of peripheral nerve stimulation (PNS) (median radial, ulnar, or peroneal nerve) and TMS of the corresponding areas in two SCI patients with motor-incomplete chronic SCI (one para- and one tetraplegic) in an unblinded proof-of-principle demonstration. The patients received PAS for three sessions/week for 20–24 weeks combined with rehabilitation. The paraplegic patient had an improvement in the lower limbs, and the tetraplegic patient regained grasping ability, which was maintained for at least 1 month after the last stimulation session (Shulga et al., 2016). MEP amplitudes recorded over the tibialis anterior, gastrocnemius, abductor pollicis brevis, and abductor digiti minimi muscles were higher 1 hour after the session. Tolmacheva et al. (2017) performed 16 sessions of PAS (a combination of TMS with PNS) on the hands of five patients with chronic traumatic tetraplegia and compared the results of this approach with those of long-term PNS. PAS was given to one hand and PNS combined with sham TMS was given to the other hand of the same patient. There was an improvement in the PAS-treated hand measured using Daniels and Worthingham's Muscle Test (0–5 scale) after the last stimulation session. The improvement was significantly higher in the PAS-treated 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 hyperexcitability 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; Tolmacheva 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; Yozbatiran 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 1mA, 2mA, or sham anodal tDCS over the hand primary motor cortex, Cortes et al. (2017) observed a significant improvement in grasp (peak speed ratio) 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

compared with the sham group.

Lower extremity and gait function

Three articles investigated the effects of tDCS on lower extremity function and gait. Kumru et al. (2016a) applied 20 sessions of anodal tDCS at 2 mA over the vertex during gait rehabilitation with the Lokomat® in 12 incomplete SCI patients and performed sham tDCS in another 12 patients. The combination of 20 daily sessions of tDCS to the leg motor cortex and Lokomat® gait training resulted in an improvement in both the LEMS and gait; however, this did not differ between the patients treated with anodal or sham tDCS (Kumru et al., 2016a). In comparison, Raithatha et al. (2016) reported that anodal tDCS over the vertex during gait training with a robotic gait orthosis improved the lower extremity motor score, gait, and imbalance after 36 sessions. Yamaguchi et al. (2016) combined 1 mA anodal tDCS over the motor cortex of the tibialis anterior muscle with patterned electrical stimulation (PES; stimulating the common peroneal nerve with a train of ten 100-Hz pulses every 2 seconds for 20 minutes) in a single-masked, sham-controlled, crossover study. Simultaneous application of anodal tDCS with Patterned Electrical Stimulation significantly increased the changes in disynaptic reciprocal inhibition and long-latency presynaptic inhibition in both the healthy and SCI groups. Anodal tDCS with PES significantly increased the number of ankle movements (Yamaguchi et al., 2016).

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 these 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.

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Peer review: *Externally peer reviewed.*

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.

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Additional Table 1 Demographic and clinical features and outcome measures in studies using various TMS methods.

Author	Degree and level of SCI	*n*	Age (year)	Duration (year)	Non-pharmacological treatments	Outcome measures
Upper limb motor strength and function						
Belci et al. (2004)	ASIA-D/C_5	4	26–54	1.5–8	NA	ASIA sensory and motor scale, electrical perception threshold; CSP
Kuppuswamy et al. (2011)	ASIA-A, B, C, D/$C_{5–8}$	15	26–69	3–28	NA	Fine motor performance, grasp, grip, pinch strength, electrical perception threshold; BP, heart rate, SSR, MEP, CSP
Shulga et al. (2016)	ASIA-C/C_3-L_1	2	31-53	2	Conventional RHB	Imagination of movement, ASIA sensory and motor scale, MAS, EMG activation, MEP amplitude
Tolmacheva et al. (2017)	ASIA-A, B, C/$C_{3–7}$	5	28–54 38–68	1–6.5	-Mental concentration exercise -Sham side received peripheral stimulation	Daniels and Worthingham's Muscle Testing, NRS for pain, ADL, MAS, autonomic function, MEP, volume location, F-waves
Bunday and Perez (2012)	Incomplete/ $C_{4–8}$ Healthy subjects	19 14	47.8 ± 12.5 39.4 ± 17.8	≥ 1	NA	Nine hole peg test, corticospinal transmission by TMS, TES and C-M stimulation, F waves, motor force, EMG activation
Gomes-Osman and Field-Fote (2015)	ASIA C, D/tetraplegia Healthy subjects	13 10	18–65 18–65	6.6 ± 8.2	Repetitive task practice	Fine motor performance, pinch and grasp strength, hand function test, MT, MEP RC
Long et al. (2017)	ASIA C, D/$C_{2–7}$ Healthy subject	15 17	19–68	2–14	NA	Motor force, nine hole peg test, EMG activation, SICF, SICI, F-wave amplitude, F-wave persistence
Upper limb motor strength and function and gait						
Alexeeva and Calancia (2016)	ASIA B, C, D/$C_{5–7}$	3	26–52	0.75–3	RHB for upper and lower limb	Purdue pegboard and Minnesota dexterity tests, 2-minute treadmill walking, TUG, EMG activation, MEP amplitude, rMT, CSP, ICF, SICI, H and T reflexes
Lower limb motor strength and gait						
Roy et al. (2010)	ASIA C, D/C_3–L_3 Healthy subjects	22 16	20–69	1–35	Gait RHB in locomotor	Motor score, EMG activation, MEP RC
Benito et al. (2012)*	ASIA D/C_4–T_{12}	17	18–60	0.4–1	Over-ground gait RHB	Motor score, MAS, ten-meter walking, step length and cadence, TUG, WISCI II
Calabro et al. (2017)	ASIA C/T_{10}	1	31	1.5	Gait RHB in locomotor	Motor score, AIS, kinetic measurements, rMT, MEP amplitude, CCT, MUNE, erectile function
Kumru et al. (2016)*	ASIA C, D/C_3–T_{11}	34	19–69	1–6 months	Gait RHB in locomotor	MAS, upper and lower extremity motor score, 10MWT, WISCI II
Spasticity						
Kumru et al. (2010)*	ASIA C, D/C_4–T_{12}	15	15–68	0.17–1.5	Conventional RHB	MAS, VAS for self-evaluation for spasms, stiffness, and/or clonus, MPSFS, SCAT, SCI-SET, H and T reflexes of soleus muscle, withdrawal reflex
Nardone et al. (2014)	ASIA C, D/$C_{6–10}$ Healthy subjects	9	28–68	4–17	NA	Reciprocal inhibition, MAS, SCI-SET
Nardone et al. (2017)	ASIA-C, D/C_5–T_8	10	24–65	3–17	NA	MAS, SCAT, MEP, H/M amplitude

∗Also included non-traumatic SCI. ADL: Activity of daily living; AIS: American Spinal Injury Association Impairment Scale; ASIA: American Spinal Injury Association; BP: blood pressure; C: cervical; C-M: cervico-medullar; TUG: time up and go; 10MWT: 10 meter walking test; WISCI II: Walking Index for SCI; CSP: cortical silent period; EMG: electromyography; ICF: intracortical facilitaton; L: lumbar; NRS: numerical rating scale; MAS: modified Ashworth scale; MEP: motor evoked potential; MPSFS: Modified Penn Spasm Frequency Scale; MT: motor threshold; CCT: central conduction time; MUNE: Motor Unit Number Estimation; NA: Not available ; rMT: resting motor threshold; RC: recovery curve; RHB: rehabilitation; SCAT: Spinal Cord Assessment Tool for Spasticity; SCI: spinal cord injury; SCI-SET: Spinal Cord Injury Spasticity Evaluation Tool; SICF: short intracortical facilitation; SICI: short intracortical inhibition; SSR: sympathetic skin response; T: thoracic; TES: transcranial electrical stimulation; TMS: transcranial magnetic stimulation; VAS: visual analogue scale

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

Author	Protocol	Intensity	Frequency (Hz)	No. of sessions	Location	Outcome
Upper limb motor strength and function						
Belci et al. (2004)	Active Sham	90% MT	10 rTMS (0.1 doublets)	5	Vertex (circular coil)	Reduction in CSP, motor and sensory improvement, improvement in nine hole pegboard
Kupuswamy et al. (2011)	Active Sham	80% aMT	5 rTMS	5	Hand M1	Improvement of Action Research Arm Test, increase in motor threshold
Shulga et al. (2016)	Active Only PNS	100% MSO	PAS	3 times/week, 21 or 24 weeks	Median, radial, ulnar PNS + corresponding M1 or Peroneal, tibial PNS + corresponding M1	Improvement of imagination and performance of motor function, MEP amplitude, EMG activation
Tolmacheva et al. (2017)	Active Sham	100% MSO	PAS	16	IL hand M1 CL hand M1	Improvement of motor scores and of ADL
Bunday and Perez (2012)	STDP Reverse Control	100% MSO	TMS	1 of 100 pairs	Hand $M1^{+}$ stimulation of cervical roots and ulnar nerve	Improvement of motor output
Gomes-Osman and Field-Fote (2015)	Active Sham	80% biceps rMT	10 rTMS	3	Hand M1	Improvement of hand function test/grasp strength; no change in electrophysiology
Long et al. (2017)	I-wave Control	120–90% rMT	Paired-pulse TMS	1 of 180 pairs	Hand M1	Improvement of motor function, increase of F wave amplitude-persistence and EMG activation, reduction of SICI
Upper limb motor strength and function and gait						
Alexeeva and Calancia (2016)	QPS alone, physiotherapy alone, QPS + physiotherapy	80–90% MT	QPS	5-days	Hand or leg M1	Single day: increase in MEP amplitude, walking speed, MEP amplitude Five-day largest improvement in pin placement or walking speed with QPS + physiotherapy
Lower limb motor strength and gait						
Roy et al. (2010)	Active Sham	65%	PAS	1	Leg $M1^{+}$ tibial/ peroneal PNS	MEP facilitation
Benito et al. (2012)	Active Sham	90%	20 rTMS	15	Leg M1	Improvement of motor score, MAS, TUG, gait velocity, step length and cadence
Calabro et al. (2017)	Active	90% rMT	10 rTMS	9	Cz	Amelioration of ASIA motor score in lower extremities, reduction of hip and knee stiffness, increase in MEP amplitude, MUNE, and gait speed, improvement of erectile function
Kumru et al. (2016)	Acrive Sham	90% rMT of lowest rMT of UEmuscle	20 rTMS	20	Leg M1	Improvement of motor score in upper and lower extremities, more patients could realize 10MWT, no changes in spasticity
For spasticity						
Kumru et al. (2010)	Active Sham	90% rMT of biceps brachii	20 rTMS	5	Leg M1	Improvement of spasticity, no change in H_{max}/M_{max}, Twave, withdrawal reflexes
Nardone et al. (2014)	Active Sham	90% rMT of biceps brachii	20 rTMS	5	Arm M1	Improvement of spasticity, modification of reciprocal inhibition
Nardone et al. (2017)	Active Sham	80%aMT	iTBS	10	Leg M1 or Cz	Improvement in spasticity, increase in MEP amplitude, reduction in H/M amplitude

ADL: Activity of daily living; aMT: active motor threshold; ASIA: American Spinal Injury Association; CL: contralateral; CSP: cortical silent period; EMG: electromyography; IL: ipsilateral; iTBS: intermittent theta burst stimulation; M1: primary motor cortex; MAS: modified Ashworth scale; MEP: motor evoked potential; MT: motor threshold; MSO: maximum stimulator output; MUNE: Motor Unit Number Estimation; PAS: paired associative stimulation; PNS: peripheral nerve stimulation; PPC: posterior parietal cortex; QPS: quadropulse stimulation; rMT: resting motor threshold; rTMS: repetitive TMS; SICI: short intracortical inhibition; STDP: spike timing-dependent plasticity; TMS: transcranial magnetic stimulation; 10MWT: 10 meter walking test.

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

Author	Degree and level of SCI	*n*	Age (year)	Time lapse since SCI (year)	Non pharmacological treatments during tDCS	Outcome measures
Upper limb muscle strength and function						
Gomes-Osman and Field-Fote (2014)	ASIA C, D/$C_{4–7}$	24	25–59	1–28	Functional task practice	Nine-hole Peg Test, pinch force, visuomotor tracking, MEP
Murray et al. (2015)	ASIA B, C/$C_{4–6}$	9	20–56	0.75–10.5	NA	Muscle strength, MEP, EMG activation, sensory threshold, F-wave persistence
Yozbatıran et al. (2016)	ASIA C, D/$C_{3–7}$	8	36–62	0.7–20	Robot-assisted arm training	Upper Extremity Motor Score, JTHFT, AOU-MAL, ASIA MAS
Cortes et al. (2017)	ASIA B, C, D/$C_{5–7}$	11	21–63	2–22	NA	ASIA upper extremity motor scale, MAS, SCIM, quadriplegia index of function-short form, hand robot evaluation
Lower limb muscle strength and gait improvement						
Raithatha et al. (2016)	ASIA B, C, D/C_5–L_1	9 anodal 6 sham	24–67	1–39	RHB with robot-assisted gait orthosis	LEMS, 6-MWT, 10MWT, TUG, BBS, SCIM-III
Kumru et al. (2016)	ASIA C, D/C_1–T_{12}	12 anodal 12 sham	21–71	2–8 months	During Lokomat® gait training	LEMS, 10MWT, WISCI
Yamaguchi et al. (2016)	ASIA C, D/C_1–T_{11} Healthy subjects	11 10	28–64	0.5–12	Simultaneous patterned electrical stimulation	Ankle movement, reciprocal inhibition and presynaptic inhibition of soleus H-reflex, ankle movement

10MWT: 10-meter walk test; 6MWT: 6-meter walk test; AOU-MAL: Amount of Use Scale of Motor Activity Log; ASIA: American Spinal Injury Association; BBS: Berg Balance Scale; C: cervical; EMG: electromyography; JTHFT: Jebson Taylor Hand Function Test; L: lumbar; LEMS: lower extremity motor score; MAS: modified Ashworth scale; MEP: motor evoked potential; NA: not available; RHB: rehabilitation; SCIM-III: Spinal Cord Independence Measure-III; SCI: spinal cord injury; SCIM: spinal cord independence measure; T: thoracic; tDCS: transcranial direct current stimulation; TUG: Timed Up and Go Test; WISCI: walking index for spinal cord injury.

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

Author	Type of stimulation	Protocol	Results
Upper limb muscle strength and function			
Gomes-Osman and Field-Fote (2014)	Anodal tDCS 1 mA Vibration TENS	Single session Hand M1 30 minutes	Moderate improvement of nine-hole Peg Test, pinch force, visuomotor tracking task
Murray et al. (2015)	Anodal tDCS 1 mA Anodal tDCS 2 mA Sham	Single session Arm M1 20 minutes	Increase in MEP amplitude, reduction in sensory threshold
Yozbatıran et al. (2016)	Anodal tDCS 2 mA Sham	10 sessions Hand M1 20 minutes	Improvement in hand and arm functions
Cortes et al. (2017)	Anodal tDCS 1 mA Anodal tDCS 2 mA Sham	Single session Hand M1 20 minutes	Significant improvement in grasp function by 2 mA
Lower limb muscle strength and gait improvement			
Raithatha et al. (2016)	Anodal tDCS 2 mA, Sham	36 sessions Leg M1 20 minutes	Significant improvement in LEMS, gait and balance
Kumru et al. (2016)	Anodal tDCS 2 mA, Sham	20 sessions Vertex 20 minutes	Improvement in LEMS in active and sham group without differences between both groups, no changes in gait scales
Yamaguchi et al. (2016)	Anodal tDCS 1 mA a single-masked, sham-controlled crossover study	Single session Leg M1 20 minutes	Improvement in ankle movement, increased magnitude of disynaptic reciprocal inhibition and long-loop presynaptic inhibition, and improved LEMS

LEMS: Lower extremity motor strength; M1: primary motor cortex; MEP: motor evoked potential; tDCS: transcranial direct current stimulation; TENS: transcutaneous electrical nerve stimulation.