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Non-invasive Brain Stimulation to Characterize and Alter Motor Function after Spinal Cord Injury

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Abstract

Advances in transcranial magnetic stimulation (TMS) now permit the precise assessment of circuitry in human motor cortices that contribute to movement. Further, TMS approaches are used to promote neural plasticity within cortical and spinal circuitry in an attempt to create short-term changes in motor control. This review is focused on the application of TMS techniques in the study of characterizing and promoting neural plasticity within individuals presenting with chronic spinal cord injury. We review TMS research performed in individuals with SCI and consider new opportunities for the use of TMS approaches to promote neural plasticity for improving motor recovery.

Keywords: spinal cord injury, motor recovery, noninvasive brain stimulation, transcranial magnetic stimulation, neural plasticity

1. Introduction

Noninvasive brain stimulation (NIBS) approaches are used to both characterize and modify neural activity within the targeted cortices and the spinal cord. These approaches are, therefore, well-suited for understanding and attempting to improve functional recovery following spinal cord injury. There is, however, a gap in our present understanding of how the cortical physiology is altered in individuals with spinal cord injury (SCI). In this review, we focus on the characterization of motor cortical circuitry in individuals with SCI using transcranial magnetic stimulation (TMS). This basic knowledge is essential to developing therapies that aim to induce long-term changes in neural circuits that participate in motor control. NIBS ap-

proaches are also capable of inducing short-term plasticity within motor cortical neural circuits and may be combined with other techniques to promote greater functional changes in individuals with SCI. Therefore, the second goal of this review is to survey the literature that has utilized NIBS approaches for promoting neural plasticity within the motor system in individuals with SCI. We subsequently explore new opportunities for the use of NIBS to characterize and promote neural plasticity in SCI for improving motor recovery.

2. Noninvasive brain stimulation to characterize motor function

NIBS provides an opportunity to assess the neural circuitry within motor cortical areas as well as the excitatory and inhibitory influences on neural output to specific muscles. These circuits may originate within the motor cortex (intracortical) and/or operate between cortical areas (intercortical) or hemispheres (interhemispheric). Following SCI, the excitability of the motor cortex and the corresponding cortical circuits may be altered, and these changes may be, in part, related to the functional reorganization of the central nervous system. TMS techniques offer the opportunity to characterize alterations in cortical circuits following SCI and are described following. Importantly, these techniques are ideal for monitoring changes that accompany motor recovery in SCI populations.

2.1. Motor-evoked potentials (MEPs)

TMS delivered over the motor cortex trans-synaptically activates corticospinal neurons that ultimately give rise to a motor-evoked potential (MEP) recorded in the target muscle. The amplitude of the MEP represents the overall corticospinal excitability including contributions from the upper and lower motorneurons and the functional integrity of the corticospinal path [1]. The MEP amplitude may be modulated by factors such as action planning [2, 3], pharmaceuticals [4], or neuromuscular diseases [5–7]. The evaluation of MEP amplitude is a commonly used method to quantify changes in excitability within the descending motor pathways following experimental manipulation [8] or during the process of recovery [9]. The MEP latency provides an additional source of neurophysiological information and represents the conduction time for descending signals originating within the motor cortex to travel to the muscle effector, a measure that serves a diagnostic purpose for a number of disease states [10].

Following SCI, MEP amplitude and latency are often altered. When using TMS to assess muscles caudal to the spinal lesion level, smaller amplitude and longer latency MEPs are reported [11, 12]. This is thought to be due to the structural damage to descending corticospinal fibers including fewer intact axons and significant demyelination surrounding the lesion [13]. In individuals with SCI, such decrements in MEP amplitude may be lessened by introducing low level active contraction in the muscle of interest [14]. However, voluntary control of a muscle is not necessarily indicative of corticospinal connectivity to that particular muscle since MEPs may be elicited in muscles not under volitional control in individuals with SCI [15].

The origin of MEPs is complex, as pyramidal tract neurons are influenced directly and indirectly (trans-synaptically) in response to cortical stimulation. Additionally, MEPs depend on spinal motorneuron excitability and are influenced by cortical areas outside of motor cortex such as the premotor and supplementary motor areas [8]. As such, the ambiguity in the origin of the MEP creates challenges in its interpretation. Nonetheless, MEP characteristics have a value for assessing motor recovery following SCI such that both MEP amplitude and latency, in the acute stage of injury, predict the recovery of ambulation and hand function [10].

2.2. Motor threshold (MT)

MT is defined as the minimal stimulation intensity that elicits a MEP in a target muscle. MT can be assessed in two ways. Resting motor threshold (RMT) is often obtained by finding the lowest stimulation intensity that produces a MEP of at least 50 µV in 5 out of 10 consecutive trials, while the target muscle is relaxed [16, 17]. Furthermore, motor threshold can be determined while the participant maintains low levels of muscle contraction (i.e., active motor threshold or AMT). AMT is commonly defined as the lowest stimulation intensity to elicit MEPs of at least 200 µV in 5 out of 10 consecutive trials, while the participant maintains a contraction corresponding to 10–15% of their maximum [16]. RMT represents the resting membrane excitability throughout the efferent system at both cortical and spinal levels [18]. During this resting state, spinal motorneurons require a number of descending volleys from the cortex to summate in order to produce a MEP. This requirement for greater corticospinal summation at rest has been speculated to be due to glutamatergic synaptic activity [18]. Pharmacological studies have shown that AMT and RMT depend on the axon membrane excitability, specifically on voltage-gated sodium channel activity [19]. Application of various drugs that block the action of these channels such as carbamazepine and lamotrigine increase the required stimulation intensity to elicit RMT and AMT (see Paulus et al. 2008 for review) [18]. Despite the fact that pharmacological studies have not been able to isolate changes in RMT without a simultaneous change in AMT [18], differences in levels of synaptic excitability have been inferred from studies of MT latency, where RMT is seen to have a longer latency than AMT [20]. By maintaining a small contraction, low levels of synaptic firing are sustained and are thought to be more reliant on levels of excitability at the axonal membrane.[18].

Individuals with SCI may demonstrate increases in RMT and AMT. Davey et al. [11] found that RMT and AMT were higher for muscles below the level of injury whereas muscles innervated by fibers rostral to the injury had thresholds similar to the uninjured control group. Other research has shown that alterations following SCI are more prevalent when examining AMT [21, 22]. Bailey et al. [22] demonstrated increased AMT elicited from the flexor carpi radialis muscle of the forearm in participants with chronic cervical SCI. They suggested that this increase in AMT without a corresponding increase in RMT may be due to abnormalities in regulation of membrane excitability via voltage-gated ion channels. Collectively, the published data suggest that RMT may or may not be altered while AMT is increased in SCI participants. However, it has been established that changes in both RMT and AMT are dependent on the location of the target muscle relative to the level of the lesion. Further,

changes in MT in chronic SCI are likely to differ depending on the severity and location of injury.

2.3. Motor cortical maps

The motor cortex is somatotopically organized in that cortical representations of the muscles are found in relatively predictable locations in the medial–lateral direction [23]. The extent of cortical territory occupied by a given muscle representation is thought to correspond to the amount of dexterity and fine motor control needed by the corresponding muscle such that larger representations exist for small distal muscles of the hand while smaller representations are present for larger proximal muscles of the arm and shoulder [12]. Most cortical muscle representations correspond to effectors of the contralateral limb although some degrees of ipsilateral projections have been found in proximal upper limb muscles in uninjured individuals [24]. Motor cortical maps can be obtained by delivering TMS pulses at suprathreshold intensities using a spatial grid aligned with the precentral gyrus and recording MEPs from target muscles [25]. Motor cortical maps are typically evaluated by quantifying the area, volume, and center of gravity for the representation of each muscle of interest. Map area and volume scale linearly with increasing TMS intensity and are considered a reliable method to evaluate cortical organization [26].

Studies of motor maps following SCI revealed enlarged representations of the most proximally spared muscles that tended to shift into cortical territory corresponding to the muscles below the level of injury [27, 28]. Takeover of de-innervated territory was supported by findings in which the representation of the extensor digitorum communis muscle was shifted antero-laterally (into the hand region) following incomplete cervical SCI [21, 29]. Brouwer and Hopkins-Fosseel [12] quantified motor maps in SCI participants for a variety of contracted upper arm muscles and found that proximal muscles were represented to a greater extent than distal hand muscles, and there was an extensive overlap of different muscle representations when compared to uninjured participants. This overlap may be beneficial for organization as the neurons projecting to single muscles are not focally distributed and may act to minimize complete functional losses following neurological injury. Cortical reorganization following SCI occurs rapidly as evident by the changes in the shape and location of biceps brachii motor cortical maps only 6–17 days following SCI [29]. More recently, a study using neuroimaging techniques demonstrated that representations of the tongue were significantly shifted in their location within motor cortex in participants with cervical SCI compared to uninjured participants [30]. Collectively, the motor cortical maps indicate that the reorganization of motor cortex somatotopy takes place following SCI, suggesting that plasticity may compensate for the loss of neuronal communication between the cortex and the muscles of the body. Although the mechanisms for such reorganization are unknown in humans, it may be speculated that changes in cortical organization are shaped through GABA mediated lateral inhibitory circuits [31].

A number of practical considerations are important for cortical mapping studies using TMS. Mapping protocols require many grid points with approximately 3–10 pulses delivered to each point to capture cortical organization with appropriate resolution. This may require a number

of hours to generate a motor map if a large number of points are used [26]. Furthermore, heightened motor thresholds commonly accompany SCI, requiring higher stimulation intensities to elicit MEPs, and this may impact the comfort of the participant and increase the likelihood of coil heating.

2.4. Short-interval intracortical inhibition (SICI)

SICI is an inhibitory circuit within the motor cortex that is comprised of low-threshold GABAergic interneurons [18] and can be evaluated using paired-pulse TMS. By delivering an initial subthreshold conditioning stimulus (CS) approximately 1–5 ms prior to a suprathreshold test stimulus (TS) to the motor cortex, the resulting MEP is reduced when compared to MEPs produced when the TS is applied alone [32]. The subthreshold CS is typically set at an intensity of 70–90% of AMT, showing that the MEP modulation is of cortical origin as no descending volleys to the muscles are produced at these intensities [32]. The mechanism of inhibition involves presynaptic inhibition as inhibitory postsynaptic potentials are generated on neurons upstream of the corticospinal output neurons [18]. $GABA_A$ receptors are implicated in SICI since The delivery of Lorazepam or Diazepam ($GABA_A$ Receptor agonist) reduces SICI [33, 34].

It is well documented that SICI is reduced in individuals with SCI. One case report examined SICI in the relaxed extensor digitorum communis muscle using various interstimulus intervals and a single CS intensity [35]. This method was also used elsewhere in the relaxed first dorsal interosseous muscle [36]. Both cases demonstrated a reduction in SICI when compared to controls [35, 36]. However, the aforementioned studies used a single CS and TS intensity, making interpretation difficult, as the required stimulator output to produce MEPs in SCI participants is typically greater relative to able-bodied individuals. Roy et al. [37] explored SICI in SCI participants by measuring recruitment curves whereby CS intensities were altered from 60 to 110% AMT. They recorded responses from both tibialis anterior in the lower leg and the first dorsal interosseous muscle of the hand during contraction of each muscle. The results indicated a reduction of SICI responses in SCI participants compared to controls, although both retained a U-shaped recruitment curve. Individuals with SCI were seen to have a smaller range of CS intensities eliciting inhibition of the MEP when compared to the recruitment curves of uninjured individuals [37]. Therefore, recruitment characteristics of SICI appear to be unchanged following SCI while the overall amount of inhibition is reduced. The authors speculate that this may be due to spinal inhibitory mechanisms, or to reductions in GABAergic activity following cortical reorganization that occurs with SCI. Mi et al. [38] examined SICI in chronic cervical SCI. Similar to the results found by Roy et al. [37], the authors identified a smaller range of CS intensities to elicit SICI in the flexor carpi radialis muscle of the forearm compared to controls. In this case, significant inhibition of the TS-evoked response was only seen at 90% AMT in SCI compared to the wider range of 70, 80, and 90% AMT in controls [38]. This may reflect the reduced excitability of corticospinal neurons following SCI as the pattern of recruitment is maintained, while the range of inhibition is reduced. Therefore, impairment in GABAergic circuitry mediating SICI in the motor cortex has been established following lesion to the spinal cord.

2.5. Long-interval intracortical inhibition (LICI)

LICI represents intracortical circuitry that acts to modulate MEPs and can be observed via paired-pulse TMS to the motor cortex. The inhibitory pathways involved in LICI can be probed by delivering a suprathreshold CS before a subsequent suprathreshold TS with an interval between 50 and 200 ms to the motor cortex [39, 40]. This produces two MEPs; however, the amplitude of the second MEP is reduced (i.e., inhibited) compared to the MEP evoked by delivery of the single TS pulse. Similar to SICI, the interneuron interactions leading to MEP inhibition are mediated by GABA as seen in pharmacological studies [41, 42]. The longer interstimulus intervals leading to the inhibition are due to $GABA_B$ receptor activity which has been confirmed in studies using $GABA_B$ receptor agonists such as baclofen to increase the inhibitory response [43].

Limited research has examined alterations in LICI after SCI. Barry et al. [43] compared LICI in SCI versus uninjured controls in the resting and active muscle states to examine the effects of $GABA_B$ agonist Baclofen. They examined the first dorsal interosseous muscle of the hand, which showed a decrease in LICI in the active state in the control group as well as in SCI individuals that were taking Baclofen. However, SCI participants not medicated with Baclofen did not show a reduction in LICI during active contraction. This finding suggests abnormal $GABA_B$ receptor activity following SCI as the MEP responses continue to be further inhibited with increasing tonic efferent activity introduced by sustained muscle contraction. Interestingly, this decrease in LICI associated with muscle contraction appears to be rectified by the application of Baclofen, normalizing the inhibitory response in SCI to that of the control group. Another study examined the recruitment of the LICI circuitry in the active muscle state by applying CS intensities at 10% increments from 90 to 130% AMT to capture the pattern of $GABA_B$ mediated response in SCI [38]. An increase in LICI was observed in SCI participants at higher CS intensities (120 and 130% AMT), while the uninjured group did not show any LICI with increasing CS intensity. The authors attributed the increase in inhibition to Baclofen, which as a $GABA_B$ agonist may return LICI circuitry to its normative state.

2.6. Intracortical facilitation (ICF)

ICF can be observed within motor cortex, demonstrating the presence of excitatory circuits impacting the descending corticospinal output. ICF is elicited by delivering a subthreshold TMS pulse over the motor representation of a muscle followed by a suprathreshold TS after an interval of 7–20 ms [32]. This paired-pulse TMS method elicits a net facilitation of the MEP as seen by increased response amplitudes when compared to MEPs evoked from the single TS [33]. Pharmacological approaches reveal that ICF is the net effect of both inhibitory and excitatory contributions. Application of $GABA_A$ receptor agonists such as Diazepam result in decreased ICF, showing an influence of GABAergic inhibition onto corticospinal output neurons [44]. This demonstrates that although ICF is affected by GABAergic activity [44], there is a large excitatory component resulting in net facilitation. Thus, it is speculated that that NMDA receptors play a role in the facilitation observed in ICF [45]. These receptors respond to glutamate when nearby AMPA receptors are active to excite postsynaptic neurons. The role of NMDA receptor activity in ICF is supported by the finding that the application of NMDA

receptor antagonists also causes a decrease in facilitation, implicating their role in the physiology of ICF [45].

A single case study examined ICF in a participant with cervical myelopathy using a CS intensity of 80% RMT and TS intensity of 120% RMT at a number of different interstimulus intervals. ICF was only observed when the interstimulus interval was 10 ms [35]. Further research with larger sample sizes and control groups should examine alterations in ICF in individuals with SCI. Collection of recruitment curves for ICF may provide a more comprehensive view of excitatory mechanisms contributing to corticospinal output following SCI.

2.7. Short and long latency afferent inhibition (SAI/LAI)

SAI demonstrates the influence of a peripherally evoked afferent volley on the MEP and is observed when an electrical stimulus applied to a peripheral nerve is followed by a single suprathreshold TMS pulse to the motor cortex. The temporal interval between the peripheral and cortical stimulation corresponds to the conduction time for the afferent volley to reach the somatosensory cortex. This timing causes the afferent information to arrive shortly before the suprathreshold TMS pulse, which is subsequently inhibited compared to the MEP evoked by the TS pulse delivered alone. This circuit is commonly studied in intrinsic muscles of the hand where the interstimulus interval is roughly 18–21 ms [46, 47]. The exact mechanisms underpinning this pathway remains unclear, although pharmacological intervention using drugs such as Scopolamine (cholinergic antagonist) or Diazepam indicate that SAI is mediated by both cholinergic and GABAergic circuits [48, 49]. LAI is another example of sensory modulation to cortical pathways involved in MEP generation. The method of eliciting LAI is similar to that of SAI with the exception of a longer interstimulus interval of ~100–200 ms [46, 50]. LAI is speculated to modulate corticospinal output by exclusively GABAergic systems, particularly those mediated by $GABA_B$ receptors [49]. The modulation of MEPs induced by sensory input suggests that SAI and LAI provide insight into sensorimotor integration [51].

The literature surrounding afferent regulation of the motor cortex following SCI is minimal. Roy et al. [14] stimulated the common peroneal nerve at the ankle to modify MEPs elicited from tibialis anterior using interstimulus intervals ranging from 30 to 80 ms. Results indicated an inhibition of MEPs from tibialis anterior when the internal between the TS pulse and the peripheral electrical stimulation corresponded to the latency of the afferent volley from the common peroneal nerve. However, this effect was reduced in the SCI group. The decrease in SAI relative to controls is expected in this population, as the transmission of afferent information from the periphery to the cortex is largely dependent on spinal mechanisms that are likely to be affected by damage to the spinal cord. Further, a recent study examined SAI within the flexor carpi radialis muscle in cervical SCI participants and found that, compared to uninjured controls SAI was reduced when the muscle was in the active and resting state [22]. The authors speculated that this impairment in SAI circuitry is due to plasticity effects in the processing and/or transmission of the information within the cortex as well as reductions in afferent transmission to the cortex. Thus, literature regarding sensory modulation of motor output suggests that afferent integration is impaired following SCI.

2.8. Cortical silent period (CSP)

The CSP represents descending inhibitory signals during active contraction of the muscle. When maintaining a constant level of muscle contraction, stimulation of the motor cortex at suprathreshold intensities produces a CSP in the active contralateral muscle. The duration of the CSP may provide some indication of functional ability. For example, the ability to modulate muscle activity following large descending efferent volleys may impact motor tasks involving fine motor control where small, precise movements are required. The CSP is commonly ~200 ms in duration and is impacted by both cortical and spinal factors. Initial inhibition (~50–75 ms) is attributed to the refractory period of efferent fibers within the spinal cord following suprathreshold TMS, while the remaining duration is thought to originate from the cortex [52–54]. This effect is physiologically mediated by multiple GABAergic systems as treatment with pharmaceuticals that reduce synaptic clearance of GABA increase CSP durations [42, 55]. At the receptor level, $GABA_A$ appears to modulate the CSP at lower TMS intensities as benzodiazepines increase the CSP duration [52]. However, at high TMS stimulation intensities, treatment with benzodiazepines shortens the CSP [56]. The latter finding suggests that $GABA_A$ activity suppresses the effects of $GABA_B$ receptors when such inputs are presented to the motor cortex [56].

The CSP duration appears to be altered in SCI. Shimizu et al. [36] investigated the CSP in three individuals with cervical SCI. In all participants, there was no observable CSP in the foot muscle, and in two individuals, the CSP was additionally absent in the hand muscles. The loss of this silent period suggests that there may have been reorganization at the level of the cortex or hyper excitability of the cortex as GABA systems are suppressed [36]. Barry et al. [43] examined the GABA system involved in producing the CSP in intrinsic hand muscles of chronic, incomplete SCI groups that either were or were not taking Baclofen. Baclofen did not alter the CSP in SCI, and all SCI participants displayed a longer CSP duration than age-matched uninjured controls [43]. Another study examined the CSP, while generating motor maps of forearm extensor muscles and reported an inverse relationship between the duration of the CSP and the amount of spinal cord atrophy via inspection of MRI images [21]. Therefore, when increases in the CSP are observed in SCI, it is likely due to intact inhibitory corticospinal projections to the muscle although spinal modulation of inhibitory circuits is impaired.

2.9. Inter-hemispheric inhibition (IHI)

IHI is a circuit that results from the extensive interconnectivity between the two cerebral hemispheres via the corpus callosum. The integrity of this cross-communication can be assessed by paired-pulse TMS over the motor cortices. By providing a suprathreshold CS over the motor representation of a muscle in one hemisphere followed by a suprathreshold TS over the homologous motor representation in the opposite hemisphere, inhibition of the MEP in response to the CS is observed [57, 58]. This suppression occurs at interstimulus intervals of 10 and 40 ms [57]. Modulation of MEP amplitude with IHI is mediated via GABAergic systems as application of $GABA_B$ agonist Baclofen induces an increase in inhibition at both paired-pulse intervals [59].

IHI in SCI has not been studied extensively. One report used an interstimulus interval of 10 ms for probing IHI in cervical SCI and found that there was neither enhancement nor suppression of the MEP when the participants were at rest or maintaining a contraction at a level that corresponded to either 30 or 70% MVC [60]. The authors speculate that the lack of change in IHI may be due to interactions with other circuitry that has been affected by injury such as SICI. One challenge in measuring IHI in the SCI population is that a MEP must be obtained with amplitude that is large enough to observe suppression following modulation from the opposite hemisphere. Decreased muscle responses are well established in SCI, making it difficult to elicit a MEP that is large enough to be modulated by the CS of the opposite hemisphere. Therefore, the IHI protocol may need to be adapted for the SCI population.

2.10. Summary

Please refer to **Table 1** for a summary of the previous findings. Changes in motor cortical excitability and circuitry follow SCI and yield alterations in corticospinal output. The available information regarding changes in cortical circuitry for motor output in SCI is limited, making a comprehensive view of neurophysiological rehabilitation difficult in this population. Thus, further studies should identify and quantify aberrant motor cortical circuits in SCI.

Measure	Source	Classification	Muscle tested	Response
Motor-evoked potentials	Davey et al. [11]	Tetraplegic	Thenar Muscles (APB)	↓Amplitude
	Brouwer and Hopkins-Rosseel [12]	Tetraplegic		↓ Amplitude (no MEP response in most SCI subjects)
	Roy et al. [37]	Para/Tetraplegic	Biceps, Triceps, Deltoid	↓Amplitude
	Roy et al. [14]	Para/Tetraplegic	TA, FDI	↓Amplitude, ↑ MEP duration
	Edwards et al. [15]	Tetraplegic	TA, FDI	=No change in amplitude
			Biceps, ECR, FCR, APB	
Motor threshold	Davey et al. [11]	Tetraplegic	Biceps, Thenar Muscles	No change in biceps (above injury level), ↑ AMT in APB (below injury level)
	Freund et al. [21]	Tetraplegic	EDC	↑ AMT (associated with amount of spinal cord atrophy)
	Bailey et al. [22]	Tetraplegic	FCR	No change in RMT, ↑ AMT
	Saturno et al. [35]	Tetraplegic	EDC	↑ RMT
Motor maps	Levy et al. [27]	Tetraplegic	Biceps, Deltoid	↑ Map area, latency, and amplitude of response inversely related in SCI
	Cohen et al. [28]	Paraplegic	TA, External Oblique	↑ Map area of obliques (above injury), no responses from TA (below injury)
	Freund et al. [21]	Tetraplegic	EDC	
	Streletz et al. [29]	Acute Tetraplegic	Biceps, APB	
	Brouwer and Hopins-Rosseel [12]	Tetraplegic	Biceps, Triceps, Deltoid	CoG shifted posteriorly
	Mikulis et al. [30]	Tetraplegic		

Measure	Source	Classification	Muscle tested	Response
			Wrist extensors, Tongue	↑ Map area of Biceps, Bicep map shifted laterally
				↓ Map volumes, No change in area
				No change in activation volume, peak response site shifted medially for tongue*
Short-interval intracortical inhibition	Saturno et al. [35] Shimizu et al. [36] Roy et al. [37] Mi et al. [38]	Ischemic Myelopathy Tetraplegic Para/Tetraplegic Tetraplegic	EDC FDI, FHB TA, FDI FDI	↓ SICI ↓SICI in FDI ↓ magnitude of active SICI, similar recruitment with increasing CS intensity No change in magnitude, reduced range of intensities showing SICI
Long-interval intracortical inhibition	Barry et al. [43] Mi et al. [38]	Tetraplegic Tetraplegic	FDI FDI	no change with baclofen, ↑ active LICI without baclofen ↑ active LICI
Intracortical facilitation	Saturno et al. [35]	Ischemic Myelopathy	EDC	No change
Short-latency afferent inhibition	Roy et al. [14] Bailey et al. [22]	Tetraplegia Tetraplegia	TA FCR	↓ SAI (absent) ↓ active and resting SAI
Cortical silent period	Shimizu et al. [36] Barry et al. [43] Freund et al. [21]	Tetraplegic Tetraplegic Tetraplegic	FDI, FHB FDI EDC	↓ CSP duration ↑ CSP duration, correlated with spinal atrophy ↑ CSP duration
Interhemispheric inhibition	Bunday and Perez [60]	Tetraplegic	FDI	No change

Table 1. Cortical circuitry in spinal cord injury.

3. NIBS to induce plasticity in individuals with SCI

NIBS provide an opportunity to modulate the neural circuits that are altered following SCI and have the potential to improve motor function. There are several NIBS protocols that have been used to promote plasticity with the two main forms including repetitive TMS (rTMS), and transcranial direct current stimulation (tDCS). RTMS and tDCS protocols are each founded in the principle of homosynaptic plasticity, while TMS and tDCS protocols paired with peripheral nerve stimulation have effects based on spike-timing dependent plasticity (STDP). Homosynaptic plasticity refers to plasticity occurring at a single synapse that is undergoing stimulation [61, 62]. STDP refers to plasticity induced by timing two stimuli, typically a cortical and a peripheral stimulus, to activate both the presynaptic and postsynaptic neurons coinci-

dentally. These protocols are able to produce effects that resemble long-term potentiation (LTP) or long-term depression (LTD) of synaptic connectivity. Typically, activation of the presynaptic neuron prior to the postsynaptic neuron lends to the generation of LTP while LTD occurs when the postsynaptic neuron is activated first [61]. STDP can be timed such that the two stimuli coincide at different levels of the central nervous system to create either spinal or cortical plasticity. We provide an overview of the literature that has used NIBS approaches to promote plasticity in the motor system in individuals with SCI.

3.1. Repetitive TMS (rTMS)

RTMS is thought to induce homosynaptic plasticity within the target cortex. RTMS may increase or decrease cortical activity via alterations in the activity of glutamatergic NMDA receptors [63]. The frequency, intensity, and duration of rTMS determine whether the plasticity effect is LTD or LTP-like [63, 64]. Typically, rTMS delivered over motor cortex at a frequency of <1 Hz results in LTD-like effects while frequencies >5 Hz yield LTP-like effects [63]. In SCI, the primary focus of rTMS is to modulate descending projections and strengthen the intact corticospinal connections.

In a study by Belci et al. [65], rTMS was applied over the motor cortex for five consecutive days using a protocol that included doublets of TMS delivered at a frequency of 10 Hz with each doublet being separated by 10 s for a total 720 stimuli. Following real rTMS, measures of CSP were reduced. Further, motor and sensory function, determined by the assessment of motor and sensory function by the American Spinal Injury Association (ASIA), was improved, as was performance in the timed peg-board task. Further, the sensory perceptual threshold to an electrical stimulus was reduced suggesting alterations within the somatosensory cortex. These measures remained improved for 2 weeks post-intervention while sham rTMS revealed no benefit [65]. Ellaway et al. [66] delivered real versus sham rTMS via 2 s trains of 5 Hz stimulation separated by 8 s for a total of 15 min over the motor cortex in individuals with SCI. The real and sham interventions were performed over 5 consecutive days. Measurements of the ASIA score, active research arm test (ARAT) which includes testing grasp, grip, pinch and gross movement, electrical stimulation perceptual threshold, MEPs, AMT, and CSP were assessed before and following intervention. Results revealed that AMT was increased and ARAT improved following rTMS compared to the sham intervention, without changes in other measures. Another study delivered real versus sham high-frequency (20 Hz) rTMS over 15 consecutive days to assess improvement in lower limb function [67]. Measurements included lower extremities motor score (LEMS), modified Ashworth scale (MAS), walking index for SCI, ten-meter walking test, step length, cadence assessment, and a timed up and go (TUG) test. At the cessation of the rTMS intervention, LEMS improved, MAS score was reduced, gait was altered (i.e., increased velocity, cadence, step length) and an improvement was observed in TUG without changes in the walking index. Effects returned to baseline 2 weeks following the last intervention [67]. Finally, an rTMS protocol consisting of 4 pulse trains (quadropulse) delivered at a frequency of 250–500 Hz with an inter-train interval of 5–6 s (250–360/day) for either 1 or 5 consecutive days (i.e., ~1000–1440 pulses per day) was delivered to individuals with SCI [68]. Hand dexterity, MEPs, and spinal excitability were measured. After

a single session of rTMS, there was no change in hand dexterity although MEPs increased and spinal excitability decreased. Further, after 5 consecutive days of rTMS there was a 10% increase in hand dexterity. These data indicate that rTMS delivered over consecutive days is more effective than single session at promoting motor improvements [68].

3.2. Transcranial direct current stimulation (TDCS)

TDCS is a neuromodulating technique that utilizes homosynaptic plasticity, similar to rTMS. However, unlike rTMS, tDCS does not produce neuronal action potentials since the static field produced by tDCS does not produce the rapid depolarization of neurons [69]. TDCS modifies spontaneous neuronal excitability by either creating tonic depolarization or hyperpolarization [69]. The direction of current flow appears to determine whether the protocol results in LTD or LTP-like effects; anodal tDCS results in neuron depolarization (LTP) while cathodal tDCS results in neuron hyperpolarization (LTD) [69, 70]. There exists one study that has shown evidence for promoting plasticity in individuals with SCI using tDCS. Murray et al. [71] delivered anodal tDCS for 20 min once per week over 3 weeks at varying intensities; 1, 2 mA and sham. Measurements of MEP amplitude, sensory threshold, and muscle strength were performed before and after intervention. MEP amplitude was significantly increased after delivery of 2 mA anodal tDCS but not 1 mA or sham conditions. Sensory threshold was significantly reduced after both 2 and 1 mA but not sham stimulation. No protocol was effective at changing muscle strength [71]. It is evident that the extent of research in tDCS aimed at altering motor function in individuals with SCI is limited. However, early results show that tDCS may be an effective tool to alter corticospinal excitability and improve motor function.

3.3. Paired associative stimulation (PAS) and spinal associative stimulation (SAS)

PAS is a plasticity inducing protocol that utilizes STDP to alter cortical or spinal function. Traditionally, PAS involves timing peripheral electrical nerve stimulation with a TMS pulse over the motor cortex. When these two stimuli are timed to arrive in the cortex at approximately the same time, the protocol is known as PAS and when they are timed to coincide at the level of the spinal cord, the technique is known as spinal associative stimulation (SAS). PAS delivered at an ISI of 25 ms and targeting motor cortex has been effective at increasing MEP amplitude in uninjured individuals [72], while PAS delivered at an ISI of 20 ms has been effective at altering spinal excitability by increasing the amplitude of the spinal H-reflex [73]. There have been three studies performed in SCI where PAS or variations of PAS have been used to induce cortical and/or spinal plasticity promoting functional recovery.
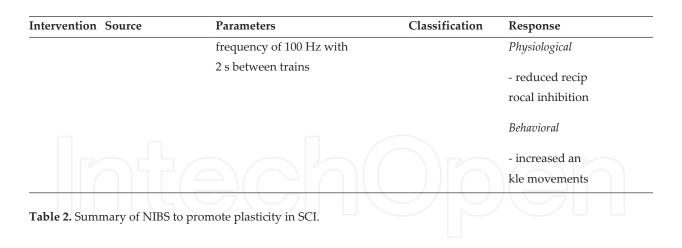
Roy et al. [14] assessed corticospinal excitability in the lower limb before and following PAS delivered at an interval to promote near coincident activation within the motor cortex (i.e., the N20 latency of somatosensory-evoked potential +6 ms). The protocol included 120 pairs of peripheral afferent stimuli and TMS pulses at a frequency of 0.2 Hz [14]. MEPs were measured during tonic 20% contraction (active MEPs) and at rest (resting MEPs). Results indicated significant increases to resting but no change to active MEPs [14]. Bunday and Perez [74] tested the SAS protocol in individuals with SCI and delivered 100 pairs of stimuli at a frequency of 0.1 Hz and timed the ISI such that the TMS efferent volley and the PNS antidromic efferent

volley arrived at the corticospinal-motorneuronal synapse at the C7 spinal level nearly simultaneously. Measurements of MEPs, spinal F-waves, voluntary motor output, and manual dexterity were performed post-intervention. Results showed increases in MEPs, no change in F-waves, and increases to both maximum voluntary EMG/force and a reduction in the time to complete the 9-hole pegboard task [74]. Finally, Yamaguchi et al. [75] paired peripheral nerve stimulation with anodal tDCS. During a 20 min, 1 mA anodal tDCS protocol peripheral electrical stimulation trains consisting of 10 pulses delivered at a frequency of 100 Hz were delivered every 2 s. Measurements of reciprocal inhibition from the tibialis anterior and ankle movement were assessed after stimulation. Results indicate reduced reciprocal inhibition, and increased ankle movements following the combination of peripheral electrical stimulation and anodal tDCS [75].

3.4. Summary

Please refer to **Table 2** for a summary of the previous findings. Collectively these studies reveal promising indications that rTMS, TCDS, and PAS approaches can modulate cortical function leading to short-term improvements in the motor system in individuals with SCI. Although, these results are not always unanimous, (i.e., differential effects on MEPs and CSP), they may relate to the specific protocol parameters as existing studies in SCI have utilized variable stimulation parameters. Further research should determine the most effective protocol at yielding changes to neural physiology and improvements in motor function in individuals with SCI. NIBS combined with other techniques might be a promising new avenue for research for the ultimate goal of creating long-term functional improvements.

Intervention	Source	Parameters	Classification	Response
rTMS	Belci et al. [65] Ellaway et al. [66] Benito et al. [67] Alexeeva et al. [68]	- Doublets of TMS delivered at a frequency of 10 Hz - 10 s between doublets - 360 doublets delivered - 90% RMT intensity - 5 consecutive days - trains of TMS delivered at a frequency of 5 HZ over 2 s - 8 s between trains - 15 min of stimulation - 5 consecutive days - TMS delivered at frequ	Incomplete tetraplegic Incomplete tetraplegic Incomplete para/ tetraplegic Incomplete para /tetraplegic	*Physiological* - improved sensory and motor scores on ASIA *Behavioral* - improved time for pegboard task *Physiological* - improved AMT *Behavioral* - improved active reach arm test *Behavioral* - improved lower

Intervention	Source	Parameters	Classification	Response
		ency of 20 Hz		extremities motor score
		- 15 consecutive days		- improved modified ashworth scale
		- 4 pulses of TMS delivered in trains at a freq uency of 250–500 Hz		- improved gait mechanics
		- 5–6 s between trains		- improved time up and go
		- 250–360 pulses delivered		*Physiological*
		- 1–5 consecutive days		- increased motor-evoked potentials
				- reduced spinal excitability
tDCS	Murray et al. [71]	- Anodal tDCS at 1 or 2 mA	Incomplete tetraplegic	*Physiological*
		- 20 min protocol		- increased motor-evoked potentials
		- once per week for 3 consecutive weeks		- reduced sensory threshold
PAS/SAS	Roy et al. [37] Bunday and Perez [74] Yamaguchi et al. [75]	- ISI of N20 + 6 ms for stimuli to arrive in M1	Incomplete para /tetraplegic Incomplete tetraplegic Incomplete para /tetraplegic	*Physiological* - increased resting motor-evoked potentials
		- 120 pairs of peripheral stimulation and TMS delivered at a frequency of 0.2 Hz		*Physiological* - increased motor-evoked potentials
		- ISI for stimuli to arrive at the C7 spinal level		- increased maximum voluntary EMG activity
		- 100 pairs of peripheral stimulation and TMS delivered at a frequency of 0.1 Hz		*Behavioral*
		- pairing of peripheral nerve stimulation with anodal tDCS		- increased maximum voluntary force production
		- 1 mA tDCS delivered over 20 min		- reduced time to complete 9-hole pegboard task
		- peripheral stimulation was trains of 10 stimuli delivered at a		

Intervention	Source	Parameters	Classification	Response
		frequency of 100 Hz with		*Physiological*
		2 s between trains		- reduced recip rocal inhibition
				Behavioral
				- increased an kle movements

Table 2. Summary of NIBS to promote plasticity in SCI.

4. Coupling NIBS with movement protocols

A primary goal of motor Training is to improve functional ability by repeated exposure to a particular task, such as treadmill training to improve walking ability. In clinical populations, motor training can promote plastic changes in unaffected motor networks by increasing the efficacy of synaptic transmission [76]. Therefore, there is an opportunity to promote neural plasticity via motor training in intact cortical and spinal motor circuitry in individuals with SCI.

4.1. Pairing NIBS with motor training

Previous studies have shown that motor training can influence corticospinal excitability. In participants with SCI, locomotor resistance training using Lokomat facilitates spinal reflexes at 20 and 80 ms in the soleus muscle and improves gait quality as assessed by LEMS, walking index for SCI and velocity [77], as well as MEP amplitudes in tibialis anterior [78]. Treadmill training in SCI participants for ~2 months (5 sessions per week for 1 h) increases MEP amplitudes in tibialis anterior, increases manual muscle strength in ankle dorsiflexors as measured by 11-point manual muscle strength score, and increases the duration of the CSP [79]. Although motor training alone promotes motor recovery, the functional outcomes are often limited and patients still exhibit substantial motor impairments.

Motor training and NIBS are each, independently effective at promoting plasticity in SCI participants. Therefore, the combination of the two may lead to plasticity effects that exceed their individual components. Few studies have tested the effects of pairing NIBS with motor training to facilitate functional motor recovery. Gomes-Osman et al. [80] evaluated upper limb function in SCI participants. They delivered 10 Hz rTMS (800 pulses at 80% RMT) with repetitive task practice involving 30 s of practice with the 9-hole pegboard task. The results revealed a decrease in the time to complete the Jebsen Taylor test following real and sham rTMS paired with repetitive task practice. However, the effects were larger following real versus sham rTMS paired with repetitive task practice. Measures of RMT and AMT were unchanged [80]. Alexeeva et al. [68] combined rTMS with motor training in SCI participants. Participants experienced 5 consecutive days of each intervention: rTMS, motor training, and rTMS + motor training. A washout period of at least 4 weeks elapsed between each interven-

tion. RTMS consisted of 4-pulse trains with a ~0.2–1.5 Hz train delivery rate at an intensity set to 80–90% RMT (i.e., quadropulse rTMS). Motor training consisted of hand tasks in participants 1 and 2 (10 tasks performed 10 times each: grasp and release, hand pronation and supination, isometric and concentric contractions of the wrist, thumb, and interphalangeal joints) and locomotor training in participant 3 (walking on a treadmill at a self-selected pace for 30 min with belt speed ≥0.05 m/s). In participant 1 and 2, "rTMS" and "motor training" improved 9-hole pegboard task performance and increased MEP amplitudes without changing SICI, ICF, or CSP. The combined intervention led to the greatest improvements in 9-hole pegboard task. In participant 3, the largest improvements in treadmill walking speeds were seen following the combined interventions as well [68]. Collectively, studies pairing NIBS with motor training reveal that larger functional gains may be induced compared to the effects of NIBS or motor training delivered in isolation.

4.2. Pairing NIBS with aerobic exercise

Using aerobic exercise to prime the brain prior to NIBS may also lead to larger changes in corticospinal excitability. Regular physical activity and aerobic exercise promote plasticity by increasing levels of growth factors including brain-derived neurotrophic factor (BDNF) and insulin-like growth factor (IGF-1) [81, 82]. Further, aerobic exercise can modify plasticity [83] via increases in cerebral blood flow [84] and angiogenesis [85]. Rojas Vega et al. [86] investigated the effects of aerobic exercise on BDNF and IGF-1 serum concentrations in SCI participants. The SCI participants completed an aerobic exercise session on a hand-bike that included a 10-min warm-up followed by a timed trial over a distance of 42 km. Blood samples were collected before, after the warm-up, and immediately following aerobic exercise. The warm-up resulted in a 1.5-fold increase in BDNF concentration, although no significant differences were seen between pre- and post-aerobic exercise measures. Additionally, IGF-1 concentrations were increased following both the warm-up and aerobic exercise [86] suggesting that aerobic exercise has the ability to prime the central nervous system for neuroplastic changes. This has been supported by recent evidence that aerobic exercise, such as cycling, is able to prime the brain prior to NIBS in healthy participants [87, 88]. In uninjured individuals, priming the cortex with aerobic exercise prior to PAS enhances the plasticity effect relative to PAS alone as measured by increases in the MEP recruitment curve slope [87]. Additionally, recent evidence suggests that individuals who exercise regularly are more prone to motor cortex plasticity following PAS relative to sedentary/low physically active individuals. Those who exercise regularly had increased MEP amplitudes and steeper input/output recruitment curves after intervention, while no significant changes were seen in sedentary/low physically active individuals [89].

4.3. Summary

There are challenges for future research focused on combining NIBS with aerobic exercise or motor training. For example, one consideration involves timing the delivery of NIBS with respect to aerobic exercise and/or motor training. Thus far, NIBS has been delivered simultaneously [80] or in advance of [68] motor training yet their combined effect may be influ-

enced by their order of delivery [90]. In addition, the outcome of pairing protocols may be dependent on parameters of NIBS, aerobic exercise, or motor training, such as intensity and number of sessions; multiple sessions may be needed to induce any significant changes in motor function [91]. Therefore, pairing NIBS with aerobic exercise and/or motor training has the potential to drive neuroplastic changes in SCI participants that may exceed the functional gains achieved by a singular intervention, but further investigation is required.

5. New opportunities for NIBS to promote motor recovery in SCI

Motor recovery in SCI participants via NIBS and paired protocols are promising. However, other forms of NIBS including theta burst stimulation (TBS), rapid rate paired associative stimulation (rPAS), or transspinal direct current stimulation (ts-CCS) have the potential to induce plasticity and promote motor recovery and have yet to be explored in SCI.

TBS is a form of rTMS at low intensity that delivers continuous (cTBS) or intermittent (iTBS) high-frequency pulses inducing homosynaptic plasticity in the stimulated area. TBS effects depend on corticospinal output depend on the nature of stimulation. iTBS over motor cortex increases the amplitude of MEPs [92, 93], while cTBS over motor cortex decreases the amplitude of MEPs [92, 94], although this pattern is not always observed [95–97]. In participants with stroke, iTBS improves hand function [98] and increases MEP amplitudes [98, 99]. In addition, applying multiple sessions of cTBS in participants with amyotrophic lateral sclerosis decrease MEP amplitudes and increase RMT [100]. Although it has yet to be tested, TBS over motor cortex representation of the affected muscle in SCI may have the potential to modulate intracortical (i.e., SICI, ICF) and corticospinal circuitry (i.e., MEP amplitude). Hence, TBS, like rTMS, may be a suitable tool to influence synaptic interactions by strengthening the residual connections [92] and therefore increase motor output from the affected muscle. Further, by modulating plasticity within the cortex, indirect changes in the spinal circuitry may occur. Hence, TBS may provide an alternate method to induce plasticity in the cortex that may lead to motor recovery in SCI participants.

RPAS is based on the principles of STDP and involves pairing 5 Hz rTMS with peripheral nerve stimulation at a specific interstimulus interval [101]. Unlike PAS, which requires ~30 min to deliver, rPAS provides a particularly fast method (i.e., ~3–4 min for 600 pulses) to induce increases in corticospinal excitability. RPAS over the motor cortex increases MEP amplitudes and reduces SAI [101–104] in uninjured individuals. However, rPAS has yet to be investigated in clinical populations presenting with motor impairments. In rPAS, the pairing of TMS with nerve stimuli activates both, afferent and efferent pathways. Recently, it has been speculated that reorganization in the cortex following afferent stimulation may be crucial in neurorehabilitation of the hand [105]. Since rPAS is highly efficient in increasing corticospinal excitability in healthy adults for prolonged periods of time, it may provide a useful tool to promote sensory-motor coupling [102] in SCI participants.

Another promising NIBS technique involves the delivery of 40 min of constant current stimulation to the spinal cord [106]. Long-lasting transspinal constant current stimulation (ts-

CCS) alters cortical, corticospinal, and spinal plasticity in uninjured participants. Knikou et al. [106] found that both cathodal tsCCS and anodal tsCCS decreased afferent-mediated MEP facilitation, increased MEP amplitudes, and decreased transspinal-evoked potentials (TEPs) of knee flexors. Further, cathodal tsCCS increased TMS-mediated tibialis anterior flexor reflex facilitation, while anodal tsCCS decreased TMS-mediated TA flexor reflex facilitation and decreased post-activation depression of TEPs for the soleus H-reflex. This technique provides a way to directly stimulate the spinal cord, changing the synaptic efficacy between descending motor axons and spinal motorneurons, cortical interneurons and descending motor axons and Ia afferents and motorneurons [106]. While more research is required to determine the efficacy of this tool at modulating changes in the cortex and spinal cord to promote motor recovery in clinical populations, it may have the potential to improve voluntary motor function in SCI participants.

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