

# Transcranial magnetic stimulation to investigate motor cortical circuitry and plasticity in spinal cord injury

## Abstract

Spinal cord injury may lead to complete or incomplete damage to ascending sensory and/or descending motor pathways and therefore alter neural circuits of the primary motor cortex. Transcranial magnetic stimulation (TMS) is a valuable tool for investigating the function of neural circuitry within primary motor cortex and also for promoting plasticity in these circuits for the ultimate purpose of improving the control of movement. For spinal cord injury, information about motor cortical circuits and TMS approaches to induce plasticity in these circuits is steadily emerging. In this review, we discuss TMS investigations of motor cortical circuitry and review TMS approaches to promote plasticity in motor cortical circuitry in spinal cord injury.

**Keywords:** Spinal cord injury, Transcranial magnetic stimulation, Motor cortex, Paired-pulse TMS, Neural plasticity, Paired associative plasticity, Intra cortical inhibition, Intra cortical facilitation, Cortical silent period, Inter hemispheric inhibition

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**Abbreviations:** SCI, spinal cord injury; TMS, transcranial magnetic stimulation; MVC, maximum voluntary contraction; FDI, first dorsal interosseous; RMT, resting motor threshold; AMT, active motor threshold; EDC, extensor digitorum communis; SICI, short interval intra cortical inhibition; TA, tibialis anterior; CS, conditioning stimulus; BB, biceps brachii; LICI, long interval intra cortical inhibition; SAI, short latency afferent inhibition; LAI, long latency afferent inhibition; APB, abductor pollicis brevis; ECR, extensor carpi radialis; FCR, flexor carpi radialis; TN, tibial nerve; CPN, common peroneal nerve; IHI, inter hemispheric inhibition; FHB, flexor hallucis brevis; STDP, spike-timing dependent plasticity; LTP, long-term potentiation; LTD, long-term depression; rTMS, repetitive transcranial magnetic stimulation; PAS, paired associative stimulation; SAS, spinal associative plasticity

## Background

In the US spinal cord injury (SCI) is estimated to cost \$9.7 billion annually,<sup>1</sup> an economic burden likely to be reduced by new treatments aimed at functional improvements. Recent experimental approaches to improve function have utilized Transcranial magnetic stimulation (TMS) protocols<sup>1,2</sup> to promote short-term neural plasticity at spinal and/or cortical synapses and have demonstrated promising improvements in function in SCI.<sup>1</sup> TMS techniques also allow for investigations of cortical inhibitory and excitatory circuits that reside in the primary motor cortex (M1), and as such, provide a unique opportunity to understand neural changes that follow SCI.

SCI is associated with complete or incomplete damage to ascending sensory and/or descending motor pathways<sup>3,4</sup> and may ultimately lead to alterations within neural circuits of M1.<sup>5-7</sup> In controls, experimentally induced differentiation reduces inhibitory, GABAergic cortical activity in sensory motor cortices<sup>8</sup> and is a mechanism proposed to mediate rapid cortical plasticity.<sup>9</sup> Reductions in GABAergic cortical activity are also suggested to promote rapid functional gains following SCI,<sup>5</sup> however, there is also evidence to suggest sustained alterations in cortical inhibition.<sup>6,7</sup> Changes in cortical inhibition in SCI may lead to alterations in motor cortical

and/or spinal circuitry. TMS techniques are capable of characterizing cortical inhibition and identifying aberrations in circuits directed to affected muscles. Further, TMS techniques are capable of inducing short-term plasticity to promote change in aberrant circuitry.

## Scope of the review

In basic and clinical sensorimotor neuroscience, TMS is gaining popularity as a non-invasive, painless method to investigate specific motor cortical circuits and create short-term changes in the activity of these circuits. For neurological conditions affecting movement, one major research initiative is to use TMS to characterize motor cortical circuitry and subsequently use TMS as a plasticity-inducing tool to promote change in abnormal circuits for the ultimate goal of improving motor control. In the last two decades, TMS has been used to characterize motor cortical circuits in SCI and only recently has it emerged as a plasticity technique in this population. This review seeks to achieve two goals: to detail TMS investigations of motor cortical circuitry and to review TMS approaches to promote plasticity in motor cortical circuitry. We begin by describing TMS evoked motor cortical circuits, their physiology, changes after SCI and highlight the practical implication of studying each circuit in SCI (Table 1). We subsequently describe TMS plasticity protocols that have been attempted in the SCI population.

## Motor cortical circuits in SCI

TMS has greatly advanced our understanding of neural circuitry that resides in M1. Using single or paired-pulse approaches and one or two distinct coils, TMS is capable of characterizing inhibitory and excitatory circuits within or between motor cortices. These circuits provide insight into the integrity of local neuronal populations mediated by specific neurotransmitter systems that operate to control muscles. In SCI, characterizing the activity within these circuits allows abnormalities to be identified, and importantly provides a marker of physiological recovery that can be measured in conjunction with therapeutic approaches. We review the literature for the several motor cortical circuits that have been studied in SCI.

**Table 1** Summary of motor circuitry in SCI.

Circuit	Mechanism Probed	Conditioning Stimulus (CS)	Test Stimulus (TS)	Interval Between CS and TS (ISI)	Changes in SCI
MEPs	Corticospinal Excitability	N/A	Supra threshold TMS	N/A	Reduced in upper and lower limbs
RMT	Neuron membrane excitability	N/A	MEP>50µV in 5/10 trials from TMS	N/A	Increased in upper and lower limbs
AMT	Number of neurons near threshold	N/A	MEP> 00µV in 5/10 trials from TMS	N/A	Increased in upper and lower limbs
SAI	Afferent regulation of cortex	Supra threshold nerve stimulation	Supra threshold TMS	N20 + ~2-8ms	Unknown at rest Reduced in TA during active
LAI	Afferent regulation of cortex	Supra threshold nerve stimulation	Supra threshold TMS	N20 + ~200ms	Unknown
SP	Intracortical inhibition, transcollosal connectivity	N/A	Subthreshold or Supra threshold TMS	N/A	Contra lateral is reduced, Ipsilateral is unknown
IHI	Interhemispheric inhibition, transcollosal connectivity	Supra threshold TMS	Supra threshold TMS	~10ms (Short) or ~40ms (Long)	Short is normal at rest, altered during active Long is unknown
SICI	Intracortical inhibition	Subthreshold TMS	Supra threshold TMS	~1 - 6ms	Reduced in TA Normal for FDI
LICI	Intracortical inhibition	Supra threshold TMS	Supra threshold TMS	~50 - 200ms	Normal in FDI at rest Increased in FDI during active
ICF	Intracortical facilitation	Subthreshold TMS	Supra threshold TMS	~10 - 25ms	Unknown

*Motor evoked potentials (MEPs)* are the resulting muscle responses to a TMS pulse that is sufficient in intensity to depolarize the spinal motor neuron pool<sup>10</sup>. The MEP amplitude is a reflection of the excitability of the cortical and spinal motor neuron pool and the latency reflects the integrity of conduction along the efferent pathway.<sup>11</sup> Muscles of the upper limb are more accessible to TMS due to their placement along the pre central gyrus while muscle representations of the lower limb are buried deep in the inter hemispheric fissure.<sup>12</sup> An increase in movement complexity or dexterity is concomitant with an increase in cortical projections to the muscles involved in those movements. Distal muscles tend to have larger MEP amplitude than proximal muscles which may stem from an increase in cortical projections due to the increased dexterity needed in these muscles.<sup>13</sup> TMS can be used to assess the activity of cortical and spinal motor neurons and conduction along the efferent paths.

After SCI the amplitude of MEPs are decreased and the latency of MEPs are increased in muscles below the level of injury<sup>11,14-16</sup>. In addition, when MEPs are present in the first dorsal interosseous (FDI) muscle at rest in SCI participants, there is an increase in MEP amplitude with increases in voluntary contraction from 10% to 50% of maximum voluntary contraction (MVC). Uninjured participants show no further increase above 10% MVC.<sup>11</sup> Changes to both MEP amplitude and latency are correlated with the severity of the injury as well as functional motor disability; smaller and more delayed MEPs are indicative of severe injuries that yield greater motor impairments<sup>14,17,21</sup>. Collectively, the data in SCI show that MEPs are abnormal when compared to uninjured and is hypothesized to be caused by the damage to the descending efferent pathways in the spinal cord. Although MEPs show abnormalities in SCI, TMS can still be used as a tool to identify muscles that are candidates for plasticity protocols to potentially restore function in those muscles. For example, MEPs are obtainable in muscles that have no voluntary

control indicating that corticospinal projections to these muscles are not completely absent and changes to M1 could potentially promote voluntary control.<sup>16</sup> Further, MEPs may be more readily obtained and larger in amplitude in the actively contracted muscle when SCI participants are capable of performing voluntary contraction of that muscle. As such, testing during muscle contraction may be the preferred method of obtaining MEPs.<sup>22,23</sup>

Motor threshold is a measure of corticospinal excitability; a muscle that responds to low TMS intensity is considered to have a low motor threshold and vice versa.<sup>24</sup> Across participants muscle responses occur at various TMS intensities resulting in different thresholds among individuals. *Resting motor threshold (RMT)* is obtained while the target muscle is relaxed and is typically defined as the minimum stimulator intensity needed to elicit a MEP of 50 micro volts in at least 5 out of 10 trials.<sup>25</sup> *Active motor threshold (AMT)* is obtained while the target muscle is actively contracted ~10-15% MVC and is typically defined as the minimum stimulator intensity needed to elicit a MEP of 200 microvolt in at least 5 out of 10 trials.<sup>25,26</sup> Pharmacological studies indicate that RMT reflects the neuronal membrane threshold<sup>27</sup> while AMT indicates the number of axons that are close to firing threshold. AMT is generally lower than RMT because the active corticospinal axons are more sensitive to the TMS pulse.<sup>24</sup>

A study conducted by Freund et al.<sup>28</sup> investigated changes in AMT following incomplete cervical SCI in the extensor Digitorum communis (EDC). The AMT in SCI was higher than uninjured participants and was correlated to the degree of cord atrophy indicating that greater cord atrophy was associated with higher AMT. Another study by Davey et al., investigated the change to both AMT and RMT in the thenar muscle, a muscle below the level of injury, and the biceps brachii (BB), a muscle above the level of injury in the incomplete SCI. Both AMT and RMT for the thenar muscles were higher in the SCI

group when compared to the uninjured group, but thresholds were similar in the BB between the two groups.<sup>11</sup> An increase MT in SCI is thought to relate to the density of surviving corticospinal neurons<sup>28</sup> and damage to descending axons.<sup>11,28</sup> Thus, after injury greater TMS intensities are needed to elicit a muscle response.<sup>28</sup>

Together the literature indicates an increase in both AMT and RMT after SCI. The evidence suggests that increases in motor threshold are due to injury in the descending efferent pathways and not due to a change to the membrane threshold since stimulating areas of the cortex responsible for controlling muscles above the level of the injury are unchanged.<sup>11,29</sup> Further, when TMS intensity increases, the spatial focality of the stimulation decreases and it is difficult to discern whether the threshold obtained is restricted to the muscle of interest or if additional muscles are recruited due to spread of the TMS pulse. This can cause a limitation in the use of these measurements to design experiments, particularly those pertaining to intra cortical and inter hemispheric inhibition.

*Short Interval Intra cortical Inhibition (SICI)* is a well-characterized inhibitory circuit that involves two sequential TMS pulses delivered through a single coil over M1. In SICI the MEP elicited by the test stimulus (TS) is reduced (i.e. inhibited) when preceded by a conditioning stimulus (CS) delivered ~1-5ms earlier.<sup>30,31</sup> The inhibitory effects are typically observed with CS intensities at sub threshold levels with the greatest inhibition occurring at 70% - 90% of motor threshold. SICI is thought to be mediated by cortical and not spinal circuits since spinal Hoffmann reflexes are unchanged during SICI<sup>30</sup> and epidural recordings show suppression of descending volleys by the CS in the later I-waves only.<sup>32</sup> The CS produces inhibitory postsynaptic potentials at the corticospinal neurons, which causes a reduction in the number of action potentials that can be elicited by the subsequent TS.<sup>33</sup> SICI is mediated by GABA<sub>A</sub> receptors and is enhanced with GABA<sub>A</sub> receptor agonists such as lorazepam and diazepam.<sup>33,34</sup> The SICI circuit is decreased during tonic contraction of agonist muscles<sup>35</sup> and the inhibition of the MEP starts to decline 95ms before onset of EMG activity with phasic muscle movements in response to an auditory cue<sup>36</sup> suggesting a role for SICI in motor control.

The SICI circuit has been investigated in both complete and incomplete SCI populations. Roy et al.<sup>23</sup> investigated SICI recruitment curves for the tibialis anterior (TA) and the FDI muscles in incomplete SCI with injury between C3-T12. SICI was tested while the muscles were contracted ~15-20% of MVC. The TS was set to an intensity that elicited MEPs near half maximum amplitude. SICI in TA showed a similar recruitment curve in SCI and uninjured, but the magnitude of inhibition was reduced in SCI. SICI in FDI showed trends similar to the TA muscle in the SCI group but no comparison was made to uninjured participants for this muscle. Thus, without any comparisons to uninjured hand muscles, it is difficult to know if SICI in FDI is altered in SCI.<sup>23</sup> Additionally, there is a case study of a 67year old woman with an episode of ischemic myelopathy at C8-T1 which occurred 23years prior to testing. SICI was absent when tested with CS and TS of 80% and 120% RMT, respectively, at inter-pulse intervals of 2, 3 and 5ms.<sup>37</sup> The reduction in SICI in the SCI population demonstrates potential changes to GABA<sub>A</sub> function following SCI. One study examined cross facilitation of corticospinal pathways in SCI with the preserved ability to elicit voluntary force with hand and arm muscles. SICI within the resting FDI muscle was reduced during 70% of MVC of the contra lateral FDI and BB in the uninjured group but not in the SCI group.<sup>38</sup> The authors proposed that

the lack of changes to SICI in SCI during movement of the contra lateral limb might be due to the lack interaction between SICI and the impaired trans callosal circuits.

In summary, for SICI circuitry, there appears to be a dysfunction of cortical GABA<sub>A</sub> function within the motor cortex in the SCI population. There are both decreases in the degree of inhibition<sup>23</sup> as well as an absence of SICI altogether<sup>37</sup> after SCI. SICI changes following injury to the spinal cord show similarities to other neurological conditions such as stroke, Multiple sclerosis and Amyotrophic lateral sclerosis.<sup>39-41</sup> However, there are limitations in the methodology of investigating the SICI circuitry. Eliciting SICI depends on the motor threshold (described above) and the achievable MEP size for the SCI participant, both of which may be altered in SCI. The CS intensity used to perform SICI depends on the motor threshold and an increase in this measure following SCI can lead to difficulties in the interpretation of SICI. Similarly, a decrease in the MEP size of the SCI population questions whether or not a reduction in MEP following CS stimulation is due the inhibitory effects of the CS or merely due to the inherent variability of the MEP itself. Future studies should consider testing SICI at multiple CS intensities (i.e. recruitment curves) since a single intensity may not encompass all the possible changes associated with SCI.

*Long Interval Intra cortical Inhibition (LICI)* circuitry can be probed when a supra threshold CS is used to inhibit a subsequent supra threshold TS at inter-pulse intervals between 50-200ms.<sup>42,43</sup> Two MEPs are generated as a result of both supra threshold stimuli while only the second MEP is inhibited. The degree of inhibition increases with CS intensity and the greatest inhibition is observed at ~150% RMT.<sup>42</sup> Epidural recordings of descending corticospinal volleys demonstrate the reduction of later I-waves at ISIs of 100-150ms<sup>31,44,45</sup> suggesting a cortical origin of the LICI circuit. LICI procures from slow IPSPs mediated by GABAB receptors, as pharmacological studies demonstrate an increase in LICI by baclofen, a GABAB receptor agonist.<sup>46</sup> Other GABAergic drugs such as tiagabine<sup>47</sup> a GABA reuptake inhibitor and vigabatrin<sup>48</sup> a GABA transmutase inhibitor, also increase LICI providing further evidence of a GABAergic involvement in the LICI circuitry. LICI appears to be involved in motor control as it is reduced in the FDI muscle with increasing levels of tonic abduction<sup>49</sup> and is non-specific in nature as it is reduced in both Go and No-Go reaction tasks.<sup>50</sup>

A recent study investigated LICI in the resting and actively contracted FDI in chronic incomplete and complete C4-C7 SCI participants. Compared to rest LICI during active contraction is decreased in uninjured and SCI participants taking baclofen medication. In contrast, SCI not taking baclofen did not show reductions in LICI during active contraction. These data indicate that baclofen creates typical modulation of LICI circuitry in the SCI population and that baclofen appears to normalize LICI function following SCI. The limited amount of research done regarding the LICI circuit within the SCI population shows an increase in the GABAB mediated circuit compared to uninjured, however the presence of baclofen appears to alter function of this circuit to similar levels of uninjured.<sup>51</sup> LICI holds much of the same methodological limitations as SICI due to the similarities in the way they are both elicited. Therefore, changes to the motor threshold and MEP amplitude can affect LICI data interpretation in SCI. Likewise, a LICI recruitment curve can prove beneficial in capturing the range of changes to the circuit where a single CS-TS pair cannot.

Afferent regulation of the motor cortex can be achieved by pairing an electrical stimulation of a peripheral nerve followed in time (~18-21ms) by a supra threshold TMS pulse to the motor cortex. This results in a suppression of the MEP in the targeted FDI of the hand<sup>52,53</sup>. Similarly, if the inter stimulus interval between the nerve stimulation and TMS pulse is 100-200ms, MEPs are suppressed<sup>53,54</sup>. The reduction of the MEP amplitude at short and long latencies is known as short latency afferent inhibition (SAI) and long latency afferent inhibition (LAI), respectively. The afferent volley can be elicited from stimulation of either a cutaneous or a mixed nerve<sup>52,55,56</sup> and SAI/LAI can be observed in muscles of both the upper and lower limb with the majority of studies focused on muscles of the upper limb. SAI and LAI are considered to be mediated by cortical mechanisms<sup>52,54</sup> and the precise neural path by which afferent inhibition is mediated remains uncertain; the afferent volley may travel via direct thalamocortical projections to M1 or via a relay through primary somatosensory cortex.<sup>57</sup> Cholinergic and GABAergic systems appear to mediate and/or modulate SAI. Scopolamine, an anti cholinergic drug, reduces SAI<sup>58,59</sup> while diazepam, a GABA<sub>A</sub> modulator, increases SAI.<sup>60</sup> LAI however, is thought to proceed through only a GABAergic system. LAI has inhibitory synaptic connections with SICI and IHI circuits, both mediated by GABAB<sup>61,62</sup>. LAI's inhibitory effect on these other circuits provide evidence they share the GABAB receptor type.<sup>57</sup>

The magnitude of SAI and LAI are affected by peripheral nerve stimulation intensity, and the depth of both SAI and LAI increases as nerve intensity increases.<sup>54,63</sup> A study conducted by Fischer and Orth<sup>63</sup> investigated how SAI in the FDI and the abductor pollicis brevis (APB) change with an increase in nerve intensity to the median and ulnar nerve. SAI was shown to increase in both muscles with an increase in stimulation intensity to both nerves<sup>63</sup>. Another study conducted by Chen et al.<sup>54</sup> investigated changes to LAI in APB, FDI and EDC with an increase in nerve stimulation to the digital nerves of the third digit. The depth of LAI (at 200ms) increased with an increase in the intensity of nerve stimulation in all muscles tested. This is due to a greater afferent volley to the cortex, resulting in a greater inhibitory effect.<sup>54,63</sup> Nerve selection can have an effect on SAI observed in a given muscle. In forearm muscles, median nerve has a stronger inhibitory effect on the extensor carpi radialis (ECR) than the flexor carpi radialis (FCR) and the ulnar nerve has a stronger inhibitory effect on the FCR than the ECR.<sup>64</sup> SAI and LAI are thought to play an important role in cutaneous reflexes in a contracting muscle by providing the early and late inhibitory effect, thus an important neural circuit in sensorimotor integration.<sup>52</sup>

Few studies in SCI have investigated SAI and LAI circuitry. One study examined the influence of afferent input on the motor cortical output to the TA muscle in incomplete SCI.<sup>22</sup> In uninjured individuals, tibial nerve (TN) stimulation facilitates the MEP recorded from TA at a latency equivalent to the arrival of the information to the motor cortex, but this facilitatory effect does not occur in SCI. Further, in uninjured individuals, common peroneal nerve (CPN) stimulation reduces the MEP recorded from TA at latency prior to the arrival of the nerve stimulus to the motor cortex suggesting a spinal mechanism for inhibition. Compared to uninjured participants, CPN stimulation has a decreased inhibitory effect on motor output in SCI.<sup>22</sup> These data indicate that cortical neurons play an important role in facilitating MEP output and neurons in the spinal cord play a role in inhibiting motor output to the lower limbs.<sup>22</sup> The decrease in both the facilitation by the TN input and depression by the CPN input can be partly explained by a decrease in the amount of afferent input arriving into the cortex<sup>22,65-67</sup> or by an decrease in the motor output as a result of damage to the efferent pathways.<sup>22</sup>

Although research in afferent regulation of motor cortex in SCI is limited, there appears to be a decrease in the sensory regulation of motor cortex (i.e. SAI and/or LAI) and this may contribute to impairments in motor control<sup>22</sup>. It is not known if this is due to a change in the amount or latency of sensory information arriving at the cortex, or whether cortical plasticity may have occurred resulting in alterations to the neural mechanisms that underpin SAI/LAI circuitry. Future studies should investigate several nerve intensities in conjunction with electroencephalography in order to:

- Quantify the amount of afferent input to the cortex and
- Distinguish if the afferent regulation of the motor cortex increases with an increase in nerve intensity.

The corpus callosum is a structure critical for the transfer of information from one hemisphere to the other.<sup>68,69</sup> A TMS paired-pulse protocol called *inter hemispheric inhibition (IHI)* can be used to assess transcallosal function by applying a supra threshold conditioning TMS pulse over a representation within motor cortex and a second supra threshold test TMS pulse over the homologous representation in the opposite motor cortex. An inhibition equivalent to about 60% of the TS is observed when the CS is present. The inhibitory effect is seen at two distinct latencies between CS and TS; the first at 10ms (IHI<sub>10</sub>) and the second at 40ms (IHI<sub>40</sub>). Evidence suggests that IHI occurs at the cortical level since Hoffman reflexes are not changed as a result of the two TMS pulses and no change is seen when Transcranial electrical stimulation (which directly activates cortico spinal axons) is used.<sup>68</sup> IHI at these two latencies is mediated by GABAB receptors as inhibition is further increased after administration of baclofen, a GABAB agonist<sup>62,69</sup>. IHI shares similar neuronal populations to LICI as both circuits inhibit SICI and are directly inhibited by LAI<sup>61,62</sup>. Activity in the limb ipsilateral to the TS can increase the amount of IHI in the opposite limb<sup>68,70</sup> and the intensity of the conditioning stimulus can increase inhibition.<sup>70</sup>

Bunday & Perez<sup>38</sup> investigated IHI<sub>10</sub> in the FDI muscle in incomplete SCI when the contra lateral limb was contracting. Test stimuli were always delivered to the cortex controlling the more affected muscle and the conditioning stimuli applied to the cortex controlling the less affected muscle. Recordings were taken from a resting muscle while the contra lateral muscle was relaxed or contracted. SCI participants did not show increases or decreases in IHI when the contra lateral limb was contracting.<sup>38</sup> This lack of change in IHI with movement may disrupt function of other motor cortical circuitry<sup>36</sup> which may contribute to motor impairments seen in SCI.<sup>38</sup>

In summary, the single study of IHI in SCI concluded there was no movement-related modulation of this circuit. However, there may be alterations in IHI that have gone undetected with the specific TMS parameters used to recruit the circuit. IHI is reliant on obtaining MEP amplitudes that allow for ~60% suppression in the uninjured population. Since it may be difficult to obtain MEPs of this magnitude in SCI, a recruitment curve to test different CS intensities may be more sensitive to the IHI circuit.

*Intra cortical facilitation (ICF)* involves a sub threshold or near-threshold CS preceded by a supra threshold TS<sup>30</sup> with the largest facilitation occurring with a CS intensity of 120% MT<sup>71</sup> and an inter-pulse interval of ~7-20ms.<sup>30</sup> ICF appears to be a net facilitation consisting of a large facilitatory and a smaller inhibitory effect on the TS.<sup>24</sup> The inhibitory effect originates from the GABA<sub>A</sub> receptor mediated IPSP, which has a duration of around 20ms<sup>72</sup> this is supported by a decrease in ICF in the presence of benzodiazepines<sup>73</sup>. The facilitatory component of ICF is most likely due to NMDA

receptor mediated excitatory postsynaptic potentials<sup>74</sup> as seen by decreases in ICF by NMDA receptor antagonists.<sup>75,76</sup> Ketamine,<sup>77</sup> a NMDA receptor antagonist, does not seem to change ICF contrary to other NMDA antagonists, suggesting ICF is mediated via NMDA and non-NMDA receptors.<sup>74</sup> ICF was tested in a case study of a 67-year-old woman with C8-T1 ischemic myelopathy with CS and TS at 80% and 120% RMT, respectively, and using inter-pulse intervals of 10 and 15ms. The presence of a facilitatory effect of the CS on the TS was observed at 10ms only<sup>37</sup> indicating that ICF continues to cause its facilitatory effects even following injury to the spinal cord.

A lack of research has been conducted regarding ICF and the changes to NMDA mediated circuits that live within the motor cortex following SCI. Existing case studies seem to show the presence of ICF in one SCI subject, but this observation requires subsequent verification. The limitations associated with motor thresholds and obtainable MEP sizes in SCI impact ICF measurements, in a manner similar to SICI and LICI, which leads to difficulties when interpreting the facilitatory effects of ICF compared to uninjured. Again, the benefits of a recruitment curve can be implemented with the ICF circuit just as with the SICI, LICI and IHI circuits that have been missing in existing studies.

The *cortical silent period (cSP)* refers to the pause in ongoing EMG activity during a tonic contraction following an MEP elicited by TMS.<sup>78</sup> The duration of the cSP increases as a function of stimulus intensity, typically lasting 200 ms.<sup>78,79</sup> The first 50-75ms of the cSP is caused by spinal cord refractoriness while the remainder of the inhibition is considered to be mediated by the cortex.<sup>45,80,81</sup> CSP tested at low stimulus intensities show activation of GABA<sub>A</sub> receptors while GABAB receptors are activated at higher stimulus intensities. Increases to cSP duration have been observed in the presence of tiagabine,<sup>47</sup> a GABA reuptake inhibitor, and vigabatrin,<sup>48</sup> an inhibitor of a GABA degrading enzyme. The duration of the cSP increases when tested at low stimulus intensities in the presence of lorazepam<sup>34,78</sup>, a benzodiazepine. This supports the idea of GABA<sub>A</sub> receptor mediated inhibition, which causes the cSP at low intensities. The cSP shortens with high stimulus intensities with both lorazepam<sup>78</sup> and diazepam<sup>82</sup> suggesting an inhibitory effect of GABA<sub>A</sub> on the GABAB receptor pathways.<sup>24</sup>

CSP has been investigated in the FDI muscle in both chronic incomplete and complete SCI participants with injuries between C4-C7 while taking or not taking baclofen. The duration of the SP during 25% of MVC increased in SCI groups irrespective of baclofen use compared with uninjured participants.<sup>51</sup> There was also no difference in the cSP between SCI participants who were or were not taking baclofen. Another study measured cSP in FDI and flexor hallucis brevis (FHB) in individuals with chronic incomplete SCI between C4 - C6.<sup>7</sup> Participant 1 showed an absence of cSP in FDI and suppression but not a pause of EMG after the MEP in the FHB muscle. Participant 2 showed no cSP for either FDI or FHB muscles. Participant 3 showed the presence of cSP in the FDI but not the FHB muscle. The authors suggest that an absence of cSP might be caused by motor cortex hyper excitability as a result of injury.<sup>7,83</sup> A recent study looked at six acute incomplete SCI patients with cervical myelopathy between levels of C3-C7 prior to spinal cord decompression surgery and again at three months post-surgery. When the same stimulation intensity was used for control, pre-, and post-surgery groups, no differences were observed in cSP.<sup>83</sup> However, a cSP recruitment curve for the TA muscle showed that maximum cSP durations were significantly longer for SCI pre-surgery compared to controls. Further, this difference in controls and

SCI was gone following the surgery, indicating a recovery of the partially affected inhibitory function. Current research in the silent period of SCI in both acute and chronic patients reveals changes to its duration and recruitment.

Existing research in the SCI population reveals that the cSP can increase in some SCI participants and completely disappear in others. This reflects alterations to spinal mechanisms as well as GABA<sub>A</sub> and GABAB mediated circuits within the motor cortex. Other motor-related disorders have also been reported to show similar changes to cSP such as stroke.<sup>84</sup> The changes to MEP may partially explain the changes to cSP in the SCI population. cSP is known to increase with an increasing TMS stimulus and together with the increase in motor threshold in the SCI population, it can be difficult to disentangle the source of the increase in cSP duration. A recruitment curve can be beneficial in future studies of cSP to gain insight on the varying differences of cSP as a function of TMS intensity.

### Reflections on motor cortical circuitry in SCI

The literature indicates alterations to motor cortical circuits in SCI. This is evident through various TMS approaches used to probe MEPs, thresholds, SICI, LICI, SAI/LAI, IHI and cSP. In contrast, ICF appears to continue to show facilitatory effects. Although several studies have been conducted with different motor cortical circuits in SCI, there remain gaps in our present understanding. The cortical circuits studied are muscle specific and a limited number of muscles have been investigated in SCI. In addition few studies attempt to separate SCI groups by incomplete and complete injury or more affected and less affected limbs, which limit the ability to distinguish differences related to injury severity. It is also known that motor cortical circuits can be altered by certain medications and insufficient research has been done to investigate how the medication status in this population affects the function of their motor cortical circuits.

### TMS approaches to promote plasticity in SCI

TMS protocols have the potential to induce short-lasting change in the neural activity of specific motor cortical and/or spinal circuits in SCI. Synaptic efficiency is altered if the presynaptic neuron consistently contributes to the firing of the postsynaptic neuron<sup>85</sup> and this forms the basis of spike-timing dependent plasticity (STDP). Specifically, synaptic efficiency increases, an effect known as long-term potentiation (LTP) when neurons are excited by pre-synaptic input in advance of postsynaptic input. Conversely, neurons excited by post-synaptic input followed by pre-synaptic input yield a decrease in synaptic efficiency called long-term depression (LTD). STDP indicates that increases or decreases in synaptic efficiency rely on the temporal sequence of pre and postsynaptic inputs to a neuron. At the level of the synapse, LTP and LTD result from the pattern of postsynaptic Ca<sup>2+</sup> influx with the former achieved by high transient influx and the latter by lower, consistent currents.<sup>86</sup> Heterosynaptic plasticity refers to changes in efficiency as a consequence of another pathway. Homosynaptic plasticity refers to changes in synaptic efficiency that are a consequence of a neuron's own activity. Animal models of homosynaptic and heterosynaptic LTP and LTD induction have instructed TMS approaches for inducing plasticity-like effects in humans. We review the TMS approaches that have been attempted in SCI for the purpose of altering motor circuitry.

*Paired Associative Stimulation (PAS)* is founded in the principles of STDP and represents a heterosynaptic approach.<sup>86</sup> In PAS electrical stimulation of a nerve is paired repeatedly with single TMS pulses

over the M1 representation of a muscle innervated by that nerve.<sup>87</sup> PAS typically involves 90 repeat pairings delivered once every 20 seconds and requires ~30 minutes to complete<sup>87–89</sup> If the two inputs are delivered such that the afferent impulse from electrical stimulation reaches the cortical neurons with their simultaneous activation by the TMS pulse (~25 ms), increases in the corticospinal output (i.e. MEP amplitude) are observed and LTP-like effects are thought to mediate the change<sup>87,88</sup> In contrast, if the activation of cortical neurons via TMS precedes their activation by the peripheral afferent input, decreases in corticospinal output (i.e. LTD-like effects) occur.<sup>88</sup> The assumption underlying PAS effects is that nerve stimulation and the TMS pulse both evoke inputs onto a common neuronal population that ultimately demonstrates short-term associative synaptic plasticity due to the repeat pairing of separate inputs. Following PAS protocols in uninjured individuals, increases in MEP amplitude<sup>87</sup> and cSP<sup>90</sup> are observed. PAS-induced increases in corticospinal excitability are mediated by glutamate and are blocked in the presence of NMDA receptor antagonists.<sup>89</sup> PAS effects are strongly dependent on the focus of directed attention<sup>91</sup> circadian rhythm,<sup>92</sup> physical exercise<sup>93</sup> and are thought to be mediated by changes in cortical<sup>87</sup> and spinal circuitry.<sup>94</sup> In incomplete SCI, a modified PAS protocol for the TA muscle was performed whereby single-pulse TMS over the TA representation in M1 was paired with stimulation to the CPN (i.e. triplets at 100 Hz). MEPs were facilitated by ~20% in half of the SCI participants, specifically in those who demonstrated MEP potentiation with CPN conditioning.<sup>22</sup> Another study demonstrated ~15–20% increases in MEP amplitude with PAS involving CPN stimulation.<sup>2</sup>

*Spinal Associative Plasticity (SAS)* is also founded in principles of STDP and similar is a hetero synaptic approach similar to PAS. SAS involves repeat pairing of peripheral nerve stimulation and TMS pulses over M1 cortex or the cervicomedullary junction to yield near simultaneous arrival of the two inputs at the alpha motor neuron pool in the spinal cord<sup>1,95–97</sup>. The protocol delivers ~100 repeat pairings once every 10 seconds<sup>1,95</sup> or 360 pairs once every 5 seconds<sup>96</sup> requiring 15–20 minutes of supra threshold nerve stimuli and TMS pulses. In controls, SAS targeting muscles of the lower limb facilitates spinal Hoffman reflexes<sup>95–97</sup> and their recruitment.<sup>95</sup> SAS targeting the FDI leads to increases in MEP amplitude that are attributed to changes in the corticospinal-motor neuron synapses and follows STDP principles.<sup>51</sup> SAS has been tested on the less impaired FDI muscle in incomplete chronic SCI and shown to be effective at facilitating MEPs, and increasing both index finger force and background EMG for 80 minutes following stimulation, effects that are attributed to STDP at corticospinal-spinal motor neuron synapses.

Repetitive TMS (rTMS) is a homosynaptic plasticity protocol and involves biphasic pulses delivered repetitively over a specific cortical locus to induce changes in the excitability of the neuronal populations within the stimulated cortex. After-effects of rTMS depend on the frequency, intensity, direction of induced current, total number of pulses and other factors (Pell et al.<sup>98</sup> for review). Typically, rTMS delivered at low frequencies (i.e. less than 1 Hz) over M1 leads to LTD-like effects and cortical excitability is reduced as measured by decreases in MEP amplitude<sup>99,100</sup> Conversely, rTMS delivered at higher frequencies (i.e. ~5 Hz) over M1 leads to LTP-like increases in cortical excitability as measured by greater MEP amplitude.<sup>101</sup> RTMS has been used extensively in uninjured and clinical populations to promote homosynaptic plasticity within targeted cortex. Varying success levels are due in part to the complex stimulation parameters and also to the heterogeneity of the participant group.

In SCI, rTMS has been used primarily for the purpose of modifying neuropathic pain and has been successful in some instances<sup>102,103</sup> but

not others.<sup>103</sup> Very high-frequency (~20 Hz) rTMS bursts separated by long inter-burst intervals (28 seconds) delivered over M1 can improve spasticity for up to one week following stimulation in SCI.<sup>104</sup> There is also evidence that rTMS in SCI is capable of modifying motor cortical circuits. Belci et al.<sup>105</sup> delivered rTMS as doublets (360 doublets) separated by 100 ms at a slow frequency (once every 10 seconds, 90% of motor threshold) for five days in a small group of individuals with incomplete SCI. RTMS was positioned over the M1 representation of the thenar muscles. Real and not sham rTMS lead to reductions in the cSP recorded from the thenar muscles and also improved somatosensory percepts and ASIA motor scores at three weeks following stimulation. Kuppuswamy et al.<sup>106</sup> delivered 900 pulses at 5 Hz in 2 second trains with an inter-train interval of 8 seconds over M1 muscle representations corresponding to hand or forearm muscles. Real or sham rTMS was delivered for five days at 80% of active motor threshold. In contrast to the previous report<sup>105</sup> the cSP and ASIA scores were unaltered while AMT increased for the FDI muscle.

## Conclusion

We reviewed TMS investigations of motor cortical circuitry and TMS approaches to promote plasticity in SCI. Alterations in motor thresholds, intra cortical and inter hemispheric inhibition and silent period exist. However, it is clear that there are remaining gaps in our knowledge and the use of recruitment curves will be beneficial in future studies to allow for a range of intensities and/or latencies to be tested. This approach will increase the opportunity to identify atypical responses that may otherwise be missed when selecting specific parameters to evoke these circuits. Second, cortical circuits should be studied in the rest and active muscle states when possible to provide insight into the capacity for typical movement-related modulation of circuitry in SCI.

TMS plasticity protocols have recently been used in SCI to promote motor cortical and spinal excitability changes. RTMS has been delivered over M1 and yielded mixed results on motor cortical circuits.<sup>105,106</sup> PAS and SAS have been attempted for the TA<sup>22</sup> and FDI<sup>1</sup> muscles, respectively, in SCI. Importantly, in SCI, TMS plasticity approaches have focused on motor cortex as the primary cortical target for inducing plasticity in cortical and/or spinal circuits. However, there is substantial evidence to indicate that somatosensory cortices are promising targets for inducing plasticity in these circuits. Decades of primate research have demonstrated the propensity for plasticity in somatosensory cortex that follows experience or practiced behaviour<sup>107,108</sup> cognitive factors of learning and attention<sup>109–112</sup> lesion of the peripheral or central nervous system<sup>113,114</sup> and direct micro-stimulation in the absence of peripheral stimulation.<sup>115</sup> It is notable that Belci et al.<sup>105</sup> observed reductions in cSP and improvements in somatic percepts, effects that may be attributed to direct stimulation of the primary somatosensory cortex.

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## Conflicts of interest

The authors declare there are no conflicts

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