Relationship between intracortical inhibition and motor behavior; implications for incomplete spinal cord injury

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The sensorimotor cortices of the human brain contain intracortical inhibitory circuits that influence the neural output to muscles. Intracortical circuits of short and long-interval intracortical inhibition (SICI and LICI) can be probed using paired-pulse TMS paradigms while recording activity from the muscles. We recently identified changes in SICI and LICI within the motor cortex in individuals with incomplete cervical spinal cord injury. Decreases in the range of intensities eliciting SICI recruitment were observed without a difference in the depth of SICI. Active LICI was increased at higher conditioning intensities relative to controls. These changes may be linked to plastic and physiological changes of GABAergic cortical systems with SCI. Here we discuss the role of SICI and LICI in motor behavior and how the observed changes in these measures that follow SCI may explain motor impairments seen in this population.

**Keywords:** Transcranial Magnetic Stimulation; Spinal Cord Injury; Intracortical Inhibition; Motor Cortex; Plasticity; Motor Behavior

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**Intracortical inhibition within primary motor cortex**

Inhibitory circuits play an important role in the modulation of cortical activity within sensorimotor areas of the human brain. Inhibitory GABAergic transmission within the primary motor cortex (M1) can be evaluated through the use of paired-pulse TMS paradigms. Specifically, short interval intracortical inhibition (SICI) can be assessed by delivering a conditioning stimulus (CS) with subthreshold intensity approximately 1-5 ms prior to a test stimulus (TS) and examining the suppression of the motor evoked potential (MEP) recorded via EMG from the muscle [1]. Extending the interstimulus interval between CS and TS delivery over M1 to a range of 50 - 200 ms also demonstrates inhibition of MEPs and has been termed long-interval intracortical inhibition (LICI) [2]. Modulation of descending efferent volleys during each of short or long intracortical inhibition is thought to be due to activation of separate neuronal populations on the basis of GABA receptor type [3-5]. Application of pharmacological agents demonstrate that SICI is influenced by ionotropic GABA_A receptors [4] while LICI is attributed to the activity of metabotropic GABA_B receptors [6]. The interactions between these two GABAergic systems has been explored recently using TMS-EEG and pharmacological intervention [5]. These researchers confirmed the cortical dependence of LICI on GABA_B activity and interactions between GABA_A and GABA_B mediated inhibition. They used TMS evoked EEG potentials...
to demonstrate that GABA\textsubscript{B} agonist (baclofen) enhanced LICI of all potentials associated with inhibition while GABA\textsubscript{A} agonist (diazepam) suppressed LICI of the later potentials but did not alter the response of the early potentials. Thus, activity of GABA\textsubscript{B} receptors is likely mediated by GABA\textsubscript{A} receptor activity, showing that SICI and LICI are not independent despite being primarily influenced by separate populations of GABAergic neurons \cite{3, 5}.

**Alterations to intracortical inhibitory action following spinal cord injury**

We recently demonstrated that SICI and LICI are altered following incomplete cervical spinal cord injury \cite{7}. In this study, individuals with cervical injury (C3 to C7) and a control group experienced paired-pulse TMS to assess SICI and LICI recruitment curves for the flexor carpi radialis (FCR) muscle of the forearm. For SICI, paired-pulse TMS to the motor cortex was assessed by delivering a range of CS intensities (60\% to 110\% of active motor threshold; AMT) at a fixed interval of 3 ms prior to the delivery of the TS during isometric contraction corresponding to 20\% of their maximum voluntary contraction (MVC) of FCR. Similarly, LICI was evaluated by delivering a range of CS intensities (90\% to 130\% AMT) with an interval of 150 ms during 20\% of MVC. Using these parameters, Mi and colleagues \cite{7} observed that SICI in incomplete SCI had comparable magnitudes of inhibition to that seen in uninjured controls. However the control group demonstrated significant SICI at CS intensities of 70, 80, and 90\% while only CS of 90\% AMT revealed significant SICI in the SCI group. Thus, the range of CS intensities capable of eliciting SICI was reduced in the SCI cohort. With regard to LICI, those with SCI showed greater LICI at the highest CS intensities (120\% and 130\% AMT) while the control group showed the opposite effect.

The authors speculate that the altered inhibitory responses following SCI may be attributed to a number of physiological and/or plastic adaptations that may occur within M1 following spinal transection \cite{8-10}. Previous studies have indicated that deafferentation of the human sensorimotor cortex results in decreased cortical concentrations of GABA \cite{11, 12} which may reduce levels of tonic inhibition within M1 circuitry influencing descending efferent signaling \cite{8}. These decrements in GABA availability within the motor cortices have been suggested to play a subsequent role in shaping plasticity following SCI \cite{9, 10}. Additionally, there may be impairments in the interactions between GABA\textsubscript{A} and GABA\textsubscript{B} receptor activity \cite{3, 8}. It has been demonstrated using pharmacological intervention that GABA\textsubscript{A} activity is impacted by transmission of GABA\textsubscript{B} receptors through presynaptic inhibition \cite{3}. Thus, it is possible that the observed differences in intracortical inhibition within M1 after SCI may be due to differences in GABA receptor activity that is independent of GABA availability. Therefore, the direct cause of altered intracortical inhibition observed in this SCI cohort is unclear.

Comprehensive explanations of the observed results are further challenged as previous literature has demonstrated that GABA\textsubscript{B} receptor agonists influence the activity of intracortical inhibition \cite{5, 6, 13}. Baclofen is one such agonist that reduces the magnitude of SICI via presynaptic inhibition of GABA\textsubscript{A} neuron populations by GABA\textsubscript{B} receptors \cite{3, 13, 14}. This medication is commonly prescribed to patients following SCI to reduce spasticity. Due to the fact that the majority of the cohort studied by Mi et al. were taking baclofen over a long period of time, the authors proposed that the narrowed range of CS intensities to elicit SICI in the SCI group was due to the influence of baclofen. This medication may also contribute to the increase in LICI at higher CS intensities in SCI relative to controls as baclofen functions to enhance GABA\textsubscript{B} receptor transmission. Therefore, regular doses of baclofen in the SCI group occlude conclusive interpretation of plasticity occurring within inhibitory motor circuits after incomplete spinal transection.

**Role of Intracortical Inhibition in Human Motor Behavior**

Intracortical interactions within M1 likely play a role in shaping motor behavior by increasing or decreasing cortical output to specific muscles during coordinated motor tasks \cite{15-18}. SICI has been studied in a variety of motor tasks, allowing us to illustrate the role of GABA\textsubscript{A} neural populations in motor behavior. First, simply activating a muscle via voluntary isometric contractions influences the magnitude of SICI. Research demonstrates that SICI of the active muscle is decreased yet remains unchanged in the antagonist muscle during tonic isometric wrist flexion and extension \cite{15}. Further, dynamic movements decrease SICI just prior to motor execution \cite{15} and increases in SICI magnitude occur as voluntary relaxation is initiated \cite{16}. Examination of neighboring muscles during more complex tasks has shown that SICI is sustained in nearby muscles that are not required for the desired movement \cite{17}. Thus, SICI appears to be participating in the selection of cortical projections that produce the desired motor outcome \cite{15-18}.

The impact of LICI on motor behavior has received less study. However, similar to SICI, LICI decreases with voluntary contraction of the target muscle \cite{18}. Another study examined the effect of volitional inhibition and found that
LICI was decreased during motor task performance \[^{19}\] illustrating that this circuit can be modulated by voluntary activity. Furthermore, vibrotactile stimulation of a muscle suppresses LICI within that muscle and increases it in surrounding muscles \[^{20}\]. These data suggest that LICI may also impact movement selection and modify motor behavior. Thus, despite the paucity of literature, it appears that the LICI circuit also plays a role in regulating motor output to the muscles during motor tasks \[^{19}\].

**Alterations to motor behavior in spinal cord injury**

The differences in both SICI and LICI following SCI that were demonstrated by Mi and colleagues \[^{7}\] may play a role in a variety of motor symptoms that are commonly experienced by patients that have sustained an SCI. Although SCI differences observed by Mi et al. \[^{7}\] reflect contributions from baclofen medication, plasticity within the deafferented sensorimotor cortices is likely to have occurred in this population \[^{8, 10, 11}\]. The influences of voluntary drive on intracortical inhibition within M1 described above may allow some inference of the impact that altered inhibition following SCI has on motor symptoms and behavior. For example, work by Rantalainen and colleagues \[^{21}\] demonstrated that SICI plays a role in force gradation. They measured SICI of the biceps under a number of different levels of tonic contraction and found that SICI was present at low submaximal force levels but became significantly reduced at higher force levels. Thus, SICI is likely to influence cortical mechanisms governing force gradation and deficits in this circuit in SCI \[^{7}\] may contribute to impaired precision performance and submaximal force control. Further, impaired precision control seen in SCI may be due to the influence that reduced SICI has on voluntary muscle relaxation \[^{16, 22}\]. A recent study in aging populations revealed that, in contrast to young healthy individuals, older adults did not show increases in SICI with voluntary grip relaxation and had longer grip relaxation times \[^{22}\]. Thus, it may be possible that the reduction in the ability of SCI populations to recruit SICI circuits impairs relaxation time following voluntary contraction. Finally, Beck and colleagues \[^{23}\] proposed that SICI plays a role in movement selection prior to motor execution. They observed changes in SICI of the abductor pollicis brevis muscle (APB) of the hand during varying levels of activity in the nearby first dorsal interosseous (FDI) muscle in participants with focal hand dystonia (FHD) \[^{23}\]. Specifically, SICI of APB was increased during initiation of the FDI movement but was unaltered throughout movement when compared to controls. Therefore, SICI may play a role in initiating surround inhibition within the cortex which has an influential role in movement selection \[^{23}\]. Drawing from the FHD research, it can be speculated that decrements in SICI recruitment following SCI may reduce the efficiency of movement selection and impair fine motor control.

Alterations in LICI in other neuromuscular diseases have demonstrated inconsistent results \[^{24}\]. Therefore, it is difficult to extend the observed differences in LICI to motor symptoms in SCI. Given the impact of LICI on motor behavior \[^{18-20}\], the lack of activity-related LICI modulation in SCI \[^{7}\] may reflect further decrement in movement selection and modulation during ongoing motor tasks. Therefore, alterations in both SICI and LICI are likely to contribute and/or be indicative of impaired control of cortical motor output.

**Conclusions**

In summary, intracortical inhibitory circuits within the motor cortex can be assessed in a number of conditions and tasks using paired-pulse TMS techniques \[^{1, 2}\]. These circuits are reflective of activity within different GABAergic neuronal populations that influence cortical motor outputs from M1 \[^{3}\]. Researchers in our lab have recently shown that these circuits are altered in SCI populations \[^{7}\]. This may be indicative of plastic or physiological changes regarding the availability and transmission of the neurotransmitter GABA, or the action of baclofen that facilitates GABA \(_{A}\) activity \[^{3, 6}\]. However, these inhibitory networks are speculated to play a role in movement regulation and behavior in both healthy and diseased states \[^{18-22}\]. These inferences, together with novel information obtained in our recent study \[^{7}\], allow for interpretation of how intracortical inhibition is linked to some of the motor symptoms that are prominent following SCI. Further research should examine whether changes in SICI and LICI are paralleled by deficits in specific motor behaviors in SCI.

**Conflicting interests**

The authors have declared that no conflict of interests exist.

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**References**


