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REVIEW | *Spinal Control of Motor Outputs*

Afferent input and sensory function after human spinal cord injury

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Ozdemir RA, Perez MA. Afferent input and sensory function after human spinal cord injury. *J Neurophysiol* 119: 134–144, 2018. First published July 12, 2017; doi:10.1152/jn.00354.2017.—Spinal cord injury (SCI) often disrupts the integrity of afferent (sensory) axons projecting through the spinal cord dorsal columns to the brain. Examinations of ascending sensory tracts, therefore, are critical for monitoring the extent of SCI and recovery processes. In this review, we discuss the most common electrophysiological techniques used to assess transmission of afferent inputs to the primary motor cortex (i.e., afferent input-induced facilitation and inhibition) and the somatosensory cortex [i.e., somatosensory evoked potentials (SSEPs), dermatomal SSEPs, and electrical perceptual thresholds] following human SCI. We discuss how afferent input modulates corticospinal excitability by involving cortical and spinal mechanisms depending on the timing of the effects, which need to be considered separately for upper and lower limb muscles. We argue that the time of arrival of afferent input onto the sensory and motor cortex is critical to consider in plasticity-induced protocols in humans with SCI. We also discuss how current sensory exams have been used to detect differences between control and SCI participants but might be less optimal to characterize the level and severity of injury. There is a need to conduct some of these electrophysiological examinations during functionally relevant behaviors to understand the contribution of impaired afferent inputs to the control, or lack of control, of movement. Thus the effects of transmission of afferent inputs to the brain need to be considered on multiple functions following human SCI.

spinal cord injury; somatosensory cortex; somatosensory evoked potentials; sensory cortex; dorsal column; sensory function

NEW CASES OF TRAUMATIC SPINAL CORD INJURY (SCI) number approximately 17,000 each year in the U.S. Worldwide, millions of people live with the consequences of SCI. Most injuries damage the spinal cord bilaterally and affect the integrity of afferent (sensory) axons projecting through the spinal cord dorsal columns to the brain. Because of their location in the spinal cord, dorsal columns pathways are especially vulnerable to SCI (Kakulas 1999; Norenberg et al. 2004). Thus examination of the ascending sensory tracts is critical to consider when the extent of the injury as well as the plasticity and recovery processes after an injury to the spinal cord are being assessed.

In this review, we discuss the most common electrophysiological techniques used to examine transmission of afferent inputs to the primary motor cortex (i.e., afferent input-induced facilitation and inhibition) and the somatosensory cortex [i.e., somatosensory evoked potentials (SSEPs), dermatomal SSEPs (dSSEPs), and electrical perceptual thresholds (EPTs)] following SCI. The dorsal columns contain the sensory axons that conduct afferent inputs from different sensory receptors to the brain via multisynaptic pathways to provide information about the ongoing state of the motor system, which is critical for motor actions (Amaral 2013; Kaas et al. 2008). Anatomically, the ascending sensory systems consist of three distinct pathways: the dorsal column–medial lemniscal pathway, the anterolateral system, and the somatosensory pathways to the cerebellum (Amaral 2013; Patestas and Gartner 2006). The dorsal column–medial lemniscal pathway involves the fasciculus gracilis, fasciculus cuneatus, and medial lemniscus, which relay discriminative tactile sense, vibratory sense, and position sense. The anterolateral system includes the spinothalamic, spinoreticular, spinomesencephalic, spinotectal, and spinohypothalamic tracts, which relay information mainly about pain, temperature sensation, nondiscriminative (crude or poorly localized) touch, pressure, and some proprioceptive sensation. The somatosensory pathways to the cerebellum include the anterior, posterior, and rostral spinocerebellar and cuneocer-

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ebellar tracts, which relay proprioceptive and some pain and pressure information. The spinocerebellar tract is involved in unconscious proprioception and transmits information necessary for the maintenance of normal muscle tone, posture, and coordination. When movements are performed, this sensory information is important, but there is very little conscious awareness of these sensations, and the precise nature of the processes contributing to active proprioception (i.e., proprioception with muscle contraction) are still unclear (Proske and Gandevia 2012). Because alterations in brain white matter structures such as the cerebellum have been reported in humans with acute and chronic SCI (Zheng et al. 2017), changes in these pathways are important to consider after injury. It is also important to note that conscious perception of sensory information from an external stimuli is largely mediated by the dorsal column–medial lemniscal pathways and the spinothalamic projections. In humans, most electrophysiological assessments of sensory function express the stimulus intensity as a percentage of the perceived electrical threshold; therefore, these pathways play a large role in these assessments.

Anatomical and electrophysiological studies have shown considerable plasticity in sensory pathways, which may contribute to functional recovery following SCI. In nonhuman primates, lesions of the dorsal columns at the cervical spinal cord level result in large-scale reorganization in multiple cortical areas, including the primary motor cortex and the somatosensory cortex (Chand and Jain 2015; Jones and Pons 1998). These lesions abolish or largely impair the ability to discriminate tactile textures, frequencies, and directions of a tactile stimulus, and in many cases, motor control (Kaas 2002; Mountcastle 2005). In humans, degenerative diseases that target the dorsal columns, such as neurosyphilis and Friedreich's ataxia, have provided insights into the impairments following a dorsal column lesion (Harrison and Braunwald 2001). Patients with these diseases present clinical deficits in two-point discrimination, proprioception and vibratory sense, indicating that the dorsal columns in humans are functionally similar to those of nonhuman primates. Although in humans complete and isolated injury to the dorsal columns is rare, histological studies in individuals with SCI have shown that large damage to the dorsal columns results in impairments in the perception of fine touch and vibration, temporal and spatial discrimination, and proprioception (Nathan et al. 1986). Note that the loss of light touch and pressure sense was associated with additional damage to the anterolateral spinal cord, likely the anterolateral spinothalamic tract, and that isolated damage to the anterolateral spinal cord did not affect tactile ability or proprioception (Nathan et al. 1986). In this review, we consider the effect of afferents from peripheral and cutaneous nerves on corticospinal excitability measured by motor evoked potentials (MEPs) elicited in upper and lower limb muscles by transcranial magnetic stimulation (TMS) over the primary motor cortex. We discuss how these effects might involve cortical and subcortical mechanisms depending on the time of afferent stimulation, which is important to consider when upper and lower limb muscles are tested in humans with SCI. We also discuss how the effect of the same sensory input can be recorded by surface electroencephalographic electrodes over the somatosensory cortex in the form of SSEPs. SSEPs are used to examine spared sensory function, together with dSSEP and EPT outcomes, which use the dermatomes defined by the International Standards for Neurological Classification of Spinal Cord Injury for their point of afferent stimulation (Ellaway et al. 2011; Haefeli and Curt 2012; Kramer et al. 2008, 2010). SSEPs have been widely used for clinical diagnosis since the 1970s, whereas TMS has been used to elicit MEPs and examine corticospinal excitability since 1985 (Barker et al. 1985). Although it was recognized soon after the development of TMS that MEPs can be used as an adjunct outcome to increase the sensitivity of clinical outcomes following SCI (Curt and Dietz 1997; Hayes et al. 1991), to date only a few studies have examined the effect of afferent input onto MEPs after injury (Bailey et al. 2015; Hayes et al. 1991; Roy et al. 2010), and this might represent an important area for future investigations.

Electrophysiological Examinations

Afferent input-induced facilitation and inhibition. Animal studies have shown that afferent input can influence motor cortical activity via dense intracortical projections between the primary motor cortex and the somatosensory cortex (Goldring et al. 1970). The stimulation of afferent fibers from the somatosensory cortex can produce both excitation and inhibition in motor cortical cells (Porter et al. 1990). In agreement, studies in humans using TMS over the primary motor cortex have shown that electrical stimulation of peripheral and cutaneous afferents, which project through the spinal cord dorsal columns, in upper limb muscles in most cases suppresses corticospinal excitability at interstimulus intervals (ISIs) around 20–40 ms (Delwaide and Olivier 1990; Lei and Perez, in press; Tokimura et al. 2000), facilitates corticospinal excitability at ISIs around 50–100 ms (Devanne et al. 2009; Komori et al. 1992), and has a second inhibitory effect at ISIs between 100 and 1,000 ms (Chen et al. 1999a). In lower limb muscles, corticospinal excitability decreases at ISIs around 20–40 ms (Poon et al. 2008; Roy et al. 2010; Urbin et al. 2017) and increases at ISIs around 45–65 ms (Deletis et al. 1992; Roy et al. 2010). Although the general pattern of facilitation and inhibition is similar in upper and lower limb muscles when conduction delays are considered, with inhibition taking place at short ISIs and facilitation at longer ISIs, note that effects at ISIs above 100 ms, to our knowledge, have not been reported in the lower limb.

Although dorsal column lesions following SCI may disrupt or abolish the integration of afferent inputs into the primary motor cortex, only a few studies have examined the effects of afferent transmission on corticospinal excitability in humans with SCI (Bailey et al. 2015; Hayes et al. 1991; Roy et al. 2010). For example, contrary to findings in healthy controls, electrical stimulus to the median nerve at an ISI around 20 ms did not suppress the size of an MEP elicited by TMS in a wrist flexor muscle in SCI participants with chronic incomplete cervical injury (Bailey et al. 2015). Similarly, a conditioning electrical stimulus to the common peroneal nerve around 20–40 ms before TMS suppressed the size of the MEPs in the tibialis anterior (TA) muscle in humans with chronic incomplete SCI to a lesser extent than in control subjects (Roy et al. 2010). Interestingly, in the lower limb, there was a tendency for MEPs to be more suppressed by electrical stimulation of homonymous (common peroneal nerve) compared with heteronymous (posterior tibial nerve) afferents (Fig. 1). Although it is unclear whether this might be related to the stronger modulation of the TA muscle by homonymous afferents (De-

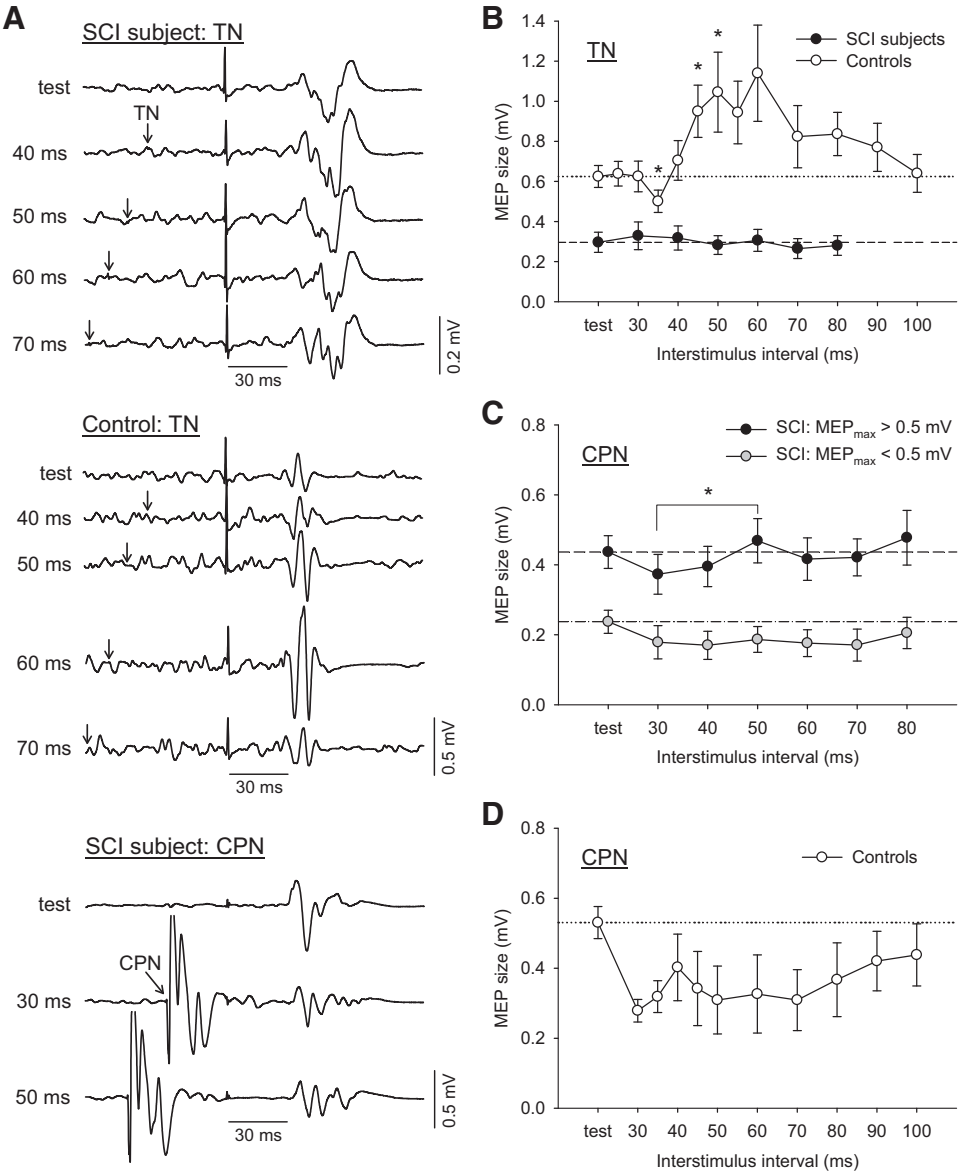

Fig. 1. Effect of peripheral nerve stimulation on motor evoked potentials (MEPs). *A*: raw traces showing the effect of a preceding tibial nerve (TN) stimulus in an SCI subject (*top* traces) and a control subject (*middle* traces) and from a preceding common peroneal nerve (CPN) stimulus (*bottom* traces) delivered at interstimulus intervals (ISI) of 40–70 ms on the tibialis anterior (TA) MEP. *B*: graph shows test MEP and conditioned MEP by TN stimulation amplitudes in 8 SCI subjects (solid circles) and 10 controls (open circles). *C*: graph shows the effect of CPN stimulation on MEPs in 11 SCI subjects having a maximum MEP (MEP_{max}) >0.5 mV (solid circles) and 5 subjects with an MEP_{max} <0.5 mV (shaded circles). *D*: graph shows the effect of CPN stimulation on MEPs in 4 controls. The test MEP in each graph is indicated by a dotted line. Error bars indicate SEs. $*P < 0.05$, significant differences compared with the test MEP in *B* and compared with the MEP at the 30-ms ISI in *C*. [Modified from Roy et al. (2010) with permission.]

letis et al. 1992) and/or to the damage by the injury, it is important to consider these differences when the aim is to assess and/or enhance the excitability of residual corticospinal projections after SCI.

An important question is, which neural mechanisms contribute to the suppressive effects of afferent input on corticospinal excitability and how are these mechanisms affected by SCI? In control subjects, the short-latency suppressive effects of peripheral and cutaneous nerve stimulation on corticospinal excitability are thought to be mediated by cortical mechanisms in upper limb muscles. Evidence has shown that the I2 and I3 waves elicited by TMS over the hand representation of the primary motor cortex, which likely result from transsynaptic activation of corticospinal neurons by intracortical circuits (Di Lazzaro et al. 2012), are reduced when afferent fibers are stimulated at a short-latency ISI (Tokimura et al. 2000). Also, a cutaneous stimulus applied at short-latency before a conditioning TMS pulse reduced the magnitude of short-interval intracortical inhibition (Ridding and Rothwell 1999), an outcome that likely reflects activation of γ-aminobutyric acid (GABA) inhibitory circuits in the primary motor cortex (Di Lazzaro et al. 2000; Hanajima et al. 1998; Ziemann et al. 2001). However, note that the suppressive effects of electrical stimulation of peripheral and cutaneous afferents on corticospinal excitability at longer ISIs around 100–1000 ms are likely related to the contribution of cortical (Chen et al. 1999b; Nakamura et al. 1997) and subcortical mechanisms (Barry et al. 2013; McNeil et al. 2009, 2011).

Because GABAergic mechanisms play a role in modulating the effect of afferent input on the primary motor cortex, transmission in GABAergic pathways is an important factor to consider when sensory processing after SCI is being examined. Studies have shown that individuals with SCI show decreased short-interval intracortical inhibition compared with controls in a resting condition (Shimizu et al. 2000). Late I waves measured by paired-pulse TMS, which are also likely to reflect to some extent activity in intracortical circuits, are impaired at rest in humans with SCI (Cirillo et al. 2016). However, transmission in this pathway also needs to be considered during voluntary activity. For example, the magnitude of short-inter-

val intracortical inhibition is altered in humans with incomplete cervical SCI compared with controls during movement preparation when subjects are instructed to stop but not to execute upcoming rapid finger movements (Federico and Perez, in press). Also, during a unilateral tonic voluntary contraction, the magnitude of short-interval intracortical inhibition is modulated to a similar extent in control and SCI participants in the contracting hand (Barry et al. 2013), but not in the primary motor cortex ipsilateral to the contracting hand (Bunday and Perez 2012a; Bunday et al. 2013). The abnormal modulation of short-interval intracortical inhibition in the ipsilateral hemisphere during voluntary activity is consistent with evidence showing that compensatory changes take place in both hemispheres after SCI (Nishimura and Isa 2009). Indeed, during some unilateral hand movements, SCI individuals show changes in both sensory and motor cortices compared with controls (Bruehlmeier et al. 1998). It is also important to consider that the somatosensory cortex (Chand and Jain 2015; Jones and Pons 1998) and the primary motor cortex (Oudega and Perez 2012) undergo substantial reorganization following SCI. Thus it is possible that abnormal effects of afferent input on MEP size represent not only deficits or failures of sensory inflow but also an altered responsiveness after injury. For example, motor cortical maps measured by MEPs elicited by TMS are enlarged and show shifts in their center of gravity (Freund et al. 2011; Levy et al. 1990; Topka et al. 1991), and MEPs have higher thresholds and longer latencies (Bunday and Perez 2012a, 2012b), after injury. SCI not only disrupts transmission in pathways that are involved in the control of voluntary actions from the cortex but also can severely impair transmission on descending neuromodulatory pathways from the brain stem (Heckman et al. 2003; Hultborn et al. 2004). Neuromodulators such as serotonin and noradrenalin facilitate persistent inward currents in motoneurons which reemerge weeks after SCI and contribute to the recovery of motor function and the development of spasticity (Heckman et al. 2005). These changes might also contribute to changes in MEP size. Motoneuron receptive fields are widened and transmission of sensory inputs to the motoneurons and spinal cord circuits is altered after injury (D'Amico et al. 2014; Johnson et al. 2013). Transmission in pathways contributing to control the quality of proprioceptive sensory inflow, such as gamma motoneurons, which play an important role in adjusting the sensitivity of muscle spindles and receive input from descending pathways (Burke et al. 1979), is also important to consider in these examinations. Indeed, single nerve action potentials recorded from lower sacral nerve roots during surgery have revealed abnormal activation patterns of gamma motoneurons in humans with SCI (Schalow 2010). These studies together suggest that after SCI, there is an impaired transmission in different pathways and/or altered compensatory mechanisms that need to be considered when these results are being interpreted.

Note that in lower limb muscles, as in upper limb muscles, electrical stimulation of a peripheral and cutaneous nerve suppresses corticospinal excitability at short ISIs and facilitates corticospinal excitability at longer ISIs. However, the suppressive effects at ISIs of 20–40 ms are thought to have a spinal origin (Roy et al. 2010; Urbin et al. 2017). Because afferent inputs from the posterior tibial nerve reach the somatosensory cortex at ISIs around 40 ms (Perez et al. 2005), it is less likely that suppressive effects noted here involved cortical mechanisms. This is in agreement with evidence showing that stimulation of cutaneous afferents at these short conditioning latencies suppresses a monosynaptic reflex response in the TA muscle (Delwaide et al. 1981; Delwaide and Crenna 1984). It is also known that at these short ISIs, Renshaw cells mediating recurrent inhibition to spinal motoneurons are present (Katz and Pierrot-Deseilligny 1999). In SCI subjects, the MEPs in the TA muscles were less suppressed by common peroneal nerve stimulation compared with controls, and these effects were delayed by around 10 ms, which is consistent with delays observed in SSEPs after SCI (see *SSEPs and dSSEPs*). This agrees with evidence showing that humans with SCI have a reduced spinal inhibition tested at similar ISIs (Knikou 2007; Norton et al. 2008). Also note that in lower limb muscles, stimulation of the tibial nerve at the ankle 45–50 ms before a TMS pulse facilitated the TA MEP size in controls but not in individuals with SCI regardless of the severity of injury (Roy et al. 2010), likely mediated by cortical mechanisms (Nielsen et al. 1997; Roy et al. 2010). Thus the effect of afferent input on corticospinal excitability might involve changes in transmission in cortical and spinal mechanisms depending on the timing of these effects, which need to be considered separately when upper and lower limb muscles are tested.

The time of arrival of afferent input onto the primary motor cortex and the spinal cord is also relevant to consider in the context of plasticity-induced protocols. Indeed, the facilitatory and inhibitory effects of paired associative stimulation (PAS) plasticity paradigms depend on the timing of arrival of peripheral inputs at the primary motor cortex (Stefan et al. 2000) and/or depolarization of spinal motoneurons (Taylor and Martin 2009). Long-lasting potentiation of synaptic strength can be induced by precisely timing the arrival of presynaptic action potentials before postsynaptic depolarizing action potentials, a process known as spike timing-dependent plasticity (STDP; Bi and Poo 1998; Dan and Poo 2004). STDP-like plasticity targeting the primary motor cortex has shown to be successful in enhancing voluntary motor output and corticospinal excitability in lower limb muscles in humans with incomplete SCI (Roy et al. 2010) (see Fig. 1). Evidence showed that when electrical stimulation of the common peroneal nerve is repetitively paired with TMS over the leg motor cortex at an ISI around 60 ms, resting MEPs in the TA muscle are facilitated for ~10 min after the intervention in humans with incomplete SCI (Roy et al. 2010). Importantly, PAS was more effective in SCI participants in whom the afferent stimuli had a larger facilitatory effect of TA MEP size, suggesting a role for the integrity of dorsal columns pathways in PAS-induced plasticity at the cortical level. PAS interventions targeting the spinal cord also have been used to strengthen spared corticospinal-motoneuronal synaptic connections in both upper (Bunday and Perez 2012b) and lower limb muscles (Urbin et al. 2017) in humans with incomplete SCI. Although these studies used supramaximal stimulation to antidromically depolarize spinal motoneurons, spinal motoneurons could also be depolarized by the arrival of afferent inputs. Notably, in lower limb muscles, the time of a conditioning electrical stimulus to the common peroneal nerve was critical for suppressing descending volleys elicited by TMS and for successfully evoking the inhibitory PAS type of plasticity (Urbin et al. 2017; Fig. 2), supporting the view that the timing of arrival of afferent input at either the

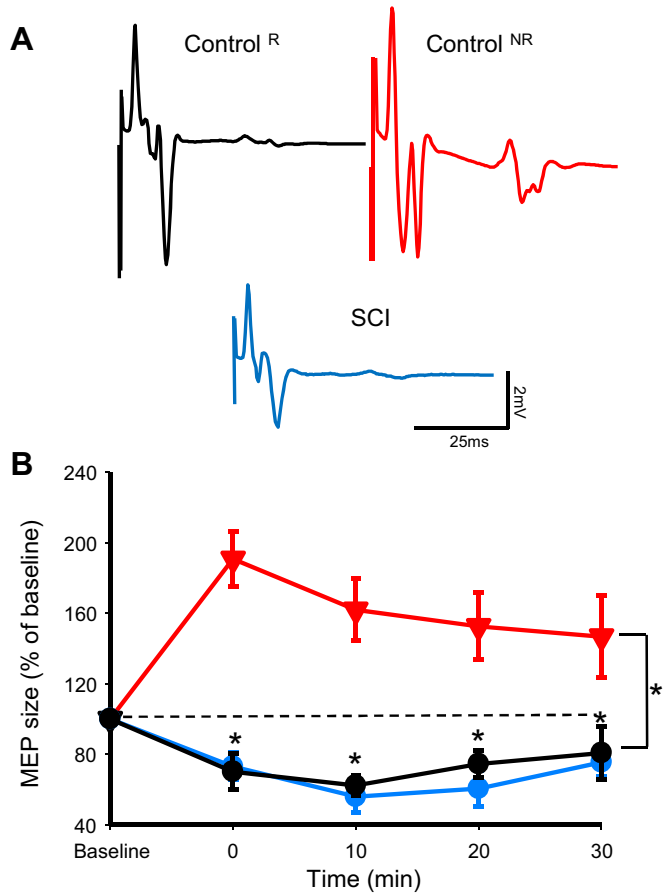

Fig. 2. Paired corticospinal-motoneuronal stimulation (PCMS). *A*: raw EMG traces from the TA muscle in representative controls (black and red lines) and in a subject with incomplete chronic SCI (blue) during inhibitory PCMS, where antidromic potentials after supramaximal electrical stimulation of the common peroneal nerve arrived 15 ms before corticospinal volleys elicited by transcranial magnetic stimulation at the spinal motoneurons. Traces show the maximal motor response (M_{max}) at a short latency. Note that MEPs following the M_{max} are suppressed in the SCI participant (blue) and in the control participant (black) who responded to the inhibitory PCMS (control responder; R); a larger MEP was observed in the control participant (red) who did not respond (control nonresponder; NR) to the inhibitory PCMS. *B*: graph shows group data (control responders, $n = 7$; control nonresponders, $n = 6$, and SCI, $n = 7$) to the inhibitory PCMS. The abscissa shows the time at which measurements were taken (baseline, immediately after *time 0*, and 10, 20, and 30 min after the stimulation). The ordinate shows the size of the MEP expressed as a percentage of the MEP at baseline in control responders (black circles), control nonresponders (red triangles), and SCI participants (blue circles). The horizontal broken line indicates the MEP size at baseline. Note that in control nonresponders, stimulation of the CPN was not adequately timed to suppress the TA MEP size, resulting in an inability to suppress MEPs by the inhibitory PCMS. Error bars indicate SEs. $*P < 0.05$. [Modified from Urbin et al. (2017) with permission.]

primary motor cortex or the spinal cord can be a critical factor to consider for future interventions to induce plasticity in humans with SCI. Also, after SCI, motoneurons have different sensitivity to neuromodulators, such as serotonin, which can have profound effects on the induced net postsynaptic depolarization effects. For example, stimulation of cutaneous afferents produces a long depolarization of motoneurons following SCI, as opposed to the cycle of excitation and inhibition observed in control participants (Norton et al. 2008), which could have effects on the aftereffects of PAS and STDP protocols.

SSEPs and dSSEPs. Another electrophysiological test widely used to examine the integrity of afferent sensory pathways to the somatosensory cortex following SCI are SSEPs and dSSEPs (Chabot et al. 1985; Chéliout-Héraut et al. 1998; Curt and Dietz 1999; Haefeli and Curt 2012; Li et al. 1990; Perot and Vera 1982). SSEPs are usually evoked by bipolar transcutaneous electrical stimulation during repeated pulses over peripheral and cutaneous nerves with a stimulation rate of 3–5 Hz and a pulse duration of 0.1–0.2 ms at 3–5 times above the sensory threshold (Cruccu et al. 2008). The placement of recording scalp electrodes generally follows 10–20 international system EEG electrode placements in which parietal electrodes are placed over CP3-CP4 while frontal electrodes are placed over F3–F4 with a noncephalic reference, preferably at earlobes ipsilateral to the stimulation. In general, 300-500 repeated pulses are averaged to extract clear SSEP waveforms. Evoked potentials can also be elicited by direct stimulation of the dorsal spinal cord through epidural electrodes and recorded from the spinal cord to monitor neurological function during surgery (Park and Hyun 2015). SSEPs are considered to reflect the full extent of sensory pathology along the dorsal column ascending tracks but do not provide information regarding the involvement of individual spinal segments. To obtain this information, studies have focused on electrical stimulation of cutaneous receptors over individual dermatomes by recording dSSEPs (Ellaway et al. 2011; Haefeli and Curt 2012; Kramer et al. 2008, 2010). dSSEPs are elicited by repetitive electrical pulses with standard surface or ring electrodes placed over the key standardized dermatomes defined by the international standard classification of SCI using an intensity above the perceptual threshold (Haefeli and Curt 2012; Kramer et al. 2010). Compared with conventional SSEPs, which are typically restricted to examine lumbar and cervical regions due to the limited number of peripheral nerve stimulation sites, dSSEPs reflect integrity of localized sensory inputs from different segments of the spinal cord (Fig. 3).

Little is known about the neural mechanisms contributing to the SSEP components after SCI. In control subjects, for medial nerve SSEPs, the P14/N20 component results from subcortical contributions, likely reflecting the arrival of medial lemniscal signals to the thalamus (Desmedt and Cheron 1981; Lee and Seyal 1998). Studies agree that the N20/P25 component reflects activation of area 3b (Allison et al. 1991; Forss et al. 1994; Huttunen et al. 2006), whereas the P25/N33 component reflects activation of area 1 (Allison et al. 1991; Ishikawa et al. 2007; Jones et al. 1978). Area 2, which has relatively dense interhemispheric connections, communicates with area 1 (Allison et al. 1991) and has reciprocal connections with the primary motor cortex (Yumiya and Ghez 1984). More comprehensive studies analyzing the effect of the injury on these different SSEP components might provide a more in depth understanding of the pathophysiology of SCI. It is also known that in control subjects, SSEPs are suppressed during voluntary activity compared with rest and that the somatosensory cortex contributes to filter irrelevant signals during a motor behavior (Borich et al. 2015). Sensory gating takes place not only in the contralateral but also in the ipsilateral somatosensory cortex to a contracting hand, likely involving transcallosal pathways (Lei and Perez, in press). Notably, to date, almost no information exists about sensory gating in the contralateral and ipsi-

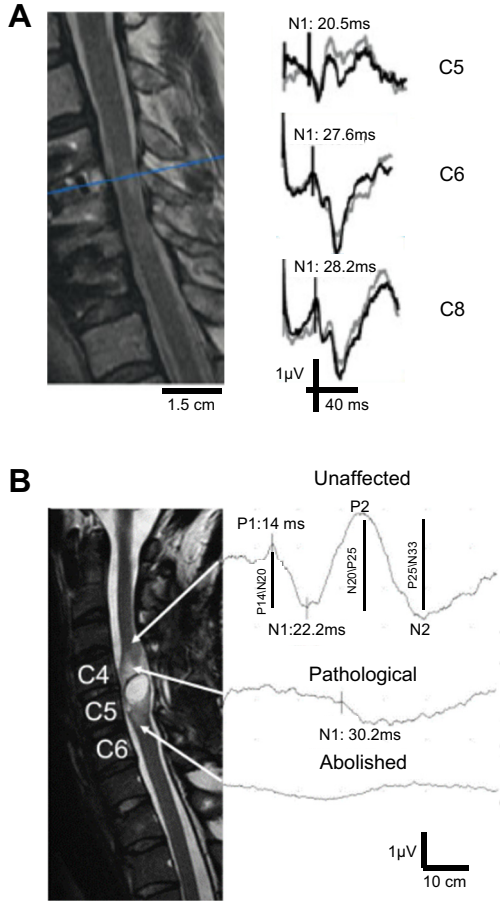

Fig. 3. Dermatomal somatosensory evoked potentials (dSSEPs). *A*: magnetic resonance image (*left*) of an incomplete (AIS D) tetraplegic individual with corresponding dSSEPs (*right*) above (C5), at (C6), and below (C8) the injury level. dSSEPs were collected at 2 consecutive trials (gray traces, first trial; black traces, second trial) to show the consistency of traces. Also notice that N1 latency is substantially increased at and below the injury level, indicating sensitivity of dSSEPs to detect injury level. [Modified from Haefeli and Curt (2012).] *B*: magnetic resonance image (sagittal T2-weighted) of an individual with complete SCI (C4, ASIA A) with dSSEPs tested above, at, and below the injury level. Distinct SSEP components (P14/N20, N20/P25, P25/N33) are identified in the unaffected waveform. Notice that dSSEP latency and waveform are comparable to those in dSSEPs from an individual with incomplete SCI (*A*) at intact dermatomes. However, dSSEPs at and the below the injury level in an individual with complete SCI (*B*) are pathological and abolished, respectively, showing the sensitivity of dSSEPs to assess level of injury. [Modified from Kramer et al. (2008) with permission.]

lateral somatosensory cortex during a voluntary motor behavior in humans with SCI.

It has been proposed that SSEPs can be used to examine the severity and level of injury; however, we discuss studies in more detail that highlight that this proposition may be less direct. For example, a study used tibial nerve stimulation to compare SSEPs between controls and individuals with SCI with different degrees of sensory and motor function deficits (Chabot et al. 1985). These individuals were tested several weeks and months after the injury following a rehabilitation period. It was found that SSEPs had delayed latencies and decreased amplitudes in humans with SCI compared with control subjects. Neither SSEP latencies nor amplitudes were different between individuals with incomplete SCI having deficits in sensory and motor function and those with complete SCI who had no sensory and motor function below the level of injury. SSEPs from individuals with chronic incomplete SCI also failed to reflect within-group variations in sensory function. Another study showed that SCI participants with absent SSEPs had higher vibration thresholds compared with those with normal and impaired SSEPs, and no vibration threshold differences were found between SCI participants with normal and impaired SSEPs (Hayes et al. 2002). The possibility of eliciting SSEPs in participants with a clinical diagnosis of complete loss of sensory function highlights discrepancies between clinical and physiological exams of sensory function described in the literature (Macklin et al. 2016, 2017). In agreement, some studies have reported that SSEPs are present in subjects with complete SCI (Chabot et al. 1985; York et al. 1983; Young 1982) and absent in those with incomplete SCI (Jacobs et al. 1995). Others who tested SSEPs and found a clear difference between individuals with complete and incomplete SCI observed that when an SSEP was not present in an individual with a clinical diagnosis of a complete injury, it was possible to detect a sensory response by using dSSEPs (Chéliout-Héraut et al. 1998). SSEPs have also been tested by electrical stimulation of the median and ulnar nerve after cervical SCI to make inferences about the level of injury (Curt and Dietz 1996). The median (C5–C7) and ulnar (C8-T1) nerves originate from different spinal cord segments; therefore, it was proposed that the anatomical level of injury could be determined for upper and lower cervical segments on the basis of the stimulated nerve. Ulnar nerve SSEPs were pathologically delayed or abolished in individuals with most higher compared with lower cervical lesions. Although this might apply in some cases, such a selective assessment it might be difficult to achieve in many other cases, because spinal injuries usually target more than one spinal cord segment at a time. In the same study, SSEPs elicited by median nerve stimulation were less sensitive to determining differences in individuals with lesions of higher and lower cervical segments. Taken together, these studies suggest that the amplitude and latency of SSEPs are variable in SCI subjects with different degrees of spared sensory function, highlighting the need for more sensitive electrophysiological outcomes to assess the severity and level of sensory function following SCI.

dSSEPs provide an opportunity to access individual segments of the spinal cord to examine the integrity of sensory pathways adjacent to the level of lesions in more detail compared with conventional SSEPs (Boakye et al. 2012; Kramer et al. 2010). Evidence has shown that dSSEPs have increased onset latencies at corresponding dermatomes compared with nonaffected dSSEPs in SCI and control subjects. Longitudinal assessments also have reported that initially pathological dSSEPs with prolonged latencies show significant changes toward normative values in individuals with SCI during the recovery period. Longer dSSEPs latencies were associated with high perceptual thresholds during electrical stimulation of the same dermatomes (Kramer et al. 2010). These results together suggest that measurements of localized sensory evoked potentials over corresponding dermatomes provide an opportunity to access individual segments of the spinal cord to examine the integrity of sensory pathways adjacent to the level of lesions in better detail compared with conventional SSEPs (Boakye et al. 2012). Although dSSEPs might improve the resolution of noninvasive electrophysiology of ascending sensory tracts in humans with SCI, more studies are needed to monitor this outcome at

multiple time points, using a larger sample size in more homogeneous SCI participants.

Most studies agree that SSEPs and dSSEPs have a good prognostic value after SCI. For example, individuals with SCI with an abolished tibial nerve SSEP at early stages postinjury had lower motor scores and showed less improvement from initial testing within the first few months postinjury compared with those with present but pathological tibial nerve SSEPs (Li et al. 1990). The presence of a tibial nerve SSEP after SCI has been related to the ability to regain ambulatory capacity (Curt and Dietz 1997; Jacobs et al. 1995) and benefit from locomotor training (Ellaway et al. 2011). The presence of pudendal SSEPs and spared conscious perineal sensation, although not commonly measured, has also been associated with the recovery of ambulatory after injury (Curt and Dietz 1997, 1999). Similarly, SSEPs recorded from median and ulnar nerve stimulation predicted outcomes of hand function in participants with acute and chronic cervical SCI (Curt and Dietz 1996). Although SSEP latencies do not change over the first year after injury and changes in SSEP amplitudes do not correlate with the amount of recovery, individuals with complete or incomplete SCI with an early presence of SSEPs showed more recovery throughout time, highlighting the importance of this outcome on prognosis (Spiess et al. 2008). Similarly, individuals with present dSSEPs below the neurological injury level within the first months postinjury had a better ambulation prognosis compared with those with absence of dSSEPs below the injury level (Chéliout-Héraut et al. 1998).

EPT. The EPT is an alternative method for the assessment of sensory function that can be easily implemented in clinical settings. EPTs are examined by using repeated electrical pulses over the key dermatomes defined by the international standard classification of SCI with the use of an intensity above the perceptual threshold (3 Hz, 0.2–0.5 ms). The EPT exam measures the sensory threshold, defined as the minimum electrical stimulus intensity needed to perceive the stimuli applied to the skin (Davey et al. 2001). It was initially used to monitor peripheral nerve function (Rendell et al. 1989) and was then adapted to be used at key dermatome points in participants with SCI (Savic et al. 2006, 2011). Evidence to date has shown that the EPT exam is a sensitive tool to assess sensory function that can complement clinical assessment of sensory function in humans with SCI (Savic et al. 2006, 2011; Macklin et al. 2016, 2017). The EPT is also reliable across examiners and has sufficient sensitivity to assess sensory function across multiple sessions (Lauschke et al. 2011; Savic et al. 2011). Studies have shown that EPT measures may be more sensitive to reveal spared sensory function at dermatomes below the injury level or subclinical sensory deficits above the injury level that are not detected by clinical assessments (Ellaway et al. 2011;

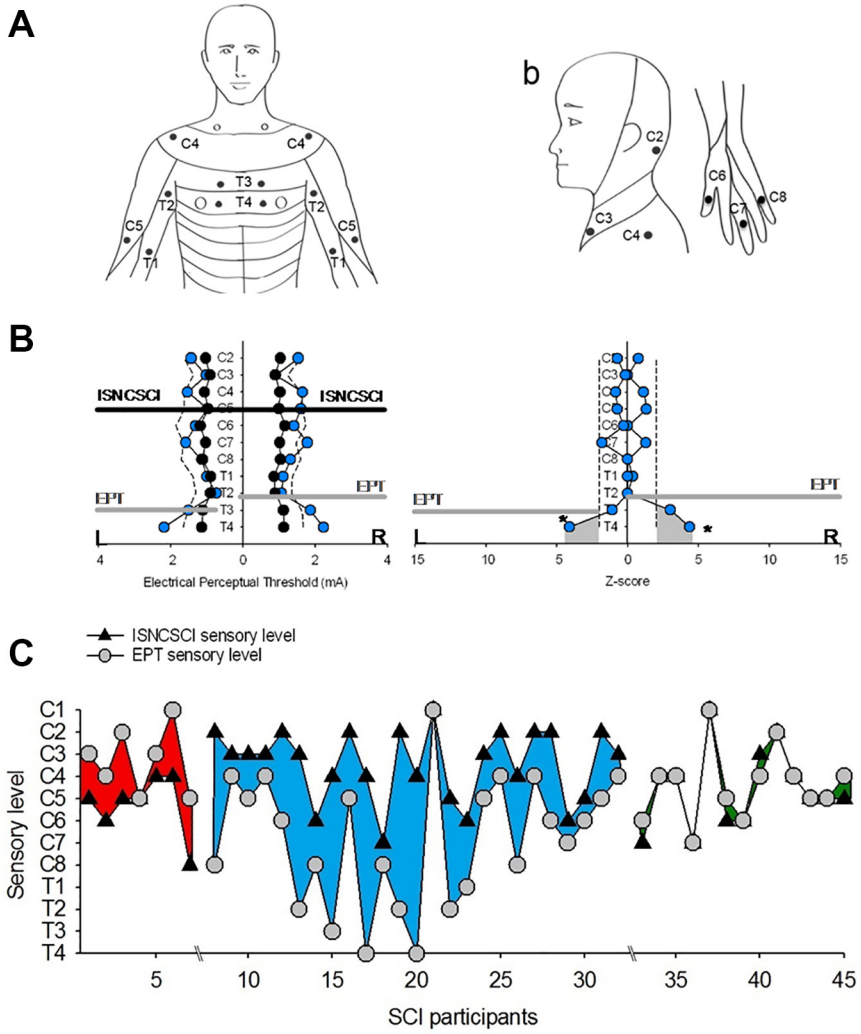

Fig. 4. Electrical perceptual threshold (EPT). *A*: sensory key points by spinal dermatomes reproduced from the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI). ISNCSCI key points in dermatomes from C2 to T4 were tested in the study of bilaterally tested participants with acute (<1 yr), chronic (>1 to 10 yr), and extended-chronic (>10 yr) incomplete cervical SCI. *B*: EPT values and *Z* scores are shown in a representative SCI subject (blue circles) and control participants (black circles). Note that a *Z* score represents the distance between the raw score and the population mean in units of the standard deviation (SD). A positive *Z* score indicates that the raw score is above the mean. Dotted lines indicate values 2SD from the mean of sex- and age-matched controls. ISNCSCI sensory level is indicated by a horizontal black line, and the EPT level is shown by a horizontal gray line. In this participant with chronic SCI, the EPT and *Z* scores show a bilateral asymmetric sensory impairment below dermatome T3 on the left side and T2 on the right side. *C*: the abscissa shows all SCI participants tested (n = 45), and the ordinate shows the sensory level detected by the EPT (gray circles) and ISNCSCI (black triangles) exams in the left side of the body in individuals with acute (red shaded area), chronic (blue shaded area), and extended-chronic SCI (green shaded area). Note that the sensory level detected by the EPT was above or below the sensory level detected by the ISNCSCI exam in the majority of SCI participants with acute and chronic SCI, respectively, whereas very small differences were observed between results from both sensory exams in individuals with extended-chronic SCI. [Modified from Macklin et al. 2017 with permission.]

Kramer et al. 2008, 2010). Indeed, more recent evidence has suggested that discrepancies in the spared level of sensory function detected by EPTs and clinical exams depend on the time postinjury (Macklin et al. 2016, 2017). Comparisons between control and SCI subjects revealed mostly comparable EPTs in dermatomes located above the level of injury but increased or abolished EPTs in SCI participants in dermatomes at or below the level of injury. EPT values accurately predict pathological and abolished dSSEP measured at the same dermatomes, suggesting that EPTs likely reflect activity in dorsal column pathways (Curt and Ellaway 2012; Kramer et al. 2008). Although the EPT has better reliability than the Semmes-Weinstein monofilament test for cutaneous sensitivity in control subjects, evidence shows that both examinations have the potential to add sensitivity and resolution to the clinical assessments in humans with SCI (Ellaway and Catley 2013).

Can EPTs provide a good prognosis in SCI? Most studies using the EPT have involved heterogeneous groups of individuals that included those in the acute and chronic phases of SCI with complete and incomplete injuries at the cervical, thoracic, and lumbar spinal cord. It is not until recently that studies have tested the EPT exam in more homogeneous groups of SCI participants. It was found that the EPT exam can reveal impaired sensory function above, below, or at the same spinal segment as the sensory clinical exam over time in individuals with chronic incomplete SCI (Macklin et al. 2017). The EPT exam detected subclinical changes in sensory function that were not identified by the clinical exam as early as the first month after injury and also in individuals more than 10 years after incomplete SCI (Macklin et al. 2016; Fig. 4). In the chronic stage of cervical SCI, the EPT exam reveals spared sensory function at lower (~5) spinal segments than the clinical sensory exam, highlighting that the EPT is a sensitive tool to assess recovery of sensory function after chronic human SCI. However, longitudinal studies that follow the same group of participants across time using EPT outcomes are still needed.

Conclusions

Although SCI often damages afferent fibers projecting through the dorsal columns to the brain, to date, limited information exists on the effect of afferent modulation on the primary motor cortex and the somatosensory cortex after injury. On one side, a few studies have suggested that afferent inputs modulate corticospinal excitability by involving cortical and spinal mechanisms depending on the timing of the effects, which need to be considered separately for upper and lower limb muscles. Because GABAergic mechanisms contribute to modulate afferent input onto the primary motor cortex, transmission in GABAergic pathways is an important factor to consider during examination of sensory processing after SCI. The time of arrival of afferent inputs onto the primary motor cortex and the spinal cord is also relevant to further understand the effects of afferent regulation of in the context of plasticity-induced protocols. The success of some of these protocols might depend on properly timing afferent input onto sensory and motor cortex and the spinal cord, highlighting the need to tailor interventions to individual subjects, considering their own physiological changes in transmission in these pathways.

On the other side, a number of studies have examined afferent inputs onto the somatosensory cortex by testing SSEPs. These studies support the view that SSEPs have a good prognostic value and are sensitive enough to detect differences between control and SCI subjects. SSEPs elicited by electrical stimulation of mixed and cutaneous nerves have a diagnostic value in distinguishing between control and complete SCI participants with no sensory function or incomplete SCI participants with severely impaired sensory functions. However, the extent to which SSEPs can be used to examine the severity and level of injury is less clear and based on less direct evidence. Importantly, to date, no data exist on how afferent input is gated in the contralateral and ipsilateral somatosensory cortex during voluntary activity and/or motor behaviors in SCI participants. Ascending potentials generating SSEPs propagate through multiple spinal levels and reflect the full extent of dorsal column impairments. More sensitive electrophysiological tools used to examine the level of spared sensory function are dSSEPs and EPTs. However, the prognostic value of dSSEPs and EPTs needs to be established, and prospective studies with multiple assessments relating dSSEP and EPT characteristics early after SCI to sensory or motor outcomes in the chronic stage are highly needed. Thus transmission of afferent inputs to the primary motor cortex and the somatosensory cortex needs to be considered on multiple functions following human SCI.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

R.A.O. and M.A.P. conceived and designed research; R.A.O. and M.A.P. performed experiments; R.A.O. and M.A.P. analyzed data; R.A.O. and M.A.P. interpreted results of experiments; R.A.O. and M.A.P. prepared figures; R.A.O. and M.A.P. drafted manuscript; R.A.O. and M.A.P. edited and revised manuscript; R.A.O. and M.A.P. approved final version of manuscript.

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