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Spinal Control of Motor Outputs

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Strategies to augment volitional and reflex function may improve locomotor capacity following incomplete spinal cord injury

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Abstract

Many studies highlight the remarkable plasticity demonstrated by spinal circuits following an incomplete spinal cord injury (SCI). Such plasticity can contribute to improvements in volitional motor recovery, such as walking function, although similar mechanisms underlying this recovery may also contribute to the manifestation of exaggerated responses to afferent input, or spastic behaviors. Rehabilitation interventions directed toward augmenting spinal excitability have shown some initial success in improving locomotor function. However, the potential effects of these strategies on involuntary motor behaviors may be of concern. In this article, we provide a brief review of the mechanisms underlying recovery of volitional function and exaggerated reflexes, and the potential overlap between these changes. We then highlight findings from studies that explore changes in spinal excitability during volitional movement in controlled tasks. The initial focus will be directed toward recovery of reflex and volitional behaviors following incomplete SCI, followed by recent work elucidating neurophysiological mechanisms underlying patterns of static and dynamic muscle activation following chronic incomplete SCI during primarily single-joint movements. We will then transition to studies of locomotor function and the role of altered spinal integration following incomplete SCI, including enhanced excitability of specific spinal circuits with physical and pharmacological interventions that can modulate locomotor output. The effects of previous and newly developed strategies will need to focus on changes in both volitional function and involuntary spastic reflexes for the successful translation of effective therapies to the clinical setting.

Keywords: exercise, locomotion, rehabilitation

INTRODUCTION

Following spinal cord injury (SCI), there are local immediate and secondary mechanisms of injury that influence the extent of damage to neuronal cell bodies, axons, glial cells, and the supplying vasculature. In the majority of cases, however, there is some preservation of motor and/or sensory function, which may result in motor incomplete SCI, indicating some volitional control below the level of the lesion. Although the initial loss of motor control appears to be the primary predictor of restoration of long-term functional gains (van Middendorp et al. 2011), including recovery of independent ambulation, there is remarkable plasticity demonstrated by neural circuits both above and below the level of the lesion that may contribute to further volitional recovery. Specific interventions can facilitate such plasticity, including physical and pharmacological strategies that increase neural excitability, and substantial research has been directed toward identifying optimal strategies to maximize recovery.

Notably, plasticity within these circuits may also result in involuntary motor behaviors, such as spasticity, spasms, and clonus, which are considered detrimental to motor function. Substantial clinical research has also been directed toward understanding the mechanisms underlying these hyperexcitable reflexes and the efficacy of strategies to reduce spastic motor behaviors. Interestingly, animal models of SCI suggest increased spinal excitability underlying these hyperexcitable reflexes may facilitate motor function, particularly when utilized during voluntary tasks (Fouad et al. 2010; Murray et al. 2010). In humans with incomplete SCI and spastic reflexes, recent data have suggested similar findings; during controlled or freely moving tasks, individuals with spastic reflexes following incomplete SCI may also utilize enhanced spinal excitability to augment volitional drive or function (Hornby et al. 2009; Kim et al. 2015). Indeed, the interventions that may increase spinal excitability to improve volitional function may elevate spastic reflexes, and a discussion of the potential implications of these findings may not be fully appreciated by researchers or clinicians.

The focus of the present review is to detail the remarkable plasticity demonstrated by spinal circuits following motor incomplete SCI, specifically as it relates to the presentation of hyperexcitable reflexes and their paradoxical contributions to motor recovery. We aim to briefly review the mechanisms underlying changes in reflex and volitional function following injury, with a primary focus on the modulatory influences of physical and pharmacological interventions on both spastic motor activity and volitional recovery. Delineation of the potential influences of various rehabilitation strategies on both involuntary and volitional motor behaviors will have important consequences for the clinical translation of promising interventions that may improve motor performance in incomplete SCI.

REORGANIZATION OF SPINAL CIRCUITS AFTER SCI

Decades of basic and applied research have demonstrated the evolution of the spinal cord's capacity to generate motor output after SCI. Immediately following injury, suppression of volitional and reflex output below the lesion level (i.e., spinal shock) (Hagen 2015; Sweis and Biller 2017) is thought to be due in part to the damage of corticospinal glutamatergic signaling, as well as loss of bulbospinal serotonergic pathways and its powerful descending modulation of spinal excitability (Jacobs and Fornal 1993). However, following this acute stage of injury there are rebound increases in motoneuronal excitability, which can lead, in part, to hyperexcitable responses to afferent input (i.e., exaggerated reflex output) (Hiersemenzel et al. 2000). These exaggerated reflexes are often characterized as spastic motor behaviors and include both spasticity and spasms. Spasticity is defined here as velocity-dependent increases in stretch reflex excitability (Katz and Rymer 1989) and, due to its velocity and reflex dependence, is a separate phenomenon from length-dependent changes in intrinsic muscle excitability (Frigon et al. 2011). Spasms, in contrast, are long-lasting, involuntary, multijoint muscle activations in response to various sensory inputs (Benz et al. 2005; Gorassini et al. 2004). In cases of incomplete SCI, recovery of volitional motor output is

commonly observed with increased reflex function, the extent of which is largely dependent on the severity of damage to descending pathways.

Although there are multiple mechanisms that underlie changes in volitional and reflex motor output post-incomplete SCI, several of these overlap and likely contribute to both phenomena. For example, specific changes that contribute to spasticity include both decreased presynaptic inhibition (Calancie et al. 1993; Faist et al. 1994) and reciprocal inhibition (Crone et al. 2003), muscle afferent and interneuron collateral sprouting partially resulting from the loss of competition from corticospinal terminals (Raineteau et al. 2001; Tan et al. 2012), and changes in motoneuron excitability and sensitivity (Li et al. 2007; Murray et al. 2010), particularly in response to residual serotonergic (5-HT) inputs. Importantly, these mechanisms overlap with those postulated to facilitate volitional motor recovery. Specific changes attributed to increased volitional recovery include augmented spinal motoneuron excitability and sensitivity to 5-HT (Fouad et al. 2010; Murray et al. 2010) and sprouting of descending (cortico-, bulbo-, and propriospinal) pathways (Ballermann and Fouad 2006; Fouad et al. 2001), as well as alterations in interneuronal pattern-generating networks (Edgerton et al. 2008; Rossignol et al. 2011). Beyond these spinal alterations, plasticity in subcortical networks (Raineteau et al. 2001) and sensorimotor cortices (Dobkin 2000; Jurkiewicz et al. 2007; Winchester et al. 2005) are also associated with changes in motor function after injury.

VOLUNTARY MUSCLE ACTIVATION IMPAIRMENT

Despite varying degrees of volitional motor function following incomplete SCI, lower extremity paresis remains the hallmark feature limiting functional recovery (van Middendorp et al. 2011). At the muscular level, marked loss of whole muscle and muscle fiber size (i.e., atrophy), alterations in fiber phenotype, and increased fatigability can negatively affect force-generating capacity (Cope et al. 1986; Shields 1995). However, deficits in excitation of spinal motor neurons by descending pathways are the primary determinant of weakness. For example, previous studies (Thomas et al. 1997, 2014) provided electrical stimulation to the peripheral nerves of specific muscle groups while participants with motor incomplete SCI performed an isometric maximal voluntary contraction (MVC). The resultant interpolated twitch response in these stimulated muscles reflected volitional activation deficits, whereas similar activation deficits were not observed in healthy control subjects. In the same study, transcranial magnetic stimulation (TMS) over the contralateral motor cortex of participants with incomplete SCI during MVCs evoked significantly less additional force output than peripheral nerve stimulation. This finding indicated that motor cortical drive was near maximal, but transmission to motoneurons was significantly impaired. Consistent impairments in voluntary activation have been demonstrated in multiple muscles (range: 34–58%) following incomplete SCI (Hornby et al. 2009; Jayaraman et al. 2006; Lin et al. 2012) compared with that demonstrated in intact subjects (>95%; Gandevia 2001).

INFLUENCE OF SPINAL REFLEX PATHWAYS ON VOLITIONAL BEHAVIORS

Although descending drive from the motor cortex plays a major role in the timing and intensity of voluntary contractions (Taylor 2009), spinal reflexes are well known to contribute substantially to the control of voluntary movement. In the case of motor incomplete SCI, afferent inputs may have a disproportionately larger influence on volitional activation than in neurologically intact adults, as observed during volitional upper extremity tasks or standing and stepping in individuals with incomplete SCI. In one study, experimenters provided different forms of concurrent sensory stimulation to individuals with SCI performing isometric MVCs of the thenar muscles (Zijdewind et al. 2012). Heat, vibration, induced spasm, or a contralateral contraction successfully increased maximal firing rates of the tested thenar motor units (MUs), suggesting peripheral inputs can further excite the voluntarily activated motor pool. The contributions of afferent inputs to locomotor tasks are well established, because many studies have

evaluated the role of afferent feedback in modifying and shaping locomotor activity in both health and disease ((Edgerton et al. 2004; Fouad and Tetzlaff 2012). Such afferent feedback has been shown in animal models and humans with SCI (De Leon RD et al. 1998a, 1998b; Maegele et al. 2002) to be important, if not critical, to locomotor output.

The overall influence of spastic motor behaviors on motoneuronal discharge and on different muscles suggests that the altered sensory input-motor output relationships could either facilitate or antagonize the intended motor command. Although there is evidence that spasticity may contribute to slower and less coordinated movements (Damiano et al. 2006), other data suggest that patients with incomplete SCI can utilize or harness their elevated spinal excitability to facilitate volitional function (Hornby et al. 2009; Jayaraman et al. 2013). One potential theory is that spasticity may develop to compensate for reduced motor output or spinal excitability in the absence of altered supraspinal inputs. Furthering this argument, reduction of sensory feedback by antispastic medications, such as diazepam ($GABA_A$-positive allosteric modulator), baclofen ($GABA_B$ agonist), and tizanidine (α_2-adrenergic agonist), appears to not only reduce exaggerated reflexes but also may reduce volitional strength and, ultimately, impede patients' ability to perform functional movements (Hornby et al. 2004; Thomas et al. 2010).

INFLUENCES OF VOLITIONAL COMMANDS ON SPINAL EXCITABILITY

Although reflex inputs can increase central activation, recent evidence indicates that spinal excitability is increased in individuals with incomplete SCI during the performance of strong voluntary contractions compared with that in neurologically intact individuals (Thomas et al. 2017). Previous data indicate that maximal effort "fatiguing" contractions known to result in reduced volitional output in intact subjects generated the opposite behavior in subjects with motor incomplete SCI. Specifically, 20 repeated isometric MVCs of the knee extensors (KEs; 5 s on, 5 s off) results in an immediate and sustained decline in peak torque production (~30–35% decrease) in intact subjects. In contrast, individuals with incomplete SCI demonstrated increased peak torque and KE electromyographic (EMG) activity by the third contraction (15–20%) (Hornby et al. 2009). In a follow-up study, we provided evidence that unexpected gains in muscle activation over repeated MVCs are partly due to increased central excitability during maximal contractions (Thompson et al. 2011b). Use of a surface electrical stimulation paradigm (2 s each of 25, 100, and 25 Hz; Collins et al. 2001, 2002) over resting muscle both before and after repeated MVCs elicited increased involuntary torque output as well as long-lasting involuntary muscle contractions only after, compared with before, the repeated MVCs.

These behavioral findings were consistent with the presence of plateau potentials (i.e., prolonged depolarizations) due to voltage-dependent persistent inward Ca^{2+} and Na^{+} currents (PICs; Heckmann et al. 2005). In the intact spinal cord, plateau potentials and their underlying PICs decrease the synaptic current necessary to elicit action potentials and are facilitated by the presence of the monoamine (e.g., 5-HT) or other modulatory influences. Their activity is characterized by regenerative trains of action potentials that continue beyond the removal of synaptic input. Following chronic SCI, PICs appear to be a direct result of increased expression of supersensitive and constitutively active 5-HT receptors that develop within inter- and motor neurons, and which are linked to the development of spasticity (Murray et al. 2010). This spinal hypersensitivity of inter- and motoneurons to monoamines is a feature that researchers have attempted to exploit in an effort to improve motor recovery following injury (D'Amico et al. 2014). In the studies revealing increased volitional motor output with maximal effort contractions, augmented reflex responses consistent with PICs were thought to contribute to elevated volitional activation and motor output.

Considering the presence of hyperexcitable reflex pathways following SCI, a potential strategy for harnessing this excitability may be to perform high-intensity volitional activities that recruit these abnormal behaviors to facilitate desired movements. Whereas many of the described studies use repeated, isometric

MVCs, interactions with the environment more often require muscle activation during dynamic tasks. Studies of motor output during voluntary shortening (concentric) and lengthening (eccentric) contractions in incomplete SCI can therefore provide important information regarding the function of spinal reflex pathways and their integration with volitional movement. Knutsson et al. (1997) first studied dynamic lengthening and shortening MVCs of both the KEs (quadriceps) and knee flexors (hamstrings) in a heterogeneous population of subjects with spastic paraparesis. Their main finding during KE MVCs was that spastic patients demonstrated overactive antagonist muscle (hamstring) EMG and decreased agonist EMG during fast shortening MVCs. In contrast, healthy controls demonstrated their highest agonist EMG levels during fast shortening MVCs, consistent with previous data (Komi et al. 1987; Westing et al. 1991). The increased antagonist EMG observed in patients was interpreted as evidence of impaired reciprocal inhibition. However, interpretation of these data are complicated by the inclusion of a mixed population, because there are etiology-dependent differences in spastic motor behaviors (Burne et al. 2005; Woolacott and Burne 2006).

In an attempt to clarify the patterns of muscle activation following incomplete SCI, we conducted a study that utilized torque and EMG measures as well as supramaximal muscle stimulation during MVCs to quantify central motor drive to the KEs. Despite overall deficits in voluntary muscle activation, individuals with SCI generated markedly increased central motor drive during lengthening compared with isometric or shortening maximal contractions (Kim et al. 2015). In contrast, intact subjects demonstrated a depression of motor drive during lengthening contractions relative to the other contraction types, consistent with many previous reports (Beltman et al. 2004; Pinniger et al. 2000; Westing et al. 1991). Whereas control participants demonstrated similar KE EMG during lengthening and shortening contractions, individuals with incomplete SCI demonstrated a dramatic 50–70% boost in KE EMG during lengthening contractions. In contrast to the Knutsson study, no differences in the activity of the antagonist hamstring muscles across contraction types were observed. The combined data suggest that stretch-related feedback during dynamic contractions did not necessarily constrain motor activity, but rather may have enhanced motor output in individuals with incomplete SCI.

In a follow-up study, Ia-α motoneuron excitability within agonist muscles appeared to partly underlie the increased activation levels observed during lengthening MVCs. In contrast to healthy controls, individuals with incomplete SCI demonstrated an absence of H-reflex inhibition during passive and active lengthening of the plantarflexors (Fig. 1). Importantly, there were significant correlations found in the group with SCI between the reduced inhibition of H-reflexes and increased voluntary activation during lengthening MVCs, suggesting enhanced efficacy of Ia-α motoneuron transmission contributed to greater activation levels. Potential mechanisms underlying this phenomenon include a reduction post-SCI in presynaptic inhibition (Faist et al. 1994) due to the loss of descending inputs to primary afferent depolarizing interneurons (for review, see Lundberg 1975), as well as a reduction in homosynaptic postactivation depression in Ia fibers (Hultborn et al. 1996; Nielsen et al. 1993; Schindler-Ivens and Shields 2000).

Marked differences in muscle activation patterns between individuals with incomplete SCI and healthy adults also have been observed during fatiguing protocols requiring repeated dynamic MVCs. Consistent with studies of repeated isometric MVCs (Hornby et al. 2009; Thompson et al. 2011b), individuals with incomplete SCI demonstrated gains in KE torque and EMG measuring 20–30% above baseline levels over repeated shortening MVCs (Kim et al. 2015). Interestingly, during lengthening MVCs, individuals with SCI did not show improvements in motor output over subsequent trials. This may be further evidence that, in the case of SCI, the motor pool is maximally activated by combined descending and afferent inputs during lengthening contractions, contributing to a ceiling effect during repeated MVCs. Regardless, the combined data support the notion that elevated reflex activity typically characterized as spasticity may boost motor performance during both static and dynamic tasks following incomplete SCI.

LOCOMOTOR FUNCTION AND RECOVERY FOLLOWING SCI

The changes in involuntary and voluntary motor function following SCI can also have a significant impact on locomotor function. As well documented, many patients with complete or incomplete SCI can retain some capacity to generate locomotor behaviors, either through epidural electrical (Dimitrijevic et al. 1998; Harkema et al. 2011) or magnetic (Sasada et al. 2014) stimulation over the lumbar spinal cord or in response to afferent inputs due to increased spinal excitability following injury. For example, greater limb loading during stepping appears to enhance stance-phase muscle activity in both animals and humans with SCI (Harkema et al. 1997; Hiebert et al. 1996), whereas stretch of hip flexors during late or terminal stance phases of walking may facilitate whole limb flexion to initiate the swing phase (Beres-Jones and Harkema 2004). Though the severity and level of the injury can greatly impact the outcome, in many cases of motor incomplete SCI there is potential for recovery of functional, independent ambulation (van Middendorp et al. 2011). Commonly, however, individuals with incomplete SCI demonstrate decreased muscle activity/power, abnormal EMG coordination (coactivation), and altered kinematics during walking (Dietz and Sinkjaer 2007; Dietz et al. 1997; Fung and Barbeau 1989), which contribute to persistent deficits in independent walking function. Many rehabilitation strategies attempt to exploit the inherent plasticity of the central nervous system following SCI to maximize functional locomotor recovery. Currently, however, locomotor training is the primary rehabilitation intervention shown to induce activity-dependent plasticity and lead to improvement in walking function following incomplete SCI.

Animal models of SCI (Cai et al. 2006; Frigon and Rossignol 2006) have detailed potential mechanisms underlying changes in spinal circuitry related to improved locomotor function following step training. For example, locomotor recovery following stepping practice appears to be related to the spinal expression of growth factors and related proteins (Vaynman and Gomez-Pinilla 2005) as well as reorganization of propriospinal circuits (Courtine et al. 2009) and growth of serotonergic fibers below the level of the lesion (Engesser-Cesar et al. 2007). Further studies indicate these effects are enhanced with larger amounts of task-specific practice (Cha et al. 2007; De Leon RD et al. 1998a, 1998b) and may be further enhanced with variable practice of stepping tasks (Shah et al. 2012; van den Brand et al. 2012).

Consistent with this evidence, large amounts of stepping practice in humans with incomplete SCI have been shown to elicit significant improvements in gait speed, endurance, and functional independence (Dobkin et al. 2006; Yang et al. 2014). Locomotor training in humans with incomplete SCI has also been associated with changes in neurophysiological measures, indicating plasticity within the motor system. For example, at the level of the spinal cord, multiple groups have noted a normalization of reflex excitability following step training (for example, see Hubli et al. 2012; Knikou 2013). Locomotor-based interventions have also been shown to lead to improvements in volitional motor output (i.e., peak muscle activity; Hajela et al. 2013), corticospinal tract function (Thomas and Gorassini 2005), and increased activation of sensorimotor cortical regions (Winchester et al. 2005).

Despite these findings, it is important to note that not all stepping-based interventions are equal and may depend on the severity of SCI and the types of stepping training performed. For example, overground and treadmill-based gait training are similarly effective when matched for the amount of stepping practice (Dobkin et al. 2006), and both approaches should be incorporated into treatment to maximize the unique benefits of each. Conversely, robotic-assisted gait training (e.g., Lokomat) has been shown to require less engagement of the neuromuscular system than therapist-assisted gait training (Israel et al. 2006) and appears to result in smaller locomotor gains than other walking strategies (Field-Fote and Roach 2011). These combined data suggest that training strategies that focus on locomotor practice appear to facilitate recovery, although greater engagement of volitional activity, which increases spinal excitability as described above, can augment the benefits of practice.

INTERVENTIONS TO MODULATE SPINAL EXCITABILITY TO PROMOTE LOCOMOTOR RECOVERY

Given the evolution of motor output following SCI and the potential utility of increasing spinal excitability, different methods to promote the recovery of locomotor function have been investigated (Barbeau et al. 2006; Hornby et al. 2011). More recently, the intensity of practice (defined as the rate of work, or power output) has been highlighted as a training parameter that may influence neural plasticity and recovery of locomotor function after neurologic injury. The underlying premise is that higher intensity locomotor tasks lead to increased spinal excitability through both glutamatergic and serotonergic input, which can lead to long-term synaptic potentiation and connectivity. Increasing the intensity of step training increases descending central drive to locomotor spinal circuits and may also lead to further strengthening of corticospinal projections that may not be observed with lower intensity interventions (Luft et al. 2008; Suzuki et al. 2004). To date, however, few studies have attempted to identify the role of training intensity to promote greater motor output and long-term walking function in patients with incomplete SCI. A possible barrier to these studies is the long-standing view that high-intensity activity exaggerates spastic motor behaviors (Kline et al. 2007), and training at intensities that require increased descending motor drive would reinforce abnormal movement patterns (Bobath 1990). In a recent study, we found that higher locomotor intensities did not degrade gait performance, but rather led to increased muscle activity, spatiotemporal metrics, joint excursions, and improved coordination (Leech et al. 2016). These findings are consistent with the results from others (Beres-Jones and Harkema 2004), which demonstrate speed-dependent changes in muscle activity and timing in individuals with complete and incomplete injuries.

The effects of long-term locomotor training intensity on walking function in patients with neurological injury are more limited, with only a few studies conducted primarily in patients poststroke. (Holleran et al. 2015; Ivey et al. 2015; Pohl et al. 2002). Our recent research (Leech et al. 2016) also investigated the long-term effects of training at high intensities in incomplete SCI. In a relatively small sample ($n = 9$) of subjects, high-intensity stepping training over 12 wk improved locomotor performance (speed) and selected kinematic patterns, without evidence of reinforcing aberrant walking patterns, despite the presence of spastic motor behaviors in all subjects. More recently, comparison of the effects of high- vs. low-intensity training in ambulatory individuals with incomplete SCI using a randomized crossover design revealed gains in walking speed when the former intervention was used. By specifically using heart rate during training as a primary determinant of intensity (and reflective of subject-specific workload), gains in walking function following high- vs. low-intensity training appear to be related to differences in training intensity or peak heart rates achieved (Brazg et al. 2017). Such data are consistent with findings from other locomotor intervention studies that investigated different training parameters that did not directly emphasize the intensity of training, but nonetheless reported differences in training intensity that could contribute to outcomes (Yang et al. 2014). Regardless, the mechanisms underlying the changes observed were not clear in either study. This emerging work highlights the need for controlled trials to evaluate the effectiveness of high-intensity interventions that demand increased descending drive in individuals with incomplete SCI.

A potential mechanism by which high-intensity exercise may facilitate neuroplastic changes in the active circuits is the intensity-dependent expression of neurotrophic factors. Specifically, the protein brain-derived neurotrophic factor (BDNF), which is released in an activity-dependent manner (Lu 2003), has been suggested to play a significant role in exercise-induced neuroplasticity in the motor system (Gómez-Pinilla et al. 2002; Vaynman et al. 2003). In animal models of incomplete SCI, there is evidence of a positive correlation between exercise intensity and amount of spinal BDNF or other markers of synaptic plasticity, particularly in the ventral horn (Neeper et al. 1996; Ying et al. 2005). Importantly, this increase in spinal BDNF and downstream effectors below the level of the lesion was also linked to the recovery of stepping following incomplete SCI (Ying et al. 2008).

Given the actions of BDNF in the motor system and the ability to regulate its expression with neural activity, the effect of exercise on BDNF in humans has become an area of significant interest. Although the cellular mechanisms are unclear, many studies have shown that single bouts of high-intensity aerobic exercise in healthy adults lead to increases in peripherally circulating BDNF (for review, see Knaepen et al. 2010). Similarly, we found that individuals with incomplete SCI were able to drive/engage the motor system to achieve relatively high levels of exercise intensity during single-session bouts of exercise; these intensities were sufficient to elicit increases in peripheral BDNF (Leech and Hornby 2017). Further work is necessary to link these intensity-dependent changes in BDNF expression to alterations in motor output and quantify the effect of chronic training at intensities that elicit increases in BDNF.

In addition to physical interventions (i.e., locomotor training), pharmacological interventions have also been explored as a means of manipulating spinal excitability to facilitate the recovery of walking after SCI. As described previously, the study and clinical use of pharmacological therapies has largely been directed toward mitigating increased spinal excitability. Traditional theories of motor recovery following SCI suggest that spasticity may be the primary determinant of impaired motor function, and these concepts often remain a fundamental tenant of medical interventions post-SCI. In patients with severe spasms/spasticity that significantly limit independent mobility (e.g., transfers, wheelchair use, or standing upright) and even cause pain, this approach may be the most appropriate. However, the evidence regarding the impact of antispastic interventions on functional mobility in individuals with less severe spasticity or spasms is conflicting (Domingo et al. 2012; Taricco et al. 2006). For example, some studies have demonstrated (with individual data presentation) that antispastics may improve some functional mobility (Norman et al. 1998; Wainberg et al. 1990), whereas more recent data suggest that a single dose of a selective pharmacological agent that depresses spinal excitability not only decreases clinical measures of spasticity and spasms (Fig. 2) but also results in greater impairments in volitional motor behaviors such as strength and walking function (Leech et al. 2014; Thompson and Hornby 2013).

Alternatively, administration of medications that increase 5-HT signaling (e.g., selective serotonin reuptake inhibitors, SSRIs) has been shown to be an effective means of the augmenting spinal excitability and motor output in humans with SCI (Stolp-Smith and Wainberg 1999; Thompson and Hornby 2013; Thompson et al. 2011a). Such findings are well established in animal models of SCI, where application of specific 5-HT agonists or their precursors increases spinal excitability (Harvey et al. 2006a, 2006b; Hounsgaard et al. 1988), particularly resulting in augmented PICs. When combined with rehabilitation interventions, selected 5-HT agents may promote greater gains in locomotor recovery than stepping training alone (Fong et al. 2005). The improvements in locomotor patterns with 5-HT may also involve BDNF-related mechanisms, as suggested by work related to respiratory recovery following incomplete SCI (Baker-Herman et al. 2004). In humans, we have previously shown that increased 5-HT signaling with a single dose of an SSRI leads to an increase in both voluntary and involuntary motor output, yet has little effect on walking ability within a single session (Leech et al. 2014; Thompson and Hornby 2013). However, previous work suggests that pairing serotonergic agents with physical interventions may promote motor recovery and enhance the effects of rehabilitation after a stroke (Chollet et al. 2011; Dam et al. 1996). The combined results point toward a potential benefit of pairing physical and pharmacological interventions following SCI to harness the increased neuronal excitability, although concerns may be related to increases in spastic motor behaviors with some of these agents (D'Amico et al. 2013). A balance between the use of modulatory influences that increase spinal excitability (serotonergic agents and high-intensity activities) vs. those that depress spinal excitability to reduce spasticity may be needed, and a consensus among researchers and clinicians has not been addressed.

SUMMARY

The plasticity of spinal circuits that underlie recovery of reflexive motor function following incomplete SCI

also appears to overlap with mechanisms underlying volitional recovery and can substantially influence performance of functional tasks such as locomotion. The present review delineates some of these mechanisms and their functional role, including recognition that many of the changes underlying involuntary, abnormal reflex function (i.e., spastic behaviors) may not necessarily impede motor function, as traditionally assumed, but may enhance volitional task performance. Physical interventions, particularly those performed at higher intensities, may augment spinal excitability and increase motor output to afferent input but also may be important for recovery of volitional motor function when provided repeatedly. Similarly, 5-HT or other agents that act to increase spinal excitability may increase spastic behaviors but also could facilitate recovery when combined with physical interventions, although those hypotheses are not well tested in humans with incomplete SCI. Understanding the physiological basis of neural circuits following incomplete SCI that contribute to both involuntary behaviors and volitional recovery has spurred development of potential rehabilitation interventions that may be translated to clinical practice. Further work along this vein will be necessary as additional interventions, such as spinal stimulation (Gerasimenko et al. 2015; Sayenko et al. 2015), are developed to understand changes in both volitional and involuntary motor behaviors. Importantly, the clinical implication of these findings will need to be effectively communicated to rehabilitation clinicians, because traditional strategies for reducing spasticity continue to influence the rehabilitation management for this patient population. Interventions directed toward improving neural function following SCI should strongly consider approaches that harness these plastic changes and evaluate both physiological and clinical changes to accelerate delivery of effective treatments to patients with incomplete SCI.

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS

T.G.H. conceived and designed research; T.G.H. performed experiments; T.G.H. analyzed data; T.G.H. interpreted results of experiments; H.E.K. and T.G.H. prepared figures; K.A.L., H.E.K., and T.G.H. drafted manuscript; K.A.L., H.E.K., and T.G.H. edited and revised manuscript; K.A.L., H.E.K., and T.G.H. approved final version of manuscript.

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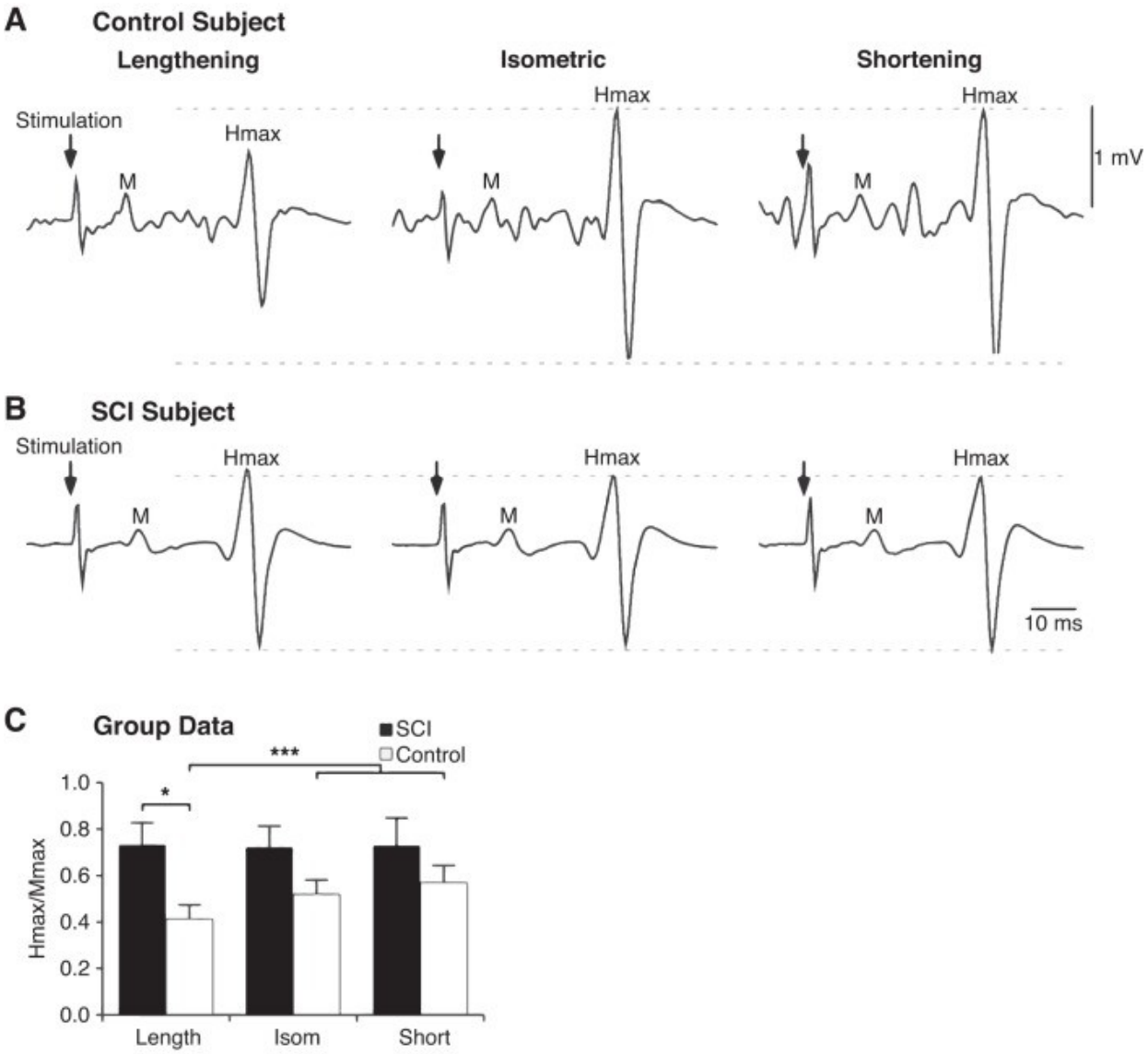
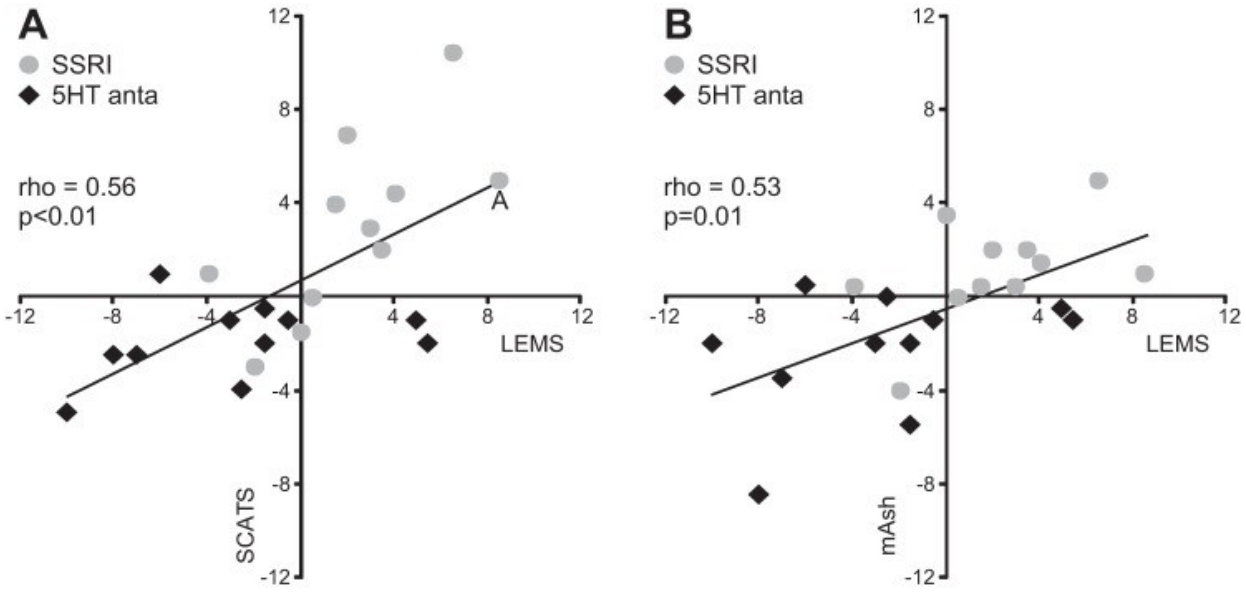
Figures and Tables

Fig. 1.



H-reflexes during contractions at 75% MVC level. *A*: representative data from a neurologically intact control subject. During strong contractions, there is potentiation of H-reflexes but specific depression of lengthening H-reflexes. *B*: representative data from a participant with incomplete SCI. There is complete disinhibition of the lengthening H-reflex. *C*: group data. During voluntary contractions, individuals with incomplete SCI continue to demonstrate a larger ratio of Hmax to Mmax (Hmax/Mmax) than controls. In addition, there are no longer any differences in Hmax/Mmax across contraction types for the group with SCI, whereas there is still depression of lengthening Hmax/Mmax for controls. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. [Reprinted from Kim et al. (2015).]

Fig. 2.



Changes in spastic motor behaviors and strength with 5-HTergic agents. *A* and *B*: changes in clinical measures of spasms (Spinal Cord Assessment Tools for Spasticity, SCATS) vs. strength (Lower Extremity Motor Scores, LEMS) (*A*) and spasticity (modified Ashworth; mAsh) vs. strength (LEMS) (*B*) in participants with motor incomplete SCI 5 h after administration of either a selective serotonin reuptake inhibitor (SSRI; escitalopram) or a 5-HT antagonist (5HT anta; cyproheptadine). Increases or decreases in spasticity/spasms are associated with increases/decreases in strength in the population tested. [Reprinted from Thompson and Hornby (2013).]