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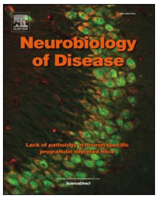

Review

What is the functional relevance of reorganization in primary motor cortex after spinal cord injury?

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ABSTRACT

Motor output maps within primary motor cortex are widely distributed and modified by motor skill learning and neurological injury. Functions that these maps represent after spinal cord injury remain debatable. Moreover, the pattern of reorganization and whether it supports recovery of compromised motor function is not well understood. A deeper understanding of the pathophysiological mechanisms of motor dysfunction after spinal cord injury is necessary to develop and optimize repair strategies. There are three purposes for this review. The first is to synthesize available research on spontaneous reorganization with primary motor cortex following spinal cord injury. The second is to draw on existing evidence from the motor skill learning and brain injury literature to interpret the form and purpose of motor maps. The third purpose is to account for the existing research on intervention-induced reorganization of primary motor cortex following spinal cord injury. We conclude with directions for future work, emphasizing the need for multi-modal investigations that construct maps with both neuroimaging and non-invasive stimulation methods to derive a cohesive understanding of the effects of spinal cord injury on reorganization within primary motor cortex.

1. Introduction

There are an estimated 285,000 individuals with spinal cord injury (SCI) currently living in the United States and 17,500 new cases reported each year (NSCISC 2017). Disruption of ascending and descending fibers within the spinal cord results in pronounced physical dysfunction below the level of injury. Quality of life is compromised by a complex interplay between this dysfunction, the associated complications, and psychosocial factors (Tramonti et al., 2014). Extensive experimentation in animals and humans with SCI has demonstrated neural reorganization is possible due to spared corticospinal fibers that connect the remaining, intact spinal cord circuitry with supraspinal structures. It has been proposed that synaptogenesis via sprouting of spared corticospinal fibers provides an alternate mode of transmission from cortical regions to the spinal cord and likely mediates recovery (Fouad and Tse, 2008; Maier and Schwab, 2006). Structural and functional changes are also evident at the level of the primary motor cortex (M1) in humans (Freund et al., 2013; Kokotilo et al., 2009; Nardone et al., 2013) but reorganization of motor maps and the associated implications for recovery are not well understood.

Brain stimulation is a viable means for constructing motor maps and demonstrating plasticity within M1 after skill learning (Kleim et al., 1998; Kleim et al., 2002a; Nudo et al., 1996a; Pascual-Leone et al., 1994; Plautz et al., 2000; Remple et al., 2001) and neurological damage (Kambi et al., 2011; Nudo and Milliken, 1996). Over the past 30 years, relatively few studies have used transcranial magnetic stimulation (TMS) to probe motor maps in humans following SCI (Brouwer and Hopkins-Rosseel, 1997; Cortes et al., 2017; Freund et al., 2011; Levy et al., 1990; Streletz et al., 1995; Topka et al., 1991), and fewer studies have documented intervention-induced alterations in maps (Hoffman and Field-Fote, 2007; Hoffman and Field-Fote, 2010; Jetté et al., 2013). Despite the limited number of studies, this work coupled with functional imaging work has shed light on the patterns of cortical reorganization that emerge following SCI. A greater understanding of how cortical motor maps reorganize, both spontaneously after injury and in response to therapeutic interventions, is necessary to develop repair strategies that maximize function and are readily translatable to clinical practice. In this review, we will address three main questions.

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First, how do motor maps reorganize following SCI? Second, what is the functional relevance of motor maps? Third, how do motor maps reorganize in response to therapeutic interventions following SCI?

2. How do motor maps reorganize following spinal cord injury?

2.1. Map reorganization in cortical stimulation studies

In animal models of SCI, motor maps are constructed with intracortical microstimulation (ICMS) which, unlike the magnetic stimulation used in humans, delivers stimuli in the form of electrical current to the cortex. Existing work demonstrates widespread reorganization of motor maps. For example, a study in adult rats showed that within 1 month of thoracic lesion, stimulation of the hindlimb motor cortex produced responses of the forelimb, whiskers, and trunk (Fouad et al., 2001). Another study demonstrated that C4-C5 cervical hemisection drastically reduced overall map size and led to expanded representations of musculature at the shoulder and elbow relative to the wrist and digits (Martinez et al., 2010). Such large-scale reorganization has been shown to persist long after injury (ie, > 5 months) to the cervical spinal cord (Tandon et al., 2013).

In humans, a disruption in corticospinal transmission is routinely observed after SCI. Multiple studies have reported a prolonged latency of the motor-evoked potential (MEP) elicited by magnetic stimulation of the cortex (Alexeeva et al., 1997, 1998; Curt et al., 1998) in both arm and leg muscles (Roy et al., 2011), at varying times after injury (Smith et al., 2000), and irrespective of whether the targeted muscle is active or relaxed (Davey et al., 1998). An increased threshold for eliciting a MEP is also commonly observed (Cariga et al., 2002; Davey et al., 1998, 1999; Smith et al., 2000). Aside from impaired corticospinal transmission, a number of studies have demonstrated alterations in the distribution of outputs from the cortex onto the pools of spinal motoneurons innervating skeletal muscle.

A common finding from studies that construct motor maps via magnetic stimulation of the cortex is that representations of less impaired muscles shift and expand, whereas representations of more impaired muscles retract or are altogether absent (Freund et al., 2011; Levy et al., 1990; Streletz et al., 1995; Topka et al., 1991). This reorganizational pattern is observed within days to weeks of injury (Streletz et al., 1995) and many years thereafter (Freund et al., 2011; Levy et al., 1990; Topka et al., 1991). Such spontaneous changes are evident after both complete (Streletz et al., 1995) and incomplete injuries (Freund et al., 2011) at cervical (Freund et al., 2011; Levy et al., 1990; Streletz et al., 1995) and thoracic levels (Topka et al., 1991). The number of stimulation sites, or cortical area, resulting in MEPs are not constrained to a particular axis within the cortex; rather, reorganization occurs in both anteroposterior and mediolateral directions (Levy et al., 1990; Streletz et al., 1995; Topka et al., 1991).

Unlike the abovementioned studies, another mapping study did not detect the abovementioned changes nor could elicit MEPs under resting conditions in most patient and control subjects (Brouwer and Hopkins-Rosseel, 1997). When the targeted musculature was activated to approximately 5–10% of maximal voluntary contraction (MVC), however, MEPs were readily elicited. Nevertheless, no differences were observed in MEP amplitude or map area for SCI subjects compared to controls. Although the inability to elicit MEPs in resting muscles is unusual, the authors speculated that the corticomotor representations of SCI and control subjects were generally less excitable than samples from previous studies and concluded that spontaneous cortical reorganization does not occur after SCI.

A more recent mapping study in humans (Freund et al., 2011) incorporated neuronavigation, making it possible to account for anatomical variability between participants. In this study, the center of gravity (CoG) for the extensor digitorum communis (EDC) muscle was calculated to derive an amplitude-weighted indication of map location that was expressed as the Euclidian distance from the hand knob within M1. Results demonstrated that Euclidian distance was decreased for individuals with C5-C8 lesions relative to controls, indicating a shift in EDC muscle representation towards intrinsic hand muscle territory. The authors reasoned that low cervical lesions in these patients damaged relatively more descending projections to intrinsic hand muscles than forearm muscles. Given the presence of axonal branching from fibers supplying intrinsic hand muscles onto forearm muscles, the shift in cortical territory was thought to reflect a compensatory strategy that maximizes output to impaired forearm muscles. These findings appear consistent with earlier mapping studies demonstrating that cortical territory for more impaired musculature is overtaken by territory for proximally-adjacent, less impaired musculature.

A view that has emerged on the basis of existing work is that muscles with expanded territory are those that are innervated by spinal segments immediately rostral to the level of injury (Freund et al., 2011; Levy et al., 1990; Streletz et al., 1995; Topka et al., 1991). However, it remains unclear what bounds, if any, exist for muscles that exhibit this reorganizational pattern in terms of distance from the level of injury. In fact, the view that muscles innervated by spinal segments immediately rostral to the injury have expanded territory is debatable because it does not align with consensus regarding the distributions of spinal segments supplying various muscles (Campbell, 2005; Romanes, 1981; Kendall et al., 2005). For example, the biceps brachii (Levy et al., 1990; Streletz et al., 1995) and anterior deltoid (Levy et al., 1990) muscles are innverated by C5–6. Levy et al. (1990) found expanded representations at the reported level of injury (C5) in one patient and Streletz et al. (1995) found expansion at the reported level of injury (C5-6) in all patients studied. Moreover, the level of injury (C1-C2) in the second patient from Levy et al. (1990) was multiple segments higher than those supplying the anterior deltoid muscle for which an expanded territory was reported. In addition, abdominal wall muscles examined in a sample of patients with thoracic SCI (T10-T12) by Topka et al. (1991) were supplied by multiple spinal segments (T6-T12). Taken together, findings from the few available studies do not appear to preclude the possibility that reorganization is more diffuse and unrestricted to segments immediately above the level of injury.

Further complicating a cohesive understanding of cortical reorganization are the findings of the most recent mapping study in humans with SCI. In 10 individuals with long-standing, cervical injuries and trace forearm muscle activation but no overt movement about the wrist joint, a marginal reduction in cortical area was observed in three of the subjects relative to a group of neurologically-intact controls (Cortes et al., 2017). The remaining subjects showed no change relative to the controls. In fact, MEPs of normal latency were observed in all subjects, albeit of lesser amplitude in half of the sample. Although the lack of cortical reorganization is inconsistent with the preponderance of evidence from prior SCI mapping studies, findings from other cortical stimulation studies in humans with SCI support a more complicated pattern of reorganization.

For example, some work has shown reduced excitability of musculature distant from the level of injury (Laubis-Herrmann et al., 2000; Lotze et al., 2006), while other work has reported excitability differences in comparably impaired forearm muscles (ie, extensor and flexor carpi radialis) supplied by the same spinal segments (Edwards et al., 2013). Specifically, in an individual with a C5 lesion, MEPs recorded from the wrist extensor muscle were of normal latency, phase, and amplitude, but characteristics of MEPs from the flexor muscle were abnormal. In another study of subjects with cervical or thoracic SCI, MEPs were recorded from upper and lower extremity muscles while the contralateral muscles were at rest or activated to 70% of MVC into index finger abduction, elbow flexion, or ankle dorsiflexion (Bunday et al., 2013). No difference in MEP size was observed between resting and active conditions for muscles 5 segments below the level of injury. However, MEP size was similar to controls in elbow flexor muscles 5 segments from the injury and considerably higher than controls in ankle dorsiflexion muscles beyond 15 segments. Although these studies did not quantify cortical territory, they do provide evidence of reorganization in map output that is not constrained to a particular range of spinal levels.

2.2. Accounting for the mixed findings on spontaneous map reorganization after SCI

How can the mixed findings on reorganization of motor maps be reconciled? Notwithstanding the small sample sizes and lack of experimental control in these mapping studies, one inherent feature that should be taken into consideration when interpreting results is that MEPs from magnetic stimulation of the cortex are mapped at the level of the muscle. Thus, there may not be 1:1 correspondence between physiological responses measured in the muscle and the topographic origins of said responses. The possibility remains that corticomotor conduction from cortex is preserved down to the level of the spinal lesion but disrupted thereafter. In fact, recent work has demonstrated that descending volleys from magnetic stimulation are desynchronized in humans with SCI, resulting in impaired recruitment of spinal motor neurons (Cirillo et al., 2016). Moreover, recent work in humans with SCI has shown evidence of neurodegeneration within dorsal and ventral horns above the level of injury, further suggesting that maps constructed with TMS likely do not reflect purely cortical phenomena (Huber et al., 2018). Thus, cortical reorganization could be the result of plastic modifications in the arrangement of spinal motoneuron pools or in areas remote to the cortex. There is, indeed, evidence of widespread reorganization in humans with SCI (Ziegler et al., 2018), but changes downstream in the corticospinal tract are likely related to cortical reorganization (Freund et al., 2012).

Other animal work that has examined cortical reorganization in somatosensory cortex highlights the integrated nature of reorganization across the neuraxis after SCI. Specifically, a study in monkeys demonstrates that reorganization within the somatosensory cortex after SCI is due to plastic changes in brainstem nuclei rather than through the growth of new cortico-cortical projections (Kambi et al., 2014). In this study, chin-related responses were measured in the hand area of somatosensory cortex after SCI. Cortical reorganization observed after SCI was abolished when the cuneate nucleus was inactivated. This was not the case when the original chin responsive area was inactivated, suggesting that normal chin-related inputs to somatosensory cortex are not essential in order to observe map expansion into the deafferented area of cortex. The authors report that sprouting from the spinal trigeminal nucleus into the cuneate nucleus likely drives the reorganization within the brainstem, as has been previously proposed (Jain et al., 2000; Pons et al., 1991). The implication of this study for motor maps is that it may be the case that the lack of afferent input after SCI drives changes in somatosensory cortex, which then promotes plasticity in M1 through reciprocal connections. Thus, it remains possible that interdependent modifications along the tract could mediate the reorganization of motor maps (Xerri, 2012). It is therefore useful to consider changes in cortical activation via brain imaging to derive a complete picture of reorganization at the level of the cortex.

2.3. Map reorganization in brain imaging studies

A previous review (Kokotilo et al., 2009) and subsequent imaging studies highlights the complex picture of cortical activity measured with functional MRI during motor tasks after SCI. As with the TMS literature, the majority of these studies have small sample sizes ($n < 12$) and often report increased variability in responses for the SCI group as compared to able-bodied controls (Cramer et al., 2005; Lundell et al., 2011). The general consensus from the imaging literature is that somatotopic organization of motor cortex is functionally preserved after SCI (Hotz-Boendermaker et al., 2008; Turner et al., 2001). However, depending on injury level and the motor task being evaluated, many studies observed reorganization where cortical representations for completely impaired movements decrease in size or strength (Cramer et al., 2005; Hotz-Boendermaker et al., 2008) while partially impaired or preserved movements may increase in size or strength (Curt, 2002).

Most studies have investigated cortical representations of foot movement and found that imagined or attempted ankle movement after SCI results in weaker activation than overt movement by able-bodied subjects (Cramer et al., 2007; Hotz-Boendermaker et al., 2008; Jurkiewicz et al., 2010). Only one study reported a larger area of activation when subjects with thoracic SCI imagined performing foot movements as compared to actual movements by able-bodied controls, though the strength of activation was equivalent between the two (Alkadhi et al., 2005). Jurkiewicz et al. (2010) conducted a longitudinal study of 6 individuals with cervical SCI over the first year of injury. Participants showed an increase in the volume of activation related to wrist movements that increased over time in a manner that correlated with the degree of recovery. Some studies have also observed a shift of activity for intact movements toward areas that were related to movements that are now impaired (Cramer et al., 2005; Lotze et al., 1999; Mikulis et al., 2002; Turner et al., 2003), though results are reported qualitatively.

Most imaging studies have focused on movements that are impaired, but one study evaluated a series of unimpaired upper limb and tongue movements in people with thoracic SCI (Curt, 2002). Findings from this study indicated that the volume of M1 activation was slightly increased for finger movements as compared to controls but was unaffected during wrist, elbow, and tongue movements. Although the effect was small, the authors suggested that the change in activation volume during finger movements supports the idea that plasticity may not be limited to adjacent spinal segments. The instruction to imagine or attempt movement can impact cortical activity and, therefore, may explain some of the differences observed across studies (Guillot et al., 2012; Foldes et al., 2017). Similar to studies of impaired movements, Turner et al. reported a posterior shift of hand-related activity in individuals with paraplegia (Turner et al., 2003).

In conclusion, the preponderance of evidence indicates that motor maps reorganize to some extent in response to SCI, but the locus of adaptation leading to reorganization cannot be established on the basis of existing work. Worth noting, most studies report modest changes in small subject samples. Understanding the link between motor dysfunction and the pattern of reorganization in motor maps elicited by damage to the spinal cord provides a theoretical framework in which to explore therapeutic strategies that serve to harness plasticity and redirect map reorganization. To this end, identifying modifications that emerge during skill development and learning can aid the interpretation of what purpose motor maps serve and what form they take in absence of SCI. Consideration of reorganizational patterns that result from injury to other locations along the corticospinal tract and how these patterns are altered by therapeutic interventions also provides a basis for understanding how it can support or hinder recovery of lost motor functions (Nudo, 2013). The next section of the review, therefore, addresses how motor maps reorganize in response to skill development and learning in the intact nervous system as well as after brain injury.

3. What is the functional relevance of motor maps?

The traditional view of a strict somatotopic representation of individual muscles within M1 (Penfield and Rasmussen, 1950) has been replaced by an accumulating body of evidence that demonstrates that M1 is a distributed system with overlapping outputs (Sanes et al., 1995; Schieber and Hibbard, 1993; Siebner and Rothwell, 2003). The strong intracortical networks that exist within this heterogeneous structure (Aroniadou and Keller, 1993; Huntley and Jones, 1991) are adaptable to behavioral experience and, therefore, allow the formation of functional synergies needed to control a large repertoire of skilled, complex movements (Capaday et al., 2013). Modifications in synaptic strength between remote M1 pyramidal cells via horizontal connections are thought to be mediated by long-term potentiation (LTP) and depression (LTD) (Hess and Donoghue, 1994; Hess et al., 1996; Rioult-Pedotti et al., 1998, 2000; Ziemann, 2004), making maps amenable to change during motor skill learning (Monfils et al., 2004). Thus, it is thought that altered intracortical connectivity underlies map plasticity, strengthening specific synergies while weakening others and allowing representations of trained movements to occupy a larger proportion of the map (Monfils et al., 2005). A number of observations in animals and humans support the view that pruning of different connections that are damaged or otherwise unnecessary serves to optimize network connectivity.

3.1. Map plasticity during development and skill learning

Experiments involving ICMS in cats show an expansion of motor maps with progressively larger distal limb movement representations during development (Chakrabarty and Martin, 2000) that corresponds to the time at which skilled paw movements emerge (Armand and Kably, 1993). Other work has shown a relationship between dexterity and map representation of the digits in squirrel monkeys (Nudo et al., 1992). Within individual monkeys, digit representation of the dominant hand is larger than that of the non-dominant hand (Nudo et al., 1992). Similar findings have also been reported in humans. For instance, the M1 contralateral to the reading hand of skilled Braille readers exhibits a larger digit representation relative to representations of the non-reading hand and those of control subjects (Pascual-Leone et al., 1993). Other work has reported a larger hand representation for the dominant hand of skilled racquetball players relative to lesser skilled players (Pearce et al., 2000). A similar study compared shoulder abductor and wrist extensor muscle representations of the dominant and non-dominant arms for volleyball players and runners (Tyč et al., 2005). Results indicated that representations were larger for dominant arm muscles relative to non-dominant arm muscles in volleyball players, but no such asymmetry was found in runners. Taken together, these studies suggest that motor maps are responsive to skill learning.

A number of animal studies demonstrate map reorganization after motor skill learning. A fundamental principle that can be inferred from these studies is that reorganization is specific to the musculature involved in the task and is skill-learning dependent, not simply use-dependent. An original investigation of map plasticity during skill learning demonstrated that monkeys performing a manual dexterity task exhibited an enlarged representation of digits and diminished representation of wrist and shoulder musculature (Nudo et al., 1996a). Conversely, another monkey that was trained on a gross, eye-bolt turning task showed an increase in wrist and shoulder representations with a reduction in digit representation. A later study examined whether reorganization is simply due to the considerable number of repetitions animals performed (ie, 13,000) or more a consequence of learning to coordinate a novel movement (Plautz et al., 2000). In this study, monkeys retrieved pellets from a small well, which contrasted the larger well that they typically grasped food from during every day feeding. Unlike monkeys retrieving pellets from a larger well, these monkeys exhibited an expansion of digit representation, indicating that map changes were due to skill learning. Additional work in rats provides further evidence that changes in maps are driven by skill learning and not by repeated muscle activations during simple (Kleim et al., 1998, 2004; Remple et al., 2001) or cyclical tasks (Kleim et al., 2002b). Even in the presence of vascular and neural adaptations in M1 brought about by endurance and resistance training, respectively, changes in map topography only result from skill learning (Adkins et al., 2006). In fact, map organization early in development appears sensitive to environmental factors that influence skill learning (Young et al., 2012).

As previously mentioned, changes in synaptic efficacy are thought to mediate reorganization of motor maps during skill acquisition. Experimental manipulations of synaptic efficacy in animals provide direct evidence to this end (Jacobs and Donoghue, 1991; Nudo et al., 1990; Teskey et al., 2002; Van Rooyen et al., 2006; Young et al., 2011). In humans, there is indirect evidence of changes in synaptic potentiation following skill learning (Ziemann, 2004). Despite the absence of a direct link between changes in synaptic efficacy and map reorganization in humans, previous work has shown that motor maps are responsive to skill learning. Specifically, expanded map representations have been reported following intensive training on skills that involve complex digit movement sequences (Cohen et al., 1995), tongue protrusion (Svensson et al., 2006), and object projection (Tyč and Boyadjian, 2011).

3.2. Intervention-induced map plasticity after brain injury

Similar to skill training, brain injury (ie, stroke) leads to extensive spontaneous cortical reorganization. The general pattern of reorganization is very similar to that which is thought to occur following SCI. That is, cortical territory corresponding to muscles impaired by brain lesions is reduced (Bütefisch et al., 2006; Traversa et al., 1997) and spared, adjacent territory is enlarged (Nishibe et al., 2010; Nudo and Milliken, 1996). Other experimental approaches have been used to simulate neurological insult and measure its effect on map reorganization on a more immediate time scale. For example, injection of a protein synthesis inhibitor has been shown to reduce map size and compromise skilled movement in the rat (Kleim et al., 2003). Similarly, forebrain cholinergic lesions disrupt motor learning and the associated map reorganization (Conner et al., 2003). Motor retraining, however, can reverse this spontaneous reorganization, reinstating (Nudo et al., 1996b; Ramanathan et al., 2006) and enlarging motor maps (Liepert et al., 1998; Liepert et al., 2000b) projecting to impaired muscles in humans.

Several motor retraining studies in individuals with post-stroke hemiparesis have demonstrated that functional gains in the impaired limb are accompanied by expanded map areas early after stroke onset (Boake et al., 2007; Liepert et al., 2000b; Platz et al., 2005) and greater than six months thereafter (Liepert et al., 1998; Liepert et al., 2000a; Liepert et al., 2006). A significant disparity in map area between the lesioned and non-lesioned hemispheres is commonly observed prior to the intervention (Liepert et al., 2000a,b, 2001). At post-intervention testing, however, map areas constructed with brain stimulation in either hemisphere have been shown to re-balance, an effect that persists up to 6 months following the intervention (Liepert et al., 2000a). Even in the absence of changes in the lesioned hemisphere, there is evidence that improved function coincides with a reduction in map area of the non-lesioned hemisphere (Stinear and Byblow, 2004). Of the various physiological parameters that respond to behavioral improvements (ie, MEP amplitude and threshold, conduction velocity), only modifications in map topography predict improved motor function (Platz et al., 2005). Aside from expanded map area, changes in the distribution of inhibition within the map of the lesioned hemisphere have also been observed (Liepert et al., 2006). Using a paired-pulse stimulation protocol to measure intracortical inhibition surrounding the CoG of an intrinsic hand muscle, Liepert et al. (2006) found that the CoG (ie, the area of densest activation as reflected by the amplitude of MEPs) shifted to the location where inhibition was lowest prior to motor retraining. This shift was correlated with clinical scales of motor function, indicating that a redistribution of inhibition is behaviorally relevant.

3.3. Time course of map plasticity relative to skill (re-)learning

An important consideration related to map expansion and skill learning or re-learning that has recently come to light is the temporal coincidence of the observed changes. In the intact nervous system, improvements in reaching accuracy (ie, skill) precede map reorganization in rats (Kleim et al., 2004). Similar trends have been observed following brain injury (Eisner-Janowicz et al., 2008), but tracking the time course of map reorganization relative to functional gains is complicated. Potential confounds include matching which neural change (eg, dendritic proliferation, axonal sprouting, etc.) corresponds to a given behavioral change (Whishaw et al., 2008) and verifying that changes are not due to resolution of pathophysiological processes (eg, edema, diaschisis, etc.) resulting from the injury. A recent study addressed the temporal coincidence of changes by measuring maps at multiple time points in separate groups of rats (Nishibe et al., 2015). One group underwent motor retraining, while the other group did not participate in training but was allowed to recover spontaneously. Retrained rats demonstrated more rapid improvement in motor performance and overall performance quality (ie, number of successful pellet retrievals) than non-retrained rats, but forelimb motor maps for both groups remained small at the end of training on post-lesion day 18. On post-lesion day 38, however, retrained rats exhibited maps that were both larger relative to non-retrained rats and within the range of normal size, with the observed improvements in motor performance at post-lesion day 18 persisting through the follow-up period. Thus, motor skill re-learning after brain injury may precede the onset of adaptive changes in map reorganization. Reconciling these findings with the existing work in humans is difficult given differences in stimulation techniques and other methodological considerations. Nevertheless, future work is needed to better understand the temporal coherence between physiological and behavioral changes during motor retraining.

Existing evidence demonstrates that motor maps undergo extensive change during the course of motor skill development and learning. These changes are the inverse of the spontaneous reorganizational patterns that emerge after brain and spinal cord injury wherein impaired muscles have reduced representation in the cortex and muscles with preserved function appear to occupy greater territory. In the case of brain injury, however, motor retraining has shown the potential to normalize maps of impaired muscles to their pre-injury state. There is some evidence to suggest that maps also reorganize in response to interventions that target dysfunction following SCI.

4. How do motor maps reorganize in response to therapeutic interventions following SCI?

Existing literature on intervention-induced map plasticity after SCI, relative brain injury, is quite limited. An initial set of studies from the same group examined the effects of a combination therapy on behavioral deficits and motor maps in individuals with SCI. The first study was a case report involving one tetraplegic male with a complete injury at the C6 level (Hoffman and Field-Fote, 2007). Therapy involved 3 weeks of bimanual massed practice training coupled with somatosensory stimulation. Although spontaneous recovery was not controlled for, results indicated that motor and sensory functional improvements were accompanied by an anterior shift in the CoG for the biceps brachii muscle. In addition, the representation of this muscle increased in size (ie, area of all stimulation sites) and volume (ie, sum of amplitudes from all sites normalized to maximum MEP amplitude). In the second study, separate groups of individuals with incomplete injuries above C8 engaged in either unimanual or bimanual practice combined with somatosensory stimulation (Hoffman and Field-Fote, 2010). Similar to the earlier case report, sensory and motor function improved in both groups, regardless of the type of practice, and an expansion of map area for the opponens pollicis muscle was observed. Thus, combination therapies were found to promote plastic changes in motor maps.

Another study examined changes in neuropathic pain and map representation of an intrinsic hand muscle after repetitive TMS (rTMS) (Jetté et al., 2013). In this cross-over study, 16 individuals with complete or incomplete injuries and neuropathic pain in different body regions (eg, arm, leg, trunk, buttock) underwent 2 sessions of rTMS (hand or leg) and 1 session of sham stimulation. The rationale for this study was based on previous work demonstrating that rTMS induces synaptic plasticity (Hoogendam et al., 2010) and restores intracortical inhibition when applied to the M1 representation of body segments with focalized pain (Lefaucheur et al., 2006). In addition, there is evidence that pain can be attenuated more readily when targeting muscle representations that do not correspond to the painful zone (Lefaucheur et al., 2004). Results demonstrated short-term reductions in pain post rTMS to the hand (ie, 0–20 min) and leg (ie, 20 min) representations. Equivalent reductions in pain with stimulation to hand and leg representations were also observed 48 h thereafter but not at subsequent test sessions. Despite an increase in overall MEP amplitude after stimulation to the hand territory, there were neither changes in map area or volume nor shifts in CoG.

One fMRI study measured the volume of activation related to wrist movements at multiple time points during the first year after SCI (Jurkiewicz et al., 2007). No specific rehabilitation intervention was tested, however 5 of the 6 subjects experienced an increase in ASIA C5/6/7 motor score that was accompanied by an increase in the volume of activation in motor cortex over the study period. The authors offer two hypotheses that may account for the observed progressive increase in motor cortex activation volume. First, it may be that afferent input to motor cortex increases as the effects of acute trauma within the cord resolves. Alternatively, areas of motor cortex that previously controlled movements below the level of the injury may become accessible through unmasking of latent lateral connections, facilitation of ineffective synapses, or the formation of new synaptic connections.

Existing evidence in humans with SCI, though minimal, suggests that motor retraining induces adaptive changes in maps of impaired muscles. However, it is unclear to what extent each modality (ie, motor retraining or somatosensory stimulation) contributes to map reorganization because combination therapies can produce different functional and plastic changes than those resulting from individual therapies. For example, a previous study in rats with incomplete injuries demonstrated that administration of Nogo-A antibody led to corticospinal tract sprouting and improved locomotor function, while treadmill training did not produce any changes in sprouting and different improvements in locomotor function; the combination of both therapies led to increased sprouting but poorer locomotor function (Maier et al., 2009). These findings suggest that functional gains and associated map reorganization may be more or less attributable to either therapeutic modality.

4.1. Dissociating the effects of combination therapies on map plasticity

A recent study in spinally transected rats attempted to disentangle the interactive effects of multiple therapies on the percentage of cells in deafferented hindlimb cortex responding to tactile stimulation of the contralateral forelimb (Foffani et al., 2015). The therapies included active training of muscles above the level of injury (ie, treadmill), passive training of muscles below the level of injury (ie, bike), administration of a serotonergic agonist (ie, quipazine), as well as combinations of these individual therapies. Results of this study indicated that active exercise and serotonergic pharmacotherapy worked in synergy such that the combination produced greater reorganization than either therapy alone. Conversely, serotonergic pharmacotherapy in tandem with passive exercise limited cortical reorganization induced by passive exercise alone. Since results of this study pertain to modulations in firing rates of cells within somatosensory cortex, it is unclear whether similar changes might be observed in motor output maps. Another recent study in rats with complete mid-thoracic transections addressed this issue (Ganzer et al., 2016). In this study, the combination of serotonergic pharmacotherapy with passive training produced extensive expansion of the axial trunk motor cortex in hindlimb motor cortex that was correlated with the extent of unassisted weight support. An unexpected finding was that caudal and rostral forelimb motor cortex areas also exhibited reorganization, which also seems to run counter to the previously discussed view that reorganization is restricted to muscles innervated by segments rostral to the level of injury. Thus, it is likely that therapies carefully selected on the basis of an understanding of the underlying and, in some cases, interacting mechanisms can have potent effects on reorganization of motor maps. Nevertheless, there is limited data available on map reorganization, both spontaneous and directed, following human SCI so it is unclear how these results may translate to a clinical setting. Therefore, the effects of individual therapies that effectively separate mechanisms driving recovery should be given consideration in human work to determine which leads to functional gains and map reorganization.

4.2. Changes in the overlap of cortical representations: Implications for functional synergies

Overall, further work on intervention-induced map plasticity in humans with SCI is needed with more in-depth examination of the precise changes in map topography. For example, whether there is a redistribution of inhibition within the maps of impaired musculature, as shown to be functionally relevant in stroke (Liepert et al., 2006), is unknown. In addition, magnetic stimulation in neurologically-intact humans demonstrates considerable overlap in the representations of proximal and distal muscles (Devanne et al., 2006) that is thought to reflect functional synergies (Overduin et al., 2012, 2014; Park et al., 2001). For example, discrete areas of M1 show excitability peaks for different motor behaviors involving forearm muscles (ie, hand grasp vs. wrist extension), and synergistic muscles show greater overlap than antagonistic muscles (Massé-Alarie et al., 2017). Alternatively, abnormal muscle co-activation in impaired muscles due to neurological injury may be due to an increase in the overlap of cortical representations. After stroke, for example, there is a coupling between shoulder abduction and elbow flexion that impairs active range of motion during reach and grasp behaviors (Sukal et al., 2007). There is electrophysiological evidence indicating that excessive overlap contributes to the loss of independent joint control in this clinical population (Yao et al., 2009).

There is also evidence emerging to suggest that cortical overlap of muscles representations is a putative neural substrate underlying coordinated grasp behaviors (eg, precision and power grip) in humans (Fricke et al., 2017). Grasp reflexes are the first finger movements observed in humans after birth but are replaced by volitional power grasps and later complemented by individuated finger movements during precision grasps (Halverson, 1931). Recent work in humans has shown distinct representations of both power and precision grasps within M1 that correspond to the ontogenetic sequence with which these grips emerge during development (Fricke et al., 2017). Specifically, each grasp type appears to be encoded in cytoarchitectonically distinct regions of M1 (Rathelot and Strick, 2006, 2009) with precision grasp represented posteriorly in the more recently evolved region. Whether overlap of representations within M1 is subject to spontaneous reorganization after SCI or is influenced by motor retraining is not known but may provide unique insight into the functional changes that occur (Giszter and Hart, 2013).

A set of recent studies that examined the effects of motor retraining on map reorganization in rats with low thoracic injuries provides some indication of the potential relevance of overlapping maps following SCI (Oza and Giszter, 2014, 2015). In the first study, separate groups underwent treadmill training, robot-assisted treadmill training, or no training. All groups showed spontaneous reorganization of trunk representations after transection, as indicated by a significantly larger representation relative to non-transected rats. Both trained groups, however, showed further expansion of maps beyond the initial spontaneous reorganization after transection. Changes in coactivation and synergy representation, expressed as overlap between muscle representations, were also noted in transected rats. Unlike non-transected rats, all transected groups showed increased coactivation of trunk and forelimb muscles. Although maps exhibited spontaneous and directed reorganization, the retraining did not lead to improved motor function.

On the basis of these findings, the authors conducted another set of experiments to examine how maps change when functional capacity is actually improved (Oza and Giszter, 2015). In this study, two groups of spinalized rats were treadmill trained for 8–10 months. In the subsequent month, groups continued treadmill training with or without the involvement of a robot. Results indicated that the robot-treadmill trained group performed approximately four times fewer weight-supported steps at the end of training with significantly higher hindlimb stepping function. The group that underwent treadmill-only training exhibited no changes in function. No difference in total trunk representation was observed between groups, but there were several other notable changes in the robot-treadmill trained group. Aside from expanded caudal trunk representations, the displacement of trunk representation shifted toward more normal topography. Interestingly, despite an increase in coactivation of trunk representations, there was a decrease in the overlap of trunk and forelimb representations. Given the minimal overlap observed in maps of the neurologically-intact rat rostral cortex (Donoghue and Wise, 1982; Neafsey et al., 1986), this somatotopic segregation was a reversal of the overlap induced by spontaneous reorganization.

4.3. Neuromodulation-induced map plasticity

Neuromodulatory strategies that make use of stimulation to direct plasticity are becoming increasingly prevalent in the treatment of neurological movement disorders. Stimulation of the vagus nerve, for example, is thought to trigger the release of neuromodulators linked to cortical plasticity (Dorr, 2006). Pairing vagus nerve stimulation (VNS) with distal or proximal forelimb movements in intact rats over five days produced an enlargement of motor cortex relative to another group of rats that only trained on a motor task (Porter et al., 2012). Thus, pairing VNS with motor training may provide a strategy for treating neurological conditions characterized by abnormal movement representations. In rat models of stroke, for example, VNS paired with motor retraining restored motor function to pre-injury levels, which is superior to retraining (Hays et al., 2014) or VNS alone (Khodaparast et al., 2014).

Additional work has shed light on the mechanisms underlying the beneficial effects of VNS and points to an important role of map plasticity (Hulsey et al., 2016). One of the nuclei indirectly activated by vagus nerve afferents that triggers the release of acetylcholine to drive cortical plasticity is the nucleus basalis. Following training on a lever-pressing task and subsequent lesion to cholinergic neurons of the nucleus basalis, rats underwent five days of motor training with VNS delivered on successful trials. Consistent with prior work, VNS paired with motor training increased cortical representation of the forelimb in rats with an intact nucleus basalis compared to untrained controls. However, alterations in map size were suppressed by lesions to the nucleus basalis, suggesting that this neural structure is a mediator of cortical plasticity and the beneficial effects of VNS.

Preliminary findings in humans with stroke appear promising (Dawson et al., 2016), but further work is needed to understand the efficacy of this neuromodulatory strategy in improving motor function. Research efforts exploring whether this therapy can be used for the same purpose after SCI are underway. For example, a recent study demonstrates that closed-loop VNS paired with motor task performance can enhance motor output in a rat model of SCI (Ganzer et al., 2018). Interestingly, VNS was found to enhance output from the corticospinal circuits onto the impaired forelimb as reflected by an eight-fold increase in the number of motor cortex sites that generated grasp movements compared to motor retraining alone. In addition, the closed-loop system elicited a five-fold increase in the number of neurons in M1 relative to training alone. Thus, there is preliminary evidence that VNS can have potent, adaptive effects on corticospinal circuitry and control of motor output after SCI.

A number of other neuromodulatory strategies targeting M1 have been used to improve motor function after SCI. These include transcranial direct current stimulation (tDCS) (Jeffery et al., 2007; Murray et al., 2015), tDCS paired with patterned electrical stimulation (PES) (Yamaguchi et al., 2016), rTMS (Alexeeva and Calancie, 2016; Belci et al., 2004; Benito et al., 2012; Kuppuswamy et al., 2011), and paired associative stimulation (Roy et al., 2010). Despite the fact that these neuromodulatory strategies are thought to exert their effects through M1, no human studies have examined map plasticity post administration. This may be because the short-term changes in plasticity do not outlast the time required to construct maps with electrophysiological or imaging techniques. However, the effects of tDCS can last up to a week (Bindman et al., 1962), rendering acute map plasticity a viable phenomenon for future research to explore in at least some of the aforementioned neuromodulatory strategies.

5. Conclusion

We still do not fully understand the nature and extent of cortical reorganization after SCI. Cortical stimulation and imaging studies have produced results that fail to provide a definitive understanding of cortical reorganization and its functional relevance. As discussed in detail in the first section of this review, this may be attributable, at least in part, to the concomitant changes that occur along descending motor pathways. Although tract integrity is likely linked to changes in cortical function (Freund et al., 2012), combining structural (ie, tractography) and functional (ie, fMRI, TMS) techniques may provide a means to disentangle mixed findings from the existing literature.

It has been assumed that the nervous system has minimal, if any, potential to recover without the ability transmit motor commands through the lesion. Recent work in completely spinalized rats has challenged this view by demonstrating that combinations of pharmacological and physical therapies can promote partial recovery of locomotion via sprouting of corticospinal axons into deafferented hindlimb cortex (Manohar et al., 2017). Thus, plasticity of connections within motor cortex coupled with motor retraining has the potential to mediate recovery of function even in cases of complete spinal cord injury. These findings emphasize the importance of understanding the functional relevance of cortical reorganization in M1 after spinal cord injury. In addition, development of brain-computer interface (BCI) technologies used to assist or replace hand function after SCI stands to benefit (Collinger et al., 2013a). Specifically, accurate maps of cortical representations would allow more precise electrode placement and assist in screening candidates prior to intervention (Collinger et al., 2013b; Flesher et al., 2016). BCIs and other forms of neurofeedback may also be used in combination with repair therapies and/or rehabilitation protocols to guide therapeutic plasticity to promote recovery. Efficacy may be improved by identifying candidates whose cortical activity suggests the potential for recovery with a given intervention. There is, indeed, tremendous potential for basic neurophysiological findings to translate into meaningful biomedical advances that improve quality of life after SCI.

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