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Cortical reorganization after spinal cord injury: always for good?

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Abstract

Plasticity constitutes the basis of behavioral changes as a result of experience. It refers to neural network shaping and re-shaping at the global level and to synaptic contacts remodeling at the local level, either during learning or memory encoding, or as a result of acute or chronic pathological conditions. ‘Plastic’ brain reorganization after central nervous system lesions has a pivotal role in the recovery and rehabilitation of sensory and motor dysfunction, but can also be “maladaptive”. Moreover, it is clear that brain reorganization it is not a “static” phenomenon but rather a very dynamic process. Spinal cord injury immediately initiates a change in brain state and starts cortical reorganization. In the long term, the impact of injury – with or without accompanying therapy – on the brain is a complex balance between supraspinal reorganization and spinal recovery. The degree of cortical reorganization after spinal cord injury is highly variable, and can range from no reorganization (i.e. “silencing”) to massive cortical remapping. This variability critically depends on the species, the age of the animal when the injury occurs, the time after the injury has occurred, and the behavioral activity and possible therapy regimes after the injury. We will briefly discuss these dependencies, trying to highlight their translational value. Overall, it is not only necessary to better understand how the brain can reorganize after injury with or without therapy, it is also necessary to clarify when and why brain reorganization can be either “good” or “bad” in terms of its clinical consequences. This information is critical in order to develop and optimize cost-effective therapies to maximize functional recovery while minimizing maladaptive states after spinal cord injury.

1. Introduction

The well-known somatotopic map of the sensorimotor cortex represents a dynamic equilibrium in the continuous interaction between the brain and the external world (Erzurumlu and Kind, 2001; Feldman and Brecht, 2005), a sort of competitive battle among different parts of the body to gain space in the cortical field: the more a part of the body is

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used, the more cortical space it gains in detriment of adjacent body parts (Elbert et al., 1995). This continuous cortical reorganization is the everyday life of the normal brain during sensorimotor learning (Holtmaat and Svoboda, 2009; Barnes and Finnerty, 2010), but it becomes particularly extreme after injuries that lead to massive deafferentation, e.g. stroke, peripheral injuries or spinal cord injury (Wall and Egger, 1971; Calford and Tweedale, 1988; Pons et al., 1991; Jain et al., 1997; Florence et al., 1998; Endo et al., 2007; Ghosh et al., 2010). In principle, cortical reorganization after deafferentation is neither “good” or “bad”: the good side of cortical reorganization can favor functional recovery (Hoffman et al., 2007; Lotze et al., 2006; Cramer et al., 2005; Curt et al. 2002), but its bad side can be maladaptive and lead to phantom sensation and neuropathic pain (Flor et al., 1995; Lotze et al., 1999; Peyron et al., 2004; Wrigley et al., 2009; Gustin et al., 2012; Makin et al., 2013). It is therefore critical to fully understand the phenomenology and the mechanisms of cortical reorganization in order to design and optimize clinical strategies to manipulate it (Engineer et al., 2011).

In the present review we will focus on cortical reorganization after spinal cord injury, which is particularly challenging due to a number of factors. In fact, the degree of cortical reorganization after spinal cord injury is highly variable, and can range from no reorganization (i.e. “silencing”) to massive cortical remapping. This variability critically depends on the species, the age of the animal when the injury occurs, the time after the injury has occurred, and the behavioral activity and possible therapy regimes after the injury. We will briefly discuss these dependencies, trying to highlight their translational value for optimizing therapeutic interventions that both maximize functional recovery and minimize pain.

2. Cortical reorganization depends on species (Fig. 1)

2.1 Cortical reorganization after spinal cord injury in humans

Cortical reorganization after spinal cord injury is commonly observed in patients. Mapping studies with transcranial magnetic stimulation (TMS) reveal enlargement of cortical sensorimotor areas that represent preserved muscles above the level of lesion in quadriplegic patients (Levy et al., 1990) and enhanced excitability of motor pathways targeting muscles rostral to the level of a spinal transection in paraplegic patients (Topka et al., 1991). PET studies confirm that patients with spinal cord injury exhibit expanded activation of cortical and subcortical brain areas during hand movements (Roelke Bruehlmeier et al., 1998; Curt et al., 2002). Intriguingly, EEG studies report reorganization of cortical motor activity to a more posterior – rather than more medial – location after spinal cord injury (Green et al., 1998), later confirmed with fMRI (Turner et al., 2003). fMRI studies also describe increased representation of non-impaired upper limb muscles in paraplegic patients (Curt et al., 2002), a medial-superior shift in cortical activation during tongue movements after cervical spinal cord injury (Mikulis et al., 2002), and a range of cortical reorganization patterns, from a relative stability of sensorimotor cortical topography in a tetraplegic patient with a rare late recovery (Corbetta et al., 2002), to abnormalities in brain motor system function during attempted and imagined movement after complete spinal cord injury (Cramer et al., 2005). Motor cortex reorganization after complete spinal cord injuries was also confirmed by

combination of TMS and fMRI (Lotze et al., 2006). More recent works point toward a tight relationship between changes in cortical physiology and changes in cortical and cortico-spinal anatomy after spinal cord injury (Wrigley et al., 2009; Henderson et al., 2011; Freund et al., 2012; Freund et al., 2012). Finally, spinal cord injury not only affects evoked sensorimotor activity, but also slows down cortical spontaneous EEG activity (Tran et al., 2004; Boord et al., 2008; Wydenkeller et al., 2009). It is worth mention that an important literature exists on central nervous system plasticity after spinal cord injury in the context of breathing (Sharma et al., 2012; Hoh et al., 2013) and bladder function (Merrill et al., 2013; de Groat and Yoshimura, 2012). However, this plasticity is mostly subcortical (but see Zemleni et al., 2010), and will not be further discussed here. Overall, cortical reorganization appears as a complex phenomenon, not necessarily somatotopic, which has been associated with both functional recovery (Hoffman and Field-Fote, 2007; Jurkiewicz et al., 2007; Green et al., 2009), phantom sensations (Moore et al., 2000), and neuropathic pain (Ness et al., 1998; Boord et al., 2008; Wydenkeller et al., 2009; Wrigley et al., 2009; Gustin et al., 2012). Well-controlled studies in animal models are thus needed to decouple functional and maladaptive consequences of cortical reorganization after spinal cord injury.

2.2 Cortical reorganization after spinal cord injury in non-human primates

Research about cortical reorganization after spinal cord injury in non-human primates mainly focuses on the effects of dorsal column lesions. After cervical dorsal column section, neurons in the deafferented area 3b become initially unresponsive to stimulation of the hand, but after few weeks the area of cortical activation to spared inputs is greatly expanded, and after few months the deafferented hand cortical area becomes responsive to inputs from the face (Jain et al., 2000, 2008). This cortical reorganization is related to sprouting in the trigeminal-dorsal column complex in the brainstem (Jain et al., 2000; Kambi et al., 2014), and can also be observed at thalamic level (Jain et al., 2008). This reactivation of the deafferented hand cortex by inputs from the face seems more likely to contribute to phantom limb sensations than to functional recovery (Kaas et al., 2008), whereas the recovery of a near-normal cortical hand representation, possibly through alternate spinal afferents, seems to correlate with the recovery of hand use (Qi et al., 2014).

Somewhat similar results were obtained after localized cervical dorsal root lesions (rhizotomy), which cause both functional cortical reorganization (Darian-Smith and Brown, 2000) and sprouting in the brainstem (Darian-Smith, 2004, 2013). Intriguingly, in this model the reorganization was associated to functional recovery (Darian-Smith and Ciferri, 2006) and to neurogenesis within the spinal cord (Vessal et al., 2007) and in the sensorimotor cortex (Vessal and Darian-Smith, 2010). However, neurogenesis does not seem to occur when there is a direct trauma to the spinal cord with consequent glial scar formation (Vessal et al., 2007).

Cortical reorganization after dorsal column section is not limited to the primary somatosensory cortex, but also extends to the secondary somatosensory cortex and parietal ventral area (Tandon et al., 2009). In addition, major reorganization of the motor cortex may depend on damage to motor pathways or proprioceptive pathways. In fact, cervical spinal cord injury also produces long-term reorganization of the motor cortex paralleling recovery

of finger dexterity (Schmidlin et al., 2004; Nishimura et al. 2007; Kambi et al., 2011), with increased expression of GAP-43 mRNA in the cortical areas involved in the functional recovery (Higo et al., 2009). At least part of the functional recovery from lesion of the corticospinal tract is mediated by reticulospinal systems (Zaaimi et al., 2012).

2.3 Cortical reorganization after spinal cord injury in rats

In rats, spontaneous cortical reorganization after spinal cord injury appears to be more limited and somewhat controversial compared to primates (at least in adult animals without any explicit therapeutic intervention). Despite early works showing thalamocortical reorganization after lesions of the dorsal columns or of the gracilis nucleus (Wall and Egger, 1971), Jain et al., (1995) reported absence of any cortical reorganization between 3 hours and 3 months after unilateral dorsal column section at thoracic level (T6-T8), with neurons in the deafferented hindlimb cortex becoming unresponsive to cutaneous stimulation of any part of the body. A similar absence of cortical reorganization was recently confirmed after complete thoracic spinal cord transection, when tested with classical electrophysiological techniques (Graziano et al., 2013). The same thoracic spinal cord transection, however, significantly affects gene expression and regulation of plasticity-related proteins in the sensorimotor cortex (Endo et al., 2007; Graziano et al., 2013), revealing a powerful molecular substrate for cortical reorganization. Indeed, using functional magnetic resonance imaging (fMRI), increased BOLD signals in response to forepaw stimuli are observed in the primary somatosensory cortex in response to stimulation of the intact forelimb after thoracic contusion (Hofstetter et al., 2003), thoracic transection (Endo et al., 2007) or thoracic bilateral dorsal section of the spinal cord (Ghosh et al., 2010). But increases in regional cerebral blood flow (rCBF) are also observed in unstimulated animals in brain structures associated with somatosensory processing – including hindpaw somatosensory cortex and thalamus – after excitotoxic dorsal horn injury (Morrow et al., 2000; Paulson et al., 2005). Interestingly, long-term cortical reorganization after thoracic bilateral dorsal section, when assessed with voltage-sensitive dye imaging (VSD), appears to be temporally confined to the first week after injury (Ghosh et al., 2010). This discrepancy between the long-term cortical reorganization after spinal cord injury observed with functional imaging (particularly fMRI) and the limited reorganization observed with classical electrophysiological techniques might be simply due to differences in stimulus intensity among studies (light tactile stimuli in Jain et al., 1995 and Graziano et al., 2013; high-intensity electrical stimuli in Hofstetter et al., 2003, Endo et al., 2007 and Ghosh et al., 2010), could reflect differences in animal handling conditions after the injury, or could instead point toward an intriguing decoupling between metabolic and neuronal activity, which will need to be properly integrated to fully understand the mechanisms of long-term cortical reorganization after spinal cord injury.

Cortical reorganization after spinal cord injury in rats has been studied both in the context of functional recovery (Ghosh et al., 2009; Ghosh et al., 2010) and in the context of neuropathic pain (Endo et al., 2008). From the point of view of neuropathic pain, there is indeed evidence of increased fMRI activation at cortical level (Endo et al., 2008), but a critical role seem to be played by altered cortico-thalamic connectivity, as measured by fMRI resting state (Seminowicz et al., 2012), and altered subcortical processing. In particular, neuropathic pain after spinal cord injury has been linked to disruption of thalamic

processing, both in lemniscal nuclei such as the VPL – mechanistically related with abnormal expression of sodium channels (Hains et al., 2005; Hains et al., 2006) – and paralemniscal nuclei such as the PO, with a critical role played by the zona incerta (Masri et al., 2009; Whitt et al., 2013). From the point of view of functional recovery, because most studies focus on somatosensory reorganization, there is a need to better investigate the reorganization of the motor cortex (Oza and Giszter, 2014), possibly focusing both on the cortico-spinal tract, which is more related to fine movements, and in the cortico-reticulo-spinal tract, which is more related to posture and gross movements, including locomotion (see e.g. Bachmann et al., 2013). Intriguingly, the motor and sensory aspects of cortical reorganization after spinal cord injury seems to be tightly linked, as suggested by the beneficial effects induced by motor cortex stimulation on central pain (Lucas et al., 2011, Cha et al., 2013; Jiang et al., 2013).

3. Cortical reorganization depends on the age of the animal at the time of injury

The ability of the cortex to spontaneously reorganize is dependent on the age of the animal at the time of the lesion. In monkeys, dorsal column lesions within the first two weeks after birth lead to functional reorganization of the motor cortex in adulthood, uncovering the potential for motor reorganization due to loss of focal sensory inputs (Qi et al., 2010). In cats (McKinley and Smith, 1990) and rats (Jain et al., 1995), as described above, spinal cord injuries inflicted during adulthood are associated with little or no responsiveness in the deafferented cortex. However, cortical mappings of the somatosensory cortex of adult cats with spinal injuries inflicted within 6 weeks after birth demonstrate substantial cortical reorganization (McKinley and Swyter, 1989; Chau and McKinley, 1991; Casanova et al., 1991), with greater reorganization in kittens spinalized at 2 weeks compared to kittens spinalized at 6 weeks (McKinley and Smith, 1990). Some degree of cortical reorganization is also observed in adult rats spinally transected in the neonatal period (Jain et al., 2003). Interestingly, this cortical reorganization in adult animals spinalized as neonates is associated with an “infant lesion effect” (Bergman and Golberger, 1983a,b,c), which indicates sparing and greater recovery of function compared to animals spinalized during adulthood. For example, adult rats with neonatal transections at the T8/T9 levels can sometimes develop weight-supported stepping (Stelzner et al., 1975; Weber and Stelzner et al., 1977; Miya et al., 1997; Kao et al., 2006) associated with reorganization of the motor cortex, with low axial muscles being recruited from the rostral cortical axial representation that normally represents the neck and upper trunk (Giszter et al., 1998). Since the ability of these animals to maintain stance in the presence of controlled perturbations depended almost completely on the forelimbs (Giszter et al., 2007), it is likely that the sensory input from the forepaws is processed by this novel sensorimotor representation, activating the axial trunk musculature to improve balance by stabilizing the trunk and reducing the load on the hindlimbs. Speculatively, a possible critical role in the surprising motor recovery of adult rats transected as neonate could also be played by plasticity of the cortico-reticulo-spinal tract (Bachmann et al., 2013). Overall, the different response to injury in early development compared to adulthood (e.g. greater loss of neurons, possible preservation of connections that would normally be lost, etc.) seems to maximize the potential of cortical plasticity after

spinal cord injury, suggesting that neonatal models might be particularly useful to unravel the key factors to maximize – or optimize – cortical reorganization in adulthood.

4. Cortical reorganization depends on the time after injury (Fig. 2)

Cortical reorganization after spinal cord injury dramatically depends on the time elapsed after the injury. In humans, functional improvements and the appearance of neuropathic pain, both of which have been separately associated to cortical reorganization, can take months-to-years to occur (Corbetta et al., 2002). In non-human primates, as commented above, cortical reorganization can take weeks-to-months to fully develop (Jain et al., 2000, 2008). Interestingly, cortical reorganization after dorsal column section is characterized by spatial shifts of digit activation sites that consist of an early moving away phase and a late returning phase, compared to the pre-lesion activation sites (Chen et al., 2012). Rat studies seem to confirm that cortical reorganization after spinal cord injury is not simply a progressive phenomenon, but can instead undergo several temporal phases. The classical long-term cortical expansion that can be observed with fMRI 1-3 months after spinal cord injury (Endo et al., 2007) is anticipated by an early expansion within the first week (Endo et al., 2007; Sydekum et al., 2014), which is also observed with VSD imaging (Ghosh et al., 2010). This early expansion of intact cortical representations is associated with an early decrease of spine density in deafferented cortical representations, both in rats (Kim et al., 2006) and mice (Ghosh et al., 2012). The relations between early and late cortical reorganization remain to be established.

In an effort to understand the early mechanisms of cortical reorganization, we recently investigated the electrophysiological changes occurring in the primary somatosensory cortex immediately (i.e. within 1-3 hours) after spinal cord injury. A complete thoracic spinal cord transection or hemisection in anesthetized rats immediately changes the state of the brain, decreasing cortical spontaneous activity as evidenced by a slowing of the frequency of anesthesia-induced oscillations (Aguilar et al., 2010; Yagüe et al., 2014). This deafferentation-dependent decrease of cortical spontaneous activity could in principle be mediated by decreased activity in primary somatosensory structures, ultimately mimicking a thalamo-cortical deafferentation (Rigas and Castro-Alamancos, 2007; Hirata and Castro-Alamancos, 2010; David et al., 2013), or by decreased activity in secondary structures regulating cortical synchrony and arousal at thalamic and brainstem, most likely involving a depression of the cholinergic system (Moruzzi and Magoun, 1949; Lindvall et al., 1974; Hobson et al., 1975; Foote et al., 1980; Aston-Jones and Bloom, 1981a,b; Satoh and Fibiger, 1986; Fox and Armstrong-James, 1986; Hallanger et al., 1987; Steriade et al., 1990; Aguilar and Castro-Alamancos, 2005; Ren et al., 2009). The latter hypothesis is supported by decreased anesthetic requirements in rats after spinal cord injury (Foffani et al., 2011), similar to the decreased requirements for general anesthesia in animals and humans after epidural anesthesia (reviewed in Foffani et al., 2011).

Because in the rat somatosensory cortex slower spontaneous activity correlates with increased somatosensory responses (Petersen et al., 2003; Sachdev et al., 2004; Hasenstaub et al., 2007; Reig and Sanchez-Vives, 2007), spinal cord transection or hemisection also immediately increases the cortical responses to stimuli delivered above the level of the

lesion (Aguilar et al., 2010; Yagüe et al., 2014). But if cortical spontaneous activity is carefully monitored, cortical responses immediately after spinal cord transection still increase, even without a change in cortical state (Humanes-Valera et al., 2013; Yagüe et al., 2014). These increased responses could be due to a change in the equilibrium between excitation and inhibition at cortical and subcortical level. Intriguingly, even though the slower spontaneous activity seems to support the increased cortical responses immediately after spinal cord injury, it might not favor cortical reorganization in the long term. In fact, brainstem cholinergic activity is critical for cortical reorganization both in physiological conditions (Kilgard and Merzenich, 1998) and after peripheral or brain injury (Juliano et al., 1991; Conner et al., 2005). The decreased cortical spontaneous activity observed immediately after spinal cord transection could therefore at least partly explain the limited cortical reorganization observed after spinal cord injury in this rat model. Interestingly, in the hemisection model the decreased cortical spontaneous activity coexists with an immediate cortical hyperexcitability to preserved spinothalamic inputs (Yague et al., 2011), which could in turn contribute to the important functional, anatomical and behavioral changes observed after incomplete spinal cord injuries (Ghosh et al., 2009; Wasner et al., 2008; Densmore et al., 2010). In any case, these results suggest that to fully assess cortical reorganization after spinal cord injury it is necessary to monitor cortical spontaneous activity, and that cortical reorganization starts immediately after the lesion.

As reviewed so far, spinal cord injury by itself induces reorganization of supraspinal structures depending on the age of the animal at the time of the lesion and on the time elapsed after the lesion. In the following sections we explore how, in addition to the enhanced plasticity of supraspinal structures in response to lesions of the spinal cord itself, cortical reorganization can be further modulated by therapeutic interventions that had previously been thought to act solely at the level of the lesion or below. Pharmacotherapy and exercise represent the two best-studied therapeutic interventions for their impact on cortical reorganization.

5) Cortical reorganization can be promoted by pharmacological therapy after injury (Fig. 3)

Spinal cord injury not only affects the ascending and descending sensorimotor pathways in the spinal cord, but also disrupts the descending monoamine projections from brainstem regions, particularly eliminating serotonin (5-HT) and modifying its receptors caudal to the site of injury (Clineschmidt et al., 1971; Yaksh and Wilson, 1979; Skagerberg and Björklund 1985; Basura et al., 2001; Garraway and Hochman, 2001; Hains et al., 2002). A large literature exist on the effects of spinal cord injury on the spinal serotonergic system, and encouraging functional improvements can be obtained with 5-HT agonists after spinal cord injury (Kim et al., 1999; Antri et al., 2002, 2003, 2005; Shumsky et al., 2005; Kao et al., 2006; Landry et al., 2006; Ung et al., 2008; Musienko et al., 2009; Courtine et al., 2009). However, the 5-HT system also plays a significant role above the level of the lesion, regulating cortical plasticity. During development, 5-HT contributes to the organization of sensory and motor systems by modulating experience dependent plasticity (Nishi and Azmitia, 1999; Lotto et al., 1999; Kirkwood, 2000). In adulthood, 5-HT can reverse deficits

after injury or insult by reducing neuronal death and dendrite loss (Ramos et al., 2004), particularly through phosphorylation of the cytoskeletal remodeling protein MAP2 (Azmitia et al., 1995), resulting in the sprouting of neurites (Fricker et al., 2005).

To assess cortical reorganization in response to 5-HT pharmacotherapy after spinal cord injury without confounding effects from spared fibers left after partial lesions, we recently studied the effect of different 5-HT agonists and doses on cortical reorganization in adult rats after a thoracic (T8/9) spinal cord transection (Ganzer et al., 2013), assessed by single-neuron responses to light, cutaneous stimuli. Combinations of 5-HT receptor agonists induce expansion of the intact forelimb somatosensory (FLS) cortex into the deafferented hindlimb sensorimotor (HLSM) cortex and into the intact forelimb motor (FLM) cortex. The magnitude of this expansion is dose-dependent and positively correlates with behavioral recovery, and its topographic organization is in good agreement with the important overlap observed between the somatosensory cortex and motor cortex in the rat (Sievert et al., 1986; Morales-Botello et al., 2012). An intriguing possibility is that the expansion of forelimb somatosensory function into forelimb motor cortex may be due, in part, as a way to maintain the correct sensorimotor overlap, likely useful for locomotion in the rat.

As reviewed in the previous sections, spinal cord injury alone (i.e. without therapy) induces a more plastic state in the brain, altering the transcriptional activities of genes and the expression of proteins associated with cortical plasticity (Endo et al., 2007; Graziano et al., 2013). It is possible that this increased plastic state of the brain after spinal cord injury returns the sensorimotor cortex to a state reminiscent of that during development, when the actions of 5-HT are associated with plasticity rather than modulation of sensory input (Bennett-Clarke et al., 1994, 1995; Inaba et al., 2009; Jones et al., 2009; Kojic et al., 1997; Normann and Clark, 2005). This idea is not completely new. For example, the 5-HT_{1A} receptor was implicated in the restoration of visual function in amblyopic rats by reinstating ocular dominance plasticity (Maya-Vetencourt et al., 2008, 2011), and the 5-HT_{2A} receptor was shown to facilitate the delivery of AMPA receptors to the postsynaptic membrane as well as other late-LTP mechanisms during reorganization of the whisker cortex after visual deprivation (Jitsuki et al., 2011). Therefore, activation of 5-HT receptors within the sensorimotor cortex after spinal cord injury, combined with improved behavioral outcome from its actions below the level of the lesion, are likely to facilitate cortical reorganization by restructuring connections that could be relevant for behavioral recovery.

The increased plastic state of the brain after spinal cord injury also suggests other alternative or complementary pharmacotherapy approaches to promote (or control) cortical reorganization after spinal cord injury. For example, spinal cord injury in rats produces upregulation in dorsal column nuclei of extracellular chondroitin sulfate proteoglycans (CSPGs) (Massey et al., 2006), which are known to limit plasticity after CNS injuries (McKeon et al., 1991; Pindzola et al., 1993; Silver and Miller, 2004), including spinal cord injury (Davies et al., 1999; Tang et al., 2003; Jones et al., 2003). The limiting effects of CSPGs on plasticity can be overcome by both chondroitinase ABC (ChABC) and BDNF (Tropea et al., 2003): after cervical dorsal column section, ChABC treatment favors sprouting both in the spinal cord (Barrit et al., 2006; Lee et al., 2010) and in the cuneate nucleus (Massey et al., 2006), and provides neuroprotection to corticospinal neurons

(Carter et al., 2008); similarly increased spinal sprouting is obtained with ChABC treatment after unilateral cervical spared-root lesion (Cafferty et al., 2008); ChABC was also shown to promote cortical reorganization after cervical dorsal column lesion in monkeys (Bowes et al., 2012). More in general, pharmacological therapies designed to reduce neuroinflammation, induce neuroprotection and affect functional and anatomical plasticity at the level of the spinal cord – including therapies targeting the Nogo signaling system (Endo et al., 2009) – are also likely to affect cortical reorganization, possibly contributing to functional outcome after spinal cord injury.

6) Cortical reorganization can be promoted by exercise therapy after injury (Fig. 4)

It is well established that exercise favors brain plasticity, mainly via activation of the BDNF system (Neeper et al., 1995, 1996; Gomez-Pinilla et al., 2002; Vaynman and Gomez-Pinilla, 2005; Vaynman et al., 2003; 2004; 2006; Ding et al., 2011). Both after peripheral injuries and traumatic brain injuries, exercise induces cortical plasticity that is related to functional recovery (Friel et al., 2000; Florence et al., 2001; Ramanathan et al., 2006; Griesbach et al., 2009). The same relation between exercise, cortical reorganization and functional recovery holds after spinal cord injury. It is important to note that a clear distinction between the effects of exercise and of use-dependent training is often problematic, except when exercise therapy is passively delivered below the level of a complete spinal lesion (in this case there are obviously no use-dependent training effects). In humans, intensive task-specific rehabilitative training with robotic locomotor therapy after incomplete spinal cord injury can promote supraspinal plasticity in the motor centers known to be involved in locomotion (Winchester et al., 2005). Similarly, a longitudinal fMRI study in patients with cervical spinal cord injury showed that improvement in function after exercise therapy is associated with the extent of motor cortex activation (Jurkiewicz et al., 2007). In addition, a case report on intensive, bimanual training of a C6 motor-complete spinal injury resulted in functional improvement and an increased representation of the involved muscles in the cortex (Hoffman et al., 2007). In adult rats spinalized as neonates, treadmill training induces a novel organization in both the somatosensory cortex (Kao et al., 2009; 2011) and the motor cortex (Giszter et al., 1998), which directly correlates with the number of weight-supported steps these animals are able to take while locomoting on the treadmill (Giszter et al., 2008; Kao et al. 2011). Interestingly, exercise produces a prophylactic neuroprotective effect on the brain for subsequent spinal cord injuries in adult rats (Gomez-Pinilla et al., 2012).

Similarly to pharmacotherapy, exercise interventions also have the capacity to promote locomotor recovery and plasticity at many levels of the sensorimotor system, both in the spinal cord and in the brain. After spinal cord injury, exercise can be administered both passively (Murphy et al., 1999) or actively (Ilha et al. 2011; Nessler et al., 2005; Timoszyk et al. 2005; Dobkin et al., 2006). In animal studies, exercise is associated with the upregulation of neurotrophic factors within the spinal cord (Keeler et al. 2012; Liu et al. 2010, 2012), which can encourage plasticity through a wide variety of molecular mechanisms (for reviews see: BDNF: Weishaupt et al., 2012; Neurotrophins: Ebadi et al., 1997; GDNF: Bohn 2004). In humans, passive bicycling exercise is a common non-invasive

therapy that can reduce spasticity (De Mello et al., 2004; Kiser et al., 2005), increase bone density (Hangartner et al., 1994; Lauer et al., 2011) and reduce lower limb blood pooling (Phillips et al., 1998). In addition, locomotor training, usually with body-weight support on a treadmill, has also an impact on functional recovery (Wernig et al., 1995; Van Hedel and Dietz, 2010; Wessels et al., 2010; Barbeau, 2003; Harkema et al., 2012a,b). It has been generally assumed that this functional recovery is due to activation and/or relearning in the spinal circuits (Dietz and Harkema, 2004; Edgerton et al., 2004; Harkema et al., 2008; Harkema et al., 2012b).

To determine whether exercise therapies targeted below the level of the lesion could have an impact in supraspinal centers, we recently assessed whether passive bicycling exercise to the hindlimbs after complete thoracic transection of the spinal cord induced any effects on the sensorimotor cortex (Graziano et al., 2013). Somewhat surprisingly, passive bicycling exercise of the paralyzed hindlimbs promotes the upregulation of plasticity-related proteins BDNF and ADCY1 within the sensorimotor cortex, accompanied by significant expansion of the forepaw somatosensory responses into the deafferented hindlimb cortex (Graziano et al., 2013). Even though the neuroendocrine and other systemic mechanisms likely mediating these effects need to be further clarified, the possible causal relationships between increased BDNF and cortical reorganization seem clearer. In fact, we already mentioned that the limiting action of CSPGs on plasticity can be overcome not only by ChABC but also – and synergistically – by BDNF (Tropea et al., 2003). This finding might well explain why exercise, by increasing BDNF levels in the brain (Graziano et al., 2013), can favor cortical reorganization (Graziano et al., 2013) and functional recovery (Wang et al., 2011) after spinal cord injury.

7) Combined therapies to manipulate cortical reorganization after spinal cord injury

There is substantial evidence that 5-HT and BDNF interact at the cellular level (Nibuya et al., 1995; Russo-Neustadt et al., 1999, 2000; Ivy et al., 2003; Garcia et al., 2003; Mattson et al., 2004), which can potentially lead to an amplification of their plastic effects when administered in combination. Since exercise increases the levels of BDNF (see above), exercise combined with 5-HT pharmacotherapy could potentially promote the rewiring of sensorimotor cortical circuits and locomotor recovery after spinal cord injury more effectively than either alone. However, the interaction might not necessarily be always functionally synergic, due to the complex state-dependent modulatory action of 5-HT throughout sensorimotor systems (Eccles, 1964; Proudfit and Anderson 1973; Waterhouse et al., 1986; Bassant et al., 1990; Lopez-Garcia and King, 1996; Sheibani and Farazifard, 2006). From a translational viewpoint, the complexity of this interaction highlights the importance of better understanding the mechanisms underlying combination therapies to maximize functional recovery after spinal cord injury. For example, the somewhat limited clinical improvement achieved by conventional locomotor training after incomplete spinal cord injury – either with or without partial body-weight-support (Morawietz and Moffat, 2013) – could be enhanced by proper concomitant therapies, such as pharmacotherapy and/or epidural stimulation (Courtine et al., 2009; Angeli et al., 2014), or even deep brain

stimulation (Bachmann et al., 2013), with a likely critical role played by plastic changes in supraspinal circuits.

In the context of promoting/controlling cortical reorganization after spinal cord injury in humans, an important clinical role could be played by non-invasive brain stimulation (NIBS), a growing family of techniques that share the common characteristic to be able to change cortical excitability and induce plastic changes in the brain. Most of these techniques are easy to use, safe, can focally stimulate the nervous system and can be easily combined with exercise and pharmacotherapy. Commonly used NIBS techniques include repetitive transcranial magnetic stimulation (rTMS; Hallett, Neuron 2007) and related techniques, transcranial direct current stimulation (tDCS; Nitsche and Paulus 2000; Priori, 2003) and related techniques, and more recently transcranial focused ultrasound brain stimulation (tFUS; Legon et al., 2014) and transcranial static magnetic field stimulation (tSMS; Oliviero et al., 2011). Few studies have already assessed the use of NIBS in patients with spinal cord injury, both to maximize functional outcome (Belci et al., 2004) and to reduce neuropathic pain (Fregni et al., 2006). Moreover, tDCS has been tested to improve the efficacy of visual illusion treatment of neuropathic pain (Soler et al., 2010). It is important to remark the need to gain deeper knowledge about the mechanisms and timing of cortical reorganization after spinal cord injury in order to optimize NIBS-based treatment. In any case, NIBS offer promising tools to manipulate cortical reorganization after spinal cord injury. Future clinical studies should demonstrate if this manipulation, possibly combined with other therapies, is clinically relevant or not.

8) Conclusions

Plasticity constitutes the basis of behavioral changes as a result of experience. It refers to neural network shaping and re-shaping at the global level and to synaptic contacts remodeling at the local level, either during learning or memory encoding, or as a result of acute or chronic pathological conditions. ‘Plastic’ brain reorganization after central nervous system lesions has a pivotal role in the recovery and rehabilitation of sensory and motor dysfunction, but can also be “maladaptive”. Moreover, it is clear that brain reorganization is not a “static” phenomenon but rather a very dynamic process. Spinal cord injury immediately initiates a change in brain state and starts cortical reorganization. In the long-term, the impact of injury – with or without accompanying therapy – on the brain is a complex balance between supraspinal reorganization and spinal recovery (e.g. the reduction of the spinal edema and of the inflammation slowly allows for an increase of the brain-to-spine and spine-to-brain connections). Therefore, it is not only necessary to better understand how the brain can reorganize after injury with or without therapy, it is also necessary to clarify when and why brain reorganization can be either “good” or “bad” in terms of its clinical consequences. This information is critical in order to develop and optimize cost-effective therapies to maximize functional recovery while minimizing neuropathic pain after spinal cord injury.

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Reorganization in the brain after SCI lesion plays a pivotal role in recovery

Brain reorganization can also be maladaptative

After spinal cord injury, this reorganization is a dynamic phenomenon

The extent of reorganization is highly variable depending on species, age and therapy regimes

Understanding reorganization can optimize cost-effective

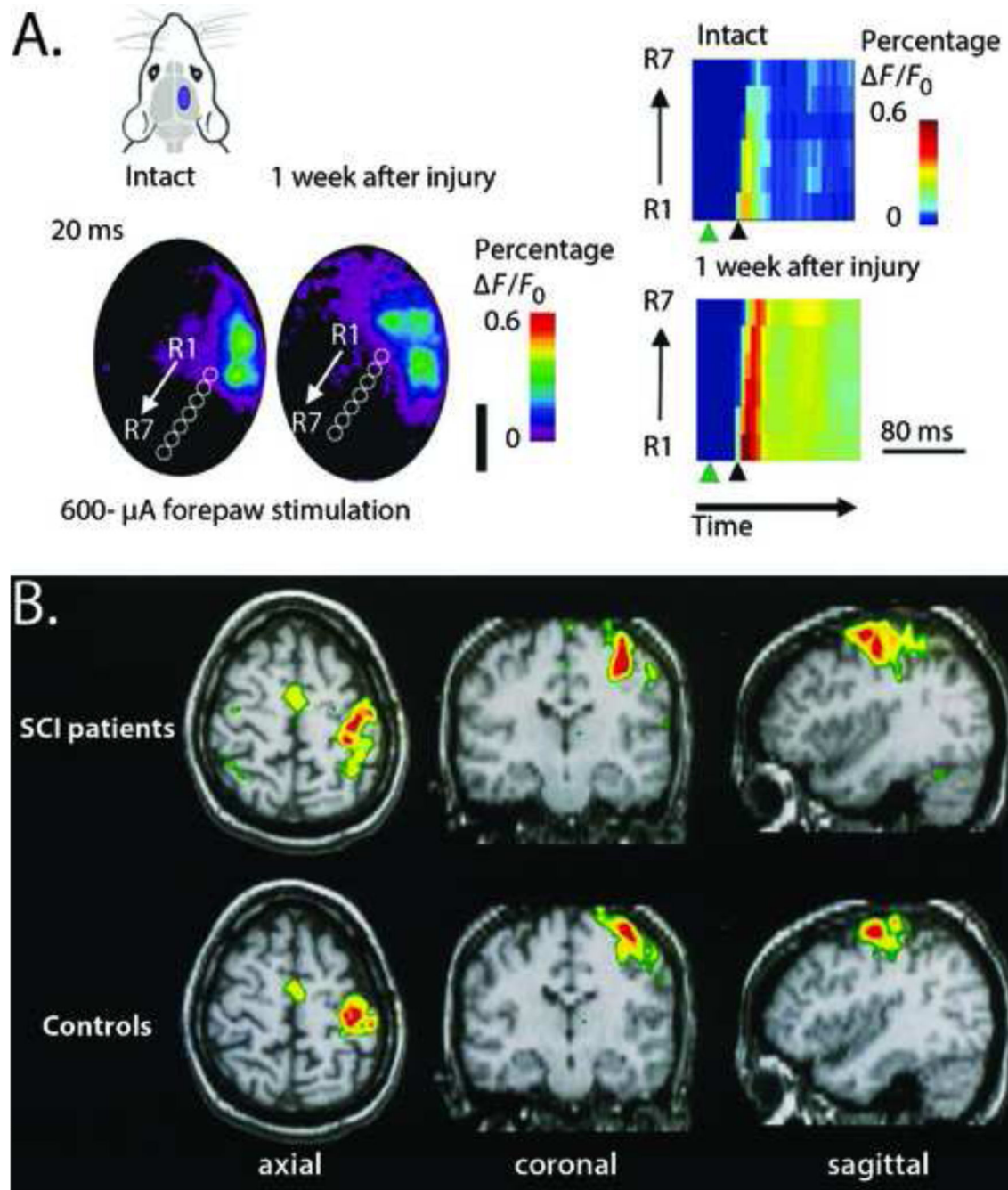


Figure 1.

Expansion of the intact cortex into the deafferented cortex after spinal cord injury occurs in several species from rat to human. **A.** Reorganization in the rat hindlimb cortex after bilateral, dorsal hemisection as measured by voltage sensitive dye (VSD) imaging. Left top left: purple region in the schematic representation of the rat head shows the region of the brain where VSD imaging was performed. Left bottom: seven regions of interest (ROIs), 300- μ m in diameter, were defined (R1–R7 white circles). R1 was placed adjacent to the forelimb representation and subsequent ROIs were placed progressively caudo-medial at an

angle of 35° from the midline. Right: activation of the voltage sensitive dye across the ROIs as a function of time in response to electrical stimulation of the forepaw. Activation begins nearest the forelimb representation and is greater one week after injury. Green arrowheads denote the time of stimulation. Black arrowhead denotes 20 ms after stimulation. Figure reproduced from Ghosh et al., (2010) with permission. **B.** Reorganization in the human cortex after spinal cord injury as measured by functional magnetic resonance imaging (fMRI). These data represent group results from nine paraplegic patients approximately 40 months after injury to the thoracic or lumbar region. Subjects were asked to repetitively perform finger-to-thumb opposition of the digits 2, 3, 4 and 5. Images show group averages. The activation patterns in the SCI patients (top row) is significantly enlarged compared to that of the controls (bottom row) with a medial and lateral expansion of the volume and an additional increase in activation in the contralateral premotor and parietal areas. Figure reproduced from Curt et al. (2002), with permission.

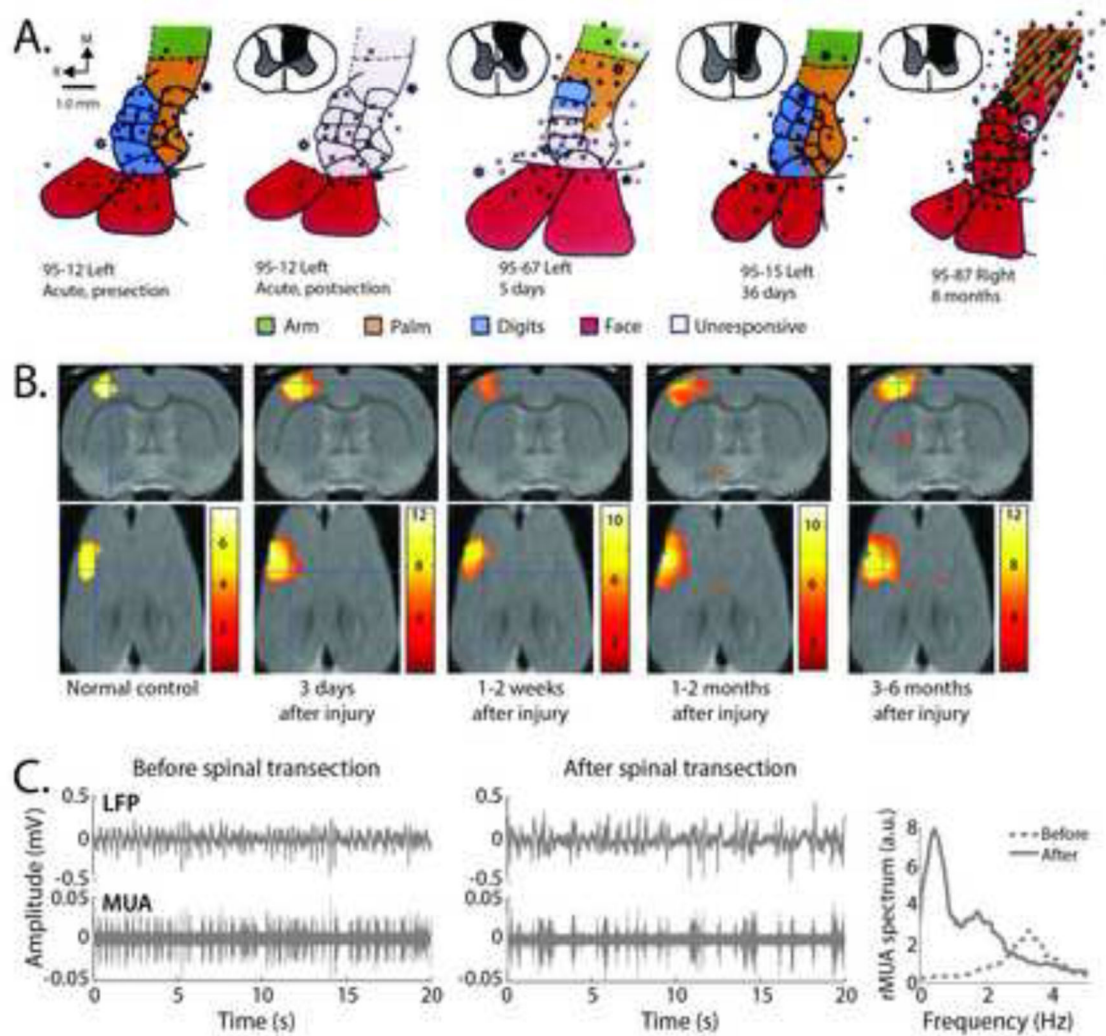


Figure 2.

The extent of reorganization after spinal cord injury is dependent on the time after injury. **A.** In primates, after unilateral, cervical dorsal column lesions, neurons in the deafferented cortex were unresponsive to sensory stimulation immediately after the lesion (95-12 acute, postsection). After 5 days, there was a significant enlargement of the intact regions above the level of the lesion (e.g. face) that then constricted by one month post-lesion. However, by 8 months post lesion, cells across the entire area 3b were responsive only to stimulation above the level of the lesion or the face (95-87 8 months). Figure reproduced from Jain et al. (1997), with permission. **B.** Similar results were found in the rat using fMRI. Group analysis of the responsiveness of cortex to electrical stimulation of the forepaw in 12 rats transected at T9. Coronal sections are along the top and horizontal sections are along the bottom. Significant enlargement of the fMRI signal, extending both medially and caudally (into the hindlimb cortex) from the original forelimb begins 3 days after injury and is then lost approximately 1-2 weeks after injury. By 1-2 months after injury, the expansion is reestablished and continues to enlarge by 3-6 months. Figure reproduced from Endo et al. (2007), with permission. **C.** Further studies in the rat show that urethane-induced delta

oscillations (1-4Hz) before spinal transection (left panels showing local field potential, LFP, and multiunit activity, MUA) transitioned to slow-wave oscillations (<1Hz) immediately (i.e. within minutes) after spinal transection (middle panels), corresponding to a reduction in spontaneous activity as evidenced by a decrease mean amplitude of the rectified multi-unit activity (rMUA) and a decreased frequency of the rMUA spectrum (right panel). Figure reproduced from Aguilar et al. (2010), with permission.

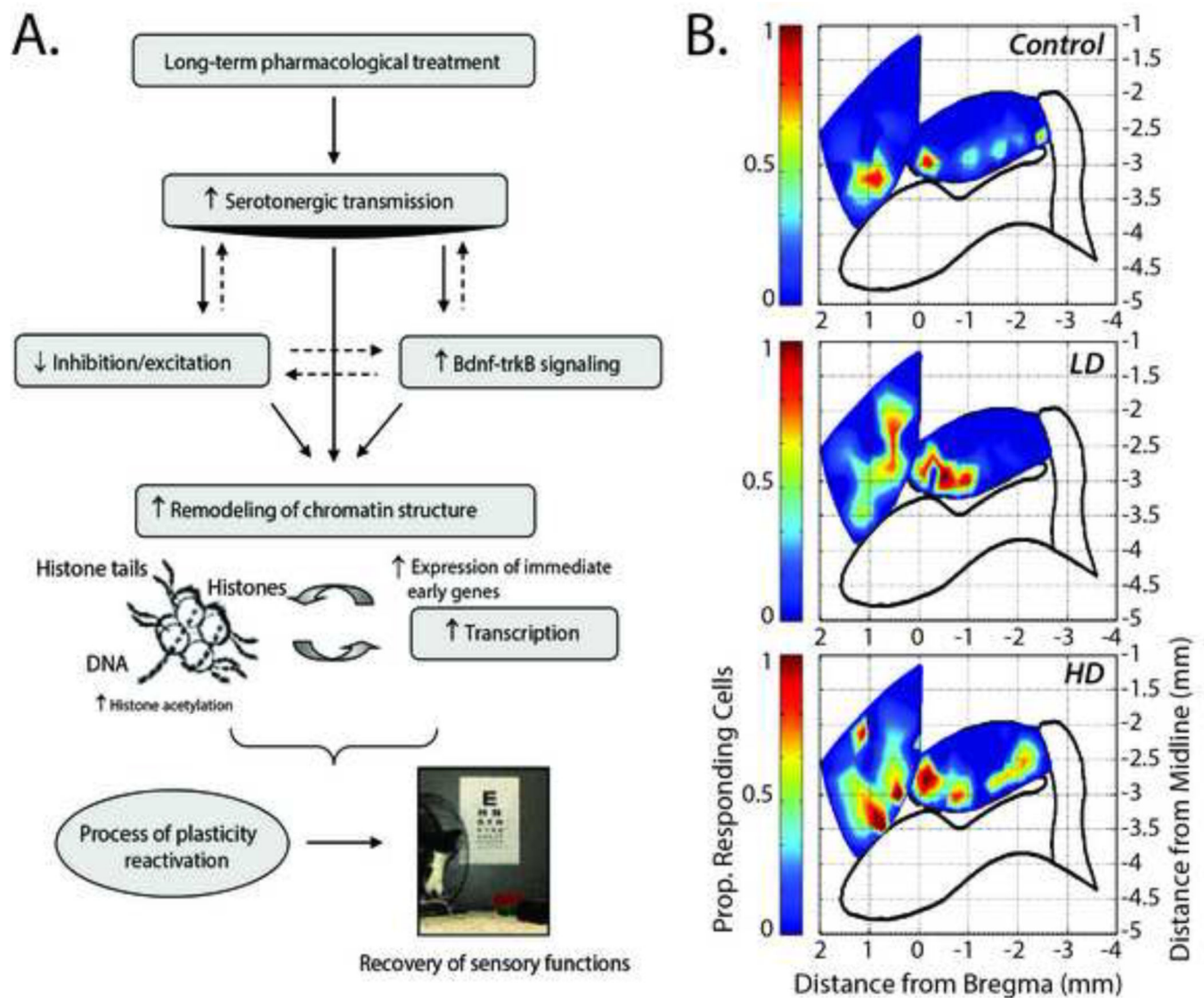


Figure 3.

Serotonin is known to promote adult cortical plasticity after injury. **A.** Studies have shown that pharmacotherapy after injury can increase BDNF-trkB signaling which increases the remodeling of chromatin structures ultimately lowering the threshold for cortical excitability, thus increasing the probability for sensory stimulation (in this case visual) to drive activity-dependent modification of synaptic transmission. Figure reproduced from Maya-Vetencourt et al. (2011), with permission. **B.** Similar results were observed after spinal cord injury. Top panel shows the responsiveness of the hindlimb sensory-motor cortex (HLSM, oval outlined in black) and forelimb motor cortex (quadrilateral located more rostrally) to tactile stimulation of the forepaw. Responsiveness is measured by the number of neurons that respond to the forepaw stimulation with increased firing rate. Middle panel shows expansion of the response into both the hindpaw sensory cortex and forepaw motor cortex after 8-weeks of a daily injection of a low dose (LD) of 5-HT agonists. Bottom panel shows greater expansion after 8-weeks of daily injection of a high dose (HD) of 5-HT

agonists. Responses in the forepaw cortex (black outline more lateral from the hindpaw are not shown). Figure reproduced from Ganzer et al. (2013), with permission.

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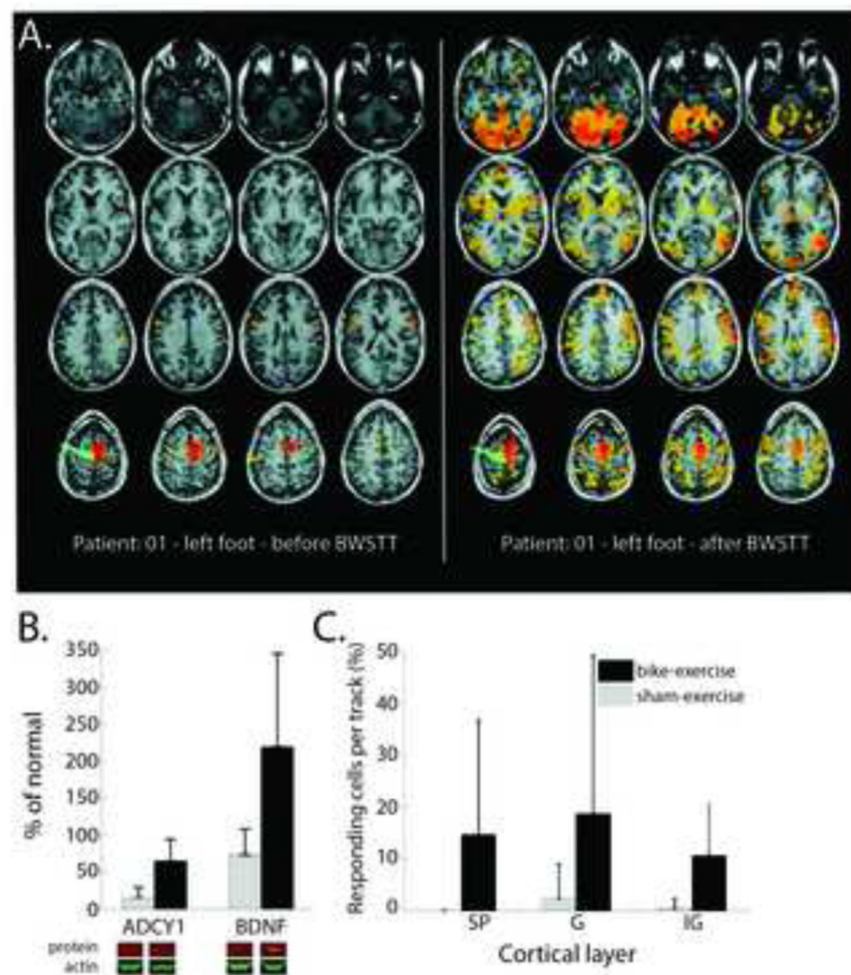


Figure 4.

Exercise promotes cortical reorganization after spinal cord injury. **A.** Robotic locomotor therapy that improved functional outcome also enhanced motor representation of the foot. Images are an example from one patient. The red-orange areas show regions of brain activation in response to voluntary ankle plantar flexion and toe flexion as measure by fMRI. Figure reproduced from Winchester et al. (2005), with permission. **B.** Similar results were found for spinalized rats after 8-weeks of passive bike exercise below the level of the lesion. The exercise increased the levels of adenylate cyclase 1 (ADY1) and brain-derived neurotrophic factor (BDNF) in the cortex. **C.** Bike exercise also increased the probability that cells in the deafferented hindlimb cortex would respond to tactile stimulation of the forelimbs across all cortical layers: supragranular (SP), granular (G) and infragranular (IG). Figure reproduced from Graziano et al. (2013), with permission.