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REVIEW

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 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.

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Key words: spinal transection, pain, exercise, brain plasticity, serotonin, brain-derived neurotrophic factor.

Contents

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 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,

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Abbreviations: 5-HT, serotonin; BDNF, brain-derived neurotrophic factor; ChABC, chondroitinase ABC; CSPGs, chondroitin sulfate proteoglycans; EEG, electroencephalogram; fMRI, functional magnetic resonance imaging; FLM, forelimb motor; FLS, forelimb somatosensory; HLSM, hindlimb sensorimotor; NIBS, non-invasive brain stimulation; ROI, region of interest; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation; VSD, voltage-sensitive dye imaging.

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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'' nor ''bad'': the good side of cortical reorganization can favor functional recovery (Manduch et al., 2002; Curt et al., 2002a; Cramer et al., 2005; Lotze et al., 2006; Hoffman and Field-Fote, 2010), 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., 2009a,b; 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.

CORTICAL REORGANIZATION DEPENDS ON SPECIES (FIG. 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). Positron emission tomography (PET) studies confirm that patients with spinal cord injury exhibit expanded activation of cortical and subcortical brain areas during hand movements (Roelcke et al., 1997; Bruehlmeier et al., 1998; Curt et al., 2002b). Intriguingly, electroencephalogram (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 functional magnetic resonance imaging (fMRI) (Turner et al., 2003). fMRI studies also describe increased representation of non-impaired upper limb muscles in paraplegic patients (Curt et al., 2002a), 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., 2009a,b; Henderson et al., 2012; Freund et al., 2011, 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 mentioning 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 Zempleni 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., 2009a,b; Gustin et al., 2010, 2012). Well-controlled studies in animal models are thus needed to decouple functional and maladaptive consequences of cortical reorganization after spinal cord injury.

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; Darian-Smith et al., 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,