CHAPTER 14

Changes in CNS structures after spinal cord lesions: implications for BMI

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Abstract: It is well established that a spinal circuitry can generate locomotor movements of the hindlimbs in absence of descending supraspinal inputs. This is based, among others, on the observation that after a complete spinalization, cats can walk with the hindlimbs on a treadmill. Does this spinal pattern generator (CPG) also participate in the recovery of locomotion after a partial spinal cord lesion (SCI)? After such SCI, functional reorganization can occur spontaneously along the whole neuraxis, namely the spinal cord circuitry below the lesion (CPG) and in supraspinal structures still partially connected to the spinal cord. This review focuses mainly on the capacity of the spinal and supraspinal structures to reorganize spontaneously after incomplete SCI in animals (rats and cats). BMI approaches to foster recovery of functions after various types of SCI should take into account these changes at the various levels of the CNS.

Keywords: spinal cord injury; central pattern generator; plasticity; cortex; locomotion; BMI.

Brain machine interface (BMI) may eventually offer viable solutions to the problem of recovery of sensorimotor functions after partial spinal cord injuries (SCIs). Indeed, it might be very appealing to consider that a device could be designed to bridge the gap made by the spinal lesion and somehow transmit or relay signals to the severed cord.

Other BMI approaches may aim at stimulating sensorimotor pathways to potentiate weak remaining descending commands. Finally, one could stimulate the spinal cord itself electrically with or without a pharmacological potentiation. Before any of these solutions become a reality, it should be realized that after a SCI, plastic changes occur throughout the central nervous system (CNS) and BMI must take into account these changes. In this context, understanding the normal CNS control of sensorimotor functions is essential but knowing how

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pathophysiological processes alter the properties of the CNS structures involved in their control is crucial. Indeed, stimulated areas of the brain and spinal cord might have changed and alternative pathways might have become more or less prominent in the control of a given function such as locomotion.

There is a large corpus of evidence showing that some degree of functional recovery occurs spontaneously after incomplete SCI, thus indicating that reorganizations within different CNS structures can compensate for the disruption of pathways subserving the altered functions. After incomplete SCI, reorganization can occur spontaneously along the whole neuraxis since part of the spinal cord circuitry remains intact and still partially connected with cortical and subcortical structures through remnant fibers. Such plastic changes might occur in preexisting circuits by modification of synaptic efficiency or could involve the formation of new circuits through sprouting and anatomical reorganizations.

This review will focus mainly on the capacity of the spinal and supraspinal systems to reorganize spontaneously after incomplete SCI in animals. Given the fact that this is a large topic reviewed in more detail elsewhere (Rossignol, 2006; Rossignol and Frigon, 2011; Rossignol et al., 2006, 2009), we will concentrate on major changes in supraspinal structures, in descending pathways as well as in changes occurring within the spinal cord itself below the SCI as illustrated in Fig. 1.

Reorganization of cortical areas after incomplete SCI

In response to incomplete SCI, the sensorimotor cortex can undergo a dramatic reorganization. Somatosensory (S1) and motor (M1) maps remodeling can be used to gain insight into the capacity of sensorimotor systems to reorganize in response to SCI. Regardless of the species used, a spinal lesion targeting the dorsal column pathways or the entire hemicord (Fig. 2a) induced an immediate abolition of somatosensory-evoked responses in the deprived area within the S1 cortex corroborating the loss of tactile perception (Jain et al., 1995, 1997; Martinez et al., 2009, 2010; Onifer et al., 2005). A few weeks later (see Fig. 2b and c), the cortical areas deprived of their prevailing sensory afferents became responsive to sensory stimuli applied to contiguous skin territories, whose afferent pathways were not affected by the spinal lesion (Jain et al., 1997; Martinez et al., 2009, 2010), as also found after nerve lesion or limb amputation (Calford and Tweedale, 1988, 1991; Faggin et al., 1997; Merzenich and Jenkins, 1993). Reorganizations also occurred in the M1 cortex, but, since the topographic organization is less clear, the interpretation of changes is more difficult (see Fig. 2d). One month after a bilateral lesion of the corticospinal tract at the thoracic spinal level in rats, intracortical stimulation that normally evoked hindlimb responses was found to evoke responses in the forelimbs, the trunk, and whiskers which are classically represented in adjacent cortical territories (Foulad et al., 2001). In the same vein, 1 month after a unilateral C4–C5 hemisection, a drastic reduction of the overall M1 map size as well as an overrepresentation of the forelimb muscles whose motoneurons were localized rostrally to the hemisection was observed (Martinez et al., 2010; see Fig. 2e). Similar results were observed after motor nerve sections (Donoghue et al., 1990; Franchi and Veronesi, 2004; Sanes et al., 1990; Schmidlin et al., 2004), indicating that cortical territories controlling intact body parts tend to enlarge and invade cortical areas that have lost their peripheral targets. Interestingly, an elegant study combining several functional imagery techniques in rats with cervical spinal cord lateral hemisections showed that the intact sensorimotor cortex (ipsilesional) also underwent a drastic reorganization (Ghosh et al., 2009). More specifically, the cortex developed an enhanced representation of the unimpaired forepaw by 12 weeks after SCI, a change hypothesized to result from an increased use of the intact forelimb. It is, however, unclear whether the changes of activity in cortical regions
causally contribute to the functional recovery or if they are induced by the development of behavioral strategies. They can, however, be considered to reflect compensatory changes in functional connectivity between the cortex and periphery that can sometimes be attributable to anatomical reorganization of neural circuits.

Reorganization of descending pathways after incomplete SCI

Physiological compensatory mechanisms: synaptic efficiency changes

SCI induce major synaptic efficiency changes within sensorimotor networks, mainly in the vicinity of the lesion. The loss of part or all of efferent inputs leads to structural changes relative to the number, size, or distribution of synaptic contacts within interneurons (including propriospinal) and motoneurons. An example of synaptic changes after SCI has been demonstrated by comparing the synaptophysin immunoreactivity (Ir), a synaptic marker, in intact versus lesioned spinal tissues (Nacimiento et al., 1995). In the intact tissue, motoneurons are surrounded by synaptophysin Ir, while they are depleted for several weeks in the lesioned territory. After the third month, however, synaptophysin expression was similar in the intact and lesioned tissues thus suggesting that new synapses formed on motoneurons soma. Although the origin of these new synapses is uncertain, they could arise from interneurons or sensory afferents transmitting tactile and proprioceptive signals.
(a) Electrophysiological recordings or stimulations location

(b) Contralesional S1 cortex intact rat

(c) Contralesional S1 cortex 60 days postlesion

Glabrous skin
Hairy skin
Noncutaneous responses
Electrode recordings location
Limit of mapped cortical area

(d) Contralesional M1 cortex intact rat

(e) Contralesional M1 cortex 60 days postlesion

Movement location
Shoulder
Elbow
Wrist
Digits
Elbow + wrist
Wrist + digits
Whiskers/behind
NR
No response
Modifications in synaptic efficiency can also be due to neurotransmission changes within neuronal networks. GABA, the main CNS inhibitory neurotransmitter, has a presynaptic inhibitory action on primary afferents and on postsynaptic membranes of interneurons and motoneurons (Alvarez et al., 1996). After complete SCI, GABA neurotransmission is increased in the spinal cord below the injury site as measured from increase in synthesizing enzymes, resulting in altered inhibition during the postlesion period (Tillakaratne et al., 2000). Along the same line, upregulation of different monoaminergic receptors such as alpha-1, alpha-2 noradrenergic receptors, and 5-HT1A receptors were observed in the lumbar region in the first month after a complete SCI (Giroux et al., 1999). These changes in synaptic efficiency and neurotransmission may be important during the period of postlesion recovery.

In addition, the propriospinal system, including short and long neurons, is known to, respectively, interconnect spinal segments as well as the brainstem and the spinal cord (Sherrington and Laslett, 1903). In intact and in the presence of staggered bilateral hemisections in in vitro neonatal rats preparations, these propriospinal neurons have been shown to be sufficient in transmitting the descending locomotor command signals from the brainstem (Cowley et al., 2008; Zaporozhets et al., 2006), suggesting that the efficiency of the latter is increased after SCI which may contribute to the rerouting of descending commands through sprouting as we will detail later (Bareyre et al., 2004).

Compensation by remnant fibers (sprouting)

In cats submitted to a unilateral thoracic hemisection (Pike et al., 1929), a spontaneous recovery of the affected hindlimb was observed and it was hypothesized that “the mechanism which takes over control of movements of the limb lying below the level of the lesion includes motor fibers coming down on the opposite side of the spinal cord, and commissural neurons lying on the spinal cord below the level of lesion.” Up to now, such a hypothesis of a compensatory role of remnant fibers is prevalent. Indeed, after a subtotal midlumbar cord section which spared the left lateral and ventral funiculi, the subsequent lumbar commissurotomy or left thoracic spinal hemisection was shown to abolish the locomotor recovery of rats, suggesting again that spared descending fibers could reach the sublesional spinal cord and mediate locomotor recovery (Harris et al., 1994). Tract tracing and immunocytochemical studies of the corticospinal axons projections after thoracic unilateral hemisection suggested an increased projection from the undamaged corticospinal tract to the denervated side of the spinal cord (Aoki et al., 1988, 1991; Goldstein et al., 1997). Indeed, a recent study in rats subjected to a cervical unilateral hemisection showed that corticospinal axons from the intact cortex (i.e., ipsilesional) sprouted to recross the midline, innervating the spinal segments below the injury in both cervical and lumbar segments. These midline-crossing axons from the cervical spinal segments revealed the formation of a new forelimb representation in the ipsilesional cortex.
In addition, lesion targeting the dorsal component of the corticospinal tract at cervical level in rats was shown to induce sprouting of ventral corticospinal axons that reconnected pools of cervical motoneurons (Weidner et al., 2001). These anatomical rearrangements were accompanied by the recovery of forelimb motor capacities. After a thoracic unilateral hemisection in rats, the reticulospinal axons coursing through the intact side of the cord and therefore spared by the lesion were found to sprout in lumbar segments and this intraspinal plasticity paralleled the locomotor recovery (Ballermann and Fouad, 2006).

Regeneration of damaged fibers

In the adult mammalian CNS, the damaged fibers have a very limited capacity to regenerate. After a spinal lesion at the thoracic level disrupting the corticospinal fibers in adult rats, the axons, disrupted from their cellular target, degenerated massively and failed to regenerate (Bregman et al., 1989). Such a report has also been made for the other descending motor tracts. Indeed, after a cervical hemisection or a thoracic transection in rats, the rubro- and reticulospinal fibers, respectively, were unable to regenerate within the damaged tissue as well as in the host tissue caudal to the spinal lesion (Houle and Jin, 2001; Menei et al., 1998). Nevertheless, recent studies have shown that the damaged motor axons have the capacity to regenerate spontaneously and form new circuits in response to spinal lesions. Transected axons from the hindlimb motor cortex have been found to sprout into the cervical gray matter after a dorsal thoracic hemisection where they made contact and formed new synapses to short and long propriospinal neurons. These propriospinal neurons were also shown to innervate the lumbar motor neurons, the original targets of the damaged corticospinal fibers, thus creating a new anatomo-functional intraspinal circuit (Bareyre et al., 2004). After a dorsal hemisection at thoracic level in rats, it was recently shown that axotomized corticospinal axons from the hindlimb sensorimotor cortex sprouted in the cervical spinal cord on fibers from the unaffected forelimb cortex such as the hindlimb cortex became responsive to forelimb inputs (Ghosh et al., 2010). Another study has demonstrated, by using similar lesion model in mice interrupting the dorsal and dorsolateral components of the corticospinal tracts, that some ventral axons expressed collaterals in the spinal segments rostral to the lesion. These collaterals bypassed the lesion via the ventral funiculus and formed terminal arborizations within the caudal spinal segments (Steward et al., 2008).

Changes in the spinal circuitry after SCI

Complete SCI and the role of spinal CPG

In many species, some recovery of hindlimb locomotion can be observed after a complete spinal cord section (Grillner, 1981; Rossignol, 1996). Since locomotion can be expressed in kittens spinalized before having "learned" to walk, it must be concluded that this behavior is genetically determined (Forssberg et al., 1980a,b; Grillner, 1973). In adults, hindlimb locomotion is subtended by a spinal circuitry (central pattern generator, CPG) that can operate even when isolated from descending command signals or afferent information (Grillner and Zanger, 1979) when stimulated by the noradrenergic precursor levor 3,4-dihydroxyphenylalanine (L-DOPA). In adult cats, noadrenergic agonists such as clonidine can evoke locomotion within minutes of a complete spinalization (Forssberg and Grillner, 1973) illustrating that the spinal CPG can immediately evoke hindlimb locomotion without the need for elaborate circuit reorganization when proper stimulation is provided (in this case, noradrenergic receptor stimulation) after SCI.

Without such neurotransmitter replacement, hindlimbs of cats with a complete SCI will be flaccid for several days or even weeks, in some cases, and only faint rhythmic movements are observed without foot placement and weight support. At this
stage, noradrenergic agonists can enhance markedly the walking pattern and increase step length and foot placement as well as hindquarter weight support. Locomotor training started early after a complete section using noradrenergic stimulation can accelerate the recovery of hindlimb stepping (Chau et al., 1998a,b). When cats have recovered spontaneous (no drug stimulation) hindlimb locomotion on a treadmill, various agonists and antagonists of neurotransmitters can exert modulatory effects on the kinetics and electromyographic (EMG) parameters (Rossignol et al., 1995). Of interest for any work attempting to revive the spinal cord through pharmacological means after SCI is the fact that the spinal receptors of various neurotransmitters synthesized in the brainstem (and therefore depleted after a complete section) are upregulated for several months after the lesion and then return to their baseline value after about 6 months (Giroux et al., 1999). It should also be mentioned that the effects of drugs (agonists and antagonists) differ importantly depending on the state of excitability of these receptors. For instance, clonidine or yohimbine will have significantly different effects when injected intrathecally in the normal, partially lesioned or completely lesioned cat (Giroux et al., 1998). Thus, if any BMI device is coupled to a pharmacological intervention, the latter should take these time-varying excitability changes after various types of spinal lesions. The changes in the excitability of receptors can be profound as recently demonstrated (Murray et al., 2010). Indeed serotonergic receptors can become constitutive after spinal lesions which will lead to a state of hyperexcitability of motoneurons that can facilitate locomotion but also may lead to unwanted symptoms such as spasticity.

**Spinal localization of the locomotor CPG**

Knowing how the spinal CPG is organized and where it is located should be of paramount importance in the design of BMI devices to restore locomotion. Besides pharmacological stimulation of spinal circuits as summarized above, electrical stimulation can be envisaged as a means of reactivating the spinal CPG either by intraspinal stimulation or by stimulation of sensory afferents. In the first case, the intraspinal stimulation seeks to activate motoneuron pools through an activation of the motoneurons themselves or through local microcircuits including local afferent inputs or local descending inputs (Guévremont et al., 2006; Saigal et al., 2004; Stein and Mushahwar, 2005). With electrical stimulation of sensory afferents (peripheral nerves or dorsal roots accessed by epidural stimulation), the aim is to activate the CPG through already existing connections with interneurons (Lavrov et al., 2008). Such epidural stimulation can evoke rather striking bipedal locomotion in the rat when coupled to serotonergic stimulation (Courtine et al., 2009). We have also used intraspinal electrical stimulation of the spinal cord in 1-week SCI decerebrate cats injected with clonidine. With a systematic exploration of the cord, we also found that dorsal areas were the most effective (1 mm lateral and 1 mm deep) in evoking locomotion and that this stimulation could be effective when applied to several segmental lumbosacral levels. However, we also found that the integrity of midlumbar segmental levels was necessary to induce locomotion with intraspinal or dorsal root stimulation (Barthélemy et al., 2006, 2007). This finding was consistent with earlier work showing that these midlumbar segments occupy a strategic role in spinal locomotion. Indeed, we had shown that pharmacological blockade by yohimbine of these segments abolished clonidine-evoked locomotion (Marcoux and Rossignol, 2000). Further, when the second complete spinalization was performed at L3–L4 in cats having recovered hindlimb locomotion after a first spinal section at T13, it was impossible to evoke locomotion although other rhythmic activities such as fast paw shake could be observed (Langlet et al., 2005). More recent work also showed that these midlumbar segments may be important even for decerebrate walking, suggesting that these premotoneuronal segments
play an important role in generating locomotion (Delivet-Mongrain et al., 2008).

Whether some segments contain neural circuits necessary for locomotion as stated above or whether certain segments are more excitable than others for the generation of locomotion (Kiehn, 2006), the design of implantable stimulating devices should take into account such regionalization to increase their effectiveness.

**Involvement of the spinal circuitry after incomplete SCI**

The above sections summarize various observations leading to the conclusion that there is a spinal CPG responsible for spinal locomotion and that this circuitry can be modulated by various pharmacological agents, sensory afferents, and intrinsic premotoneuronal inputs. It is reasonable to ask whether these mechanisms also apply to hindlimb locomotion generated after partial SCI.

One important finding in this respect is that hindlimb locomotion can be expressed quite readily after various types of partial SCI involving either bilateral dorsal/dorsolateral tracts (Jiang and Drew, 1996) or bilateral ventral/ventrolateral tracts (Brustein and Rossignol, 1998, 1999). The fact that none of the tracts appear essential for triggering hindlimb locomotion suggests that indeed the spinal circuitry plays an important role after such partial lesions.

In order to investigate more directly the involvement of the spinal cord in expressing locomotion after partial SCI, we devised a dual spinal lesion paradigm in which the spinal cord is first lesioned on one side (~lateral hemisection) at T10–T11 and then, some weeks later, a complete section at T13 (i.e., the same level as for previous spinal cats) is performed. The hypothesis underlying that paradigm was that if the spinal cord is changed to express locomotion after the hemisection, some of these changes should be detectable in the spinal cord after the subsequent complete spinalization. Indeed, we have shown that after the complete section, cats can walk within 24 h (first recording session; Barrière et al., 2008, 2010; Martinez et al., 2011; Rossignol et al., 2009) whereas it normally takes a few weeks to achieve such a locomotor performance after a complete SCI (Barbeau and Rossignol, 1987; Belanger et al., 1996; de Leon et al., 1998). The kinematic and EMG parameters of walking after the hemisection indicate that robust compensatory changes occur in the hindlimbs on both sides. In brief, after hemisection, several asymmetries between hindlimbs take place. For example, the stance phase of the hindlimb on the hemizedioned side is shortened, while the swing phase is lengthened and reciprocal changes are observed on the other side. Three weeks after hemisection, cats were able to express an active locomotor pattern and the hindlimb on the lesioned side exhibited a gradual recovery approaching the locomotor performance recorded in the intact state (Fig. 3a and b). However, the locomotor asymmetries induced by the hemisection were not spontaneously (i.e., with no specific rehabilitative strategy) compensated even 3 weeks after hemisection. At this time point, a complete spinalization was performed in T13. Of great interest is that as early as 24 h after the complete spinal section, more than 50% of the cats reexpressed a bilateral locomotor pattern such as the locomotor asymmetries documented in the hemispinal state disappeared or even reversed although with overall shortened cycle as usually the case in spinal cats (Fig. 3c). Some changes were also seen in reflex responses after hemisection and some of these alterations persist for a few days after spinalization before becoming symmetrical again after spinalization (Frigon et al., 2009).

The experiments using the dual spinal lesion paradigm thus indicate that the spinal CPG itself is altered during the hemispinal period as shown by the profound changes seen after spinalization. This strongly suggests that after partial SCI, not only are there changes in remnant supraspinal structures and in the connectivity of descending
pathways but also within the spinal cord itself. BMI approaches to foster recovery of functions after various types of SCI (whether electrical or pharmacological) should take into account these changes at the various levels of the CNS. Thus, BMI devices may target some levels of the spinal cord and be adjustable so that excitability changes in spinal circuits are taken into account.

A question often raised is whether such notions apply to humans, especially when such a strong role is considered for a spinal cord CPG. As discussed in a recent paper (Nadeau et al., 2010), there are a number of indications that the isolated spinal cord of humans also contain rhythmonic capabilities. Work by Dimitrijevic (Dimitrijevic et al., 1998) and work by Harkema and others (Harkema, 2008) rely on the existence of such spinal circuits to express locomotor rhythms that can be activated by BMI such as epidural stimulation. It can thus be concluded that BMI approaches to restore locomotor function are very promising especially when they take into consideration the built-in synergies at different levels of the CNS and the intrinsic changes that occur after SCI.

References


