And yet it moves: Recovery of volitional control after spinal cord injury

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(Article begins on next page)

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References: 292

Table of Contents

9. Synergism of neuromodulation and proprioception.

10. Conclusion.

Abstract

Preclinical and clinical neurophysiological and neurorehabilitation research has generated rather surprising levels of recovery of volitional sensory-motor function in persons with chronic motor paralysis following a spinal cord injury. The key factor in this recovery is largely activity-dependent plasticity of spinal and supraspinal networks. This key factor can be triggered by neuromodulation of these networks with electrical and pharmacological interventions. This review addresses some of the systems-level physiological mechanisms that might explain the effects of electrical modulation and how repetitive training facilitates the recovery of volitional motor control. In particular, we substantiate the hypotheses that: 1) in the majority of spinal lesions, a critical number and type of neurons in the region of the injury survive, but cannot conduct action potentials, and thus are electrically non-responsive; 2) these neuronal networks within the lesioned area can be neuromodulated to a transformed state of electrical competency; 3) these two factors enable the potential for extensive activity-dependent reorganization of neuronal networks in the spinal cord and brain, and 4) propriospinal networks play a critical role in driving this activity-dependent reorganization after injury. Real-time proprioceptive input to spinal networks provides the template for reorganization of spinal networks that play a leading role in the level of coordination of motor pools required to perform a given functional task. Repetitive exposure of multi-segmental sensory-motor networks to the dynamics of task-specific sensory input as occurs with repetitive training can functionally reshape spinal and supraspinal connectivity thus re-enabling one to perform complex motor tasks, even years post injury.

1. Introduction.

A number of observations demonstrate the presence of potentially functioning fibers travelling across the lesion in the majority (84%) of people with clinically diagnosed complete spinal cord injury (SCI) (Sherwood et al., 1992; Dimitrijevic et al., 1984, 1983). In addition, there have been several reports of postmortem anatomical evidence of a significant number of axons traversing the lesion of individuals that have been completely paralyzed for years prior to death (Kakulas, 1988). The significance of these observations has become more apparent given the rapid recovery of voluntary control of muscles below lesion in individuals that have been paralyzed for more than a year before receiving locomotor/standing training and epidural electrical stimulation (a neurorehabilitative protocol overall named electrical Enabling motor control; eEmc). It seems imperative, based on these observations, that our current knowledge on the mechanisms underlying the recovery of voluntary movement after chronic, complete paralysis must be re-examined.

2. Prognosis of recovery from a SCI in the "chronic state".

All persons with a spinal cord injury experience some extent of recovery from the first clinical assessment. This normally occurs in the first three months after the lesion, but recoveries can be observed for up to one year, and occasionally after even longer periods (Waters et al., 1992; Kirshblum et al., 2004; Fawcett et al., 2007). These recoveries are broadly termed "spontaneous", although part of them is probably due to current early surgical procedures, standard pharmacological treatments and traditional physical therapies.

Extension of recovery and consequent functional improvements were inversely related to the severity of injury (complete vs. incomplete; Marino et al., 1999). Indeed, the extent of spontaneous recovery was significantly greater for incomplete lesions, while only about 10% of persons with a clinically-defined compete injury within the first 15 days post injury progressed to C or greater within 12 months post injury (Spiess et al., 2009). Among these, as a percentage, persons with

tetraplegia demonstrated almost twice as many recoveries than those with paraplegia (Kirshblum et al., 2004; Fisher et al., 2005). Moreover, these improvements often refer only to the segments located immediately below the lesion, and can very rarely bring to real functional benefits, such as independent standing and stepping (Fawcett et al., 2007).

Paraplegic subjects with a complete spinal lesion have a scarce probability of motor recovery after six months from injury, therefore an extremely low sample size will have sufficient power to examine the effects of a new experimental intervention as a valuable tool for recovery (six to eight participants according to the Guidelines for the conduct of clinical trials on spinal cord injury, as developed by the International Campaign for Cures of Spinal Cord Injury Paralysis - ICCP panel; Fawcett et al., 2007).

Moreover, when considering even longer periods elapsing from the time of injury, and thus stable clinical conditions and less hospitalization, the recoveries can be more properly defined "spontaneous" and their appearance is even rarer. Indeed, after one year less than 2% of complete spinal cord injuries were reported to have become incomplete by the fifth year after the lesion (Kirshblum et al., 2004). Consequently, the number of participants with a chronic and complete lesion necessary to show a statistically significant motor gain due to some experimental therapy becomes even smaller (Fawcett et al., 2007).

3. Greater-than-expected recovery in the chronic state in response to spinal neuromodulation.

A first case report (Harkema et al., 2011) relates to an individual with a motor complete SCI at the level of the first thoracic segments for more than a year, who was implanted with an electrode array in the epidural space at the level of the lumbar spinal segments (L2 - S1). After a few months of stand training, the subject could maintain continuous minimally assisted full weight-bearing standing for up to four minutes. Furthermore, this person revealed significant levels of voluntary

control of the lower limbs after almost seven months of daily stimulation and stand/step training. It was speculated that this long posttreatment period left open the possibility for a potential regrowth of functional supraspinal-sublesional spinal connections attributable to axonal growth through the lesion. When this neurorehabilitative protocol eEmc was repeated in three other chronically motor complete spinally injured subjects, the recovery of voluntary movement appeared within a few weeks of stimulation and training (Angeli et al., 2014). Unlike the standing and stepping recovery, which can be explained from the perspective of the intrinsic spinal automaticity, the recovery of voluntary control requires a critical level of functional supraspinal-sublesional spinal reconnections. This hypothesis is further supported by the fact that participants in these studies have continued to improve years after implantation. Similar results as for regaining of voluntary control during rhythmic locomotor movements have also been reported in five individuals with SCI, treated with transcutaneous electrical stimulation (Gerasimenko et al., 2015). More recently, an additional person with chronic paraplegia regained volitional control of task-specific muscle activity after few sessions of epidural electrical stimulation (Grahn et al., 2017).

Overall, all ten subjects tested with a motor paralysis, who were treated with spinal electrical stimulation (average time since injury of 3.1 ± 1.2 years), regained voluntary movement of lower limbs (**Table 1**). These results are far beyond the spontaneous recovery reported after chronic SCI, pointing out that this strategy, based on the data reported so far, ranks among the most promising ones for the recovery of locomotion in spinal cord injured persons. As new developing interventions such as brain machine interfaces, stem cell implantation and robotics emerge, it seems likely that other combinations of these approaches can be combined to accommodate a wide range of needs following a wide array of dysfunctions.

4. The conceptual cores of automaticity of movement.

4.1. **Central pattern generation**. Decades of experimental work on animal preparations have resulted in a greatly improved level of understanding of the functional organization of a locomotor spinal network called Central Pattern Generator (CPG; Grillner and Zangger, 1975; Grillner and Rossignol, 1978; Lovely et al., 1986; Butt and Kiehn, 2003). A CPG is an ensemble of neurons that can generate a rhythmic motor output in the absence of any rhythmic external stimuli. This output is characterized by a highly coordinated activation pattern of motoneuronal pools. But the most impressive feature of the output of what are presumed to be CPG networks is their ability to process complex combinations of proprioceptive and tactile input in real time in *in vivo* conditions. Some observations suggest that the CPG develops, at least to some degree, with a deterministic strategy in what seems to be a well-defined number of genetically-targeted interneurons, starting from the embryonic stage that establishes distinct connections within the network (Pierani et al., 2001; Kullander et al., 2003; Lanuza et al., 2004; Gosgnach et al., 2006; Kwan et al., 2009; Wilson et al., 2010; Zhong et al., 2011). This complex and specific connectivity among the different elements of the network has been only partly elucidated. Nevertheless, even if the rhythmogenic source of the pattern is isolated in vitro, and thus deprived of its descending and afferent inputs, the rhythmic pattern can still be triggered by a wide range of electrical stimuli (Atsuta et al., 1990; Magnuson and Trinder, 1997; Marchetti et al., 2001a; Strauss and Lev-Tov, 2003; Taccola, 2011; Dose et al., 2013; Dose and Taccola, 2016a, b) and pharmacological agents (Cazalets et al., 1992; Houssaini et al., 1993; Kiehn and Kjaerulff, 1996; Marchetti and Nistri, 2001b; Taccola and Nistri, 2006) and even by an increase in extracellular K+, which can lead to a broad rise in the overall neuronal network excitability (Bracci et al., 1998). Thus, while a more exact composition and organization of the CPG evolves, it is anticipated that more precise strategies in formulating interventions will facilitate our ability to exploit the automaticity of neural networks and their plasticity.

4.2. **Brainstem Stimulation.** The origin of another source of automaticity has been demonstrated by a series of experiments indicating that tonic stimulation at selected sites within the mesencephalon can induce highly coordinated quadrupedal stepping in place on a stationary treadmill belt with full weight-bearing. In addition, it can facilitate stepping that can accommodate a range of speeds on a moving belt in an acutely decerebrated cat (Orlovskiĭ et al., 1966; Mori et al., 1977). Later, Mori and colleagues chronically implanted stimulating electrodes in a neurologically intact awake cat, but in slightly different sites of the mesencephalon than previously stimulated. Following this stimulation, the cat would stand up and begin walking, and then, when stimulating a few millimeters away, the animal would stop stepping and sit quietly (Mori et al., 1978; 1989). Furthermore, these results also demonstrate that the activation patterns of motor pools and body muscles that control standing and stepping can be triggered by a very simple tonic stimulus applied to some unspecific group of neurons. Thus, a high level of automaticity is built within the locomotor circuitry. Combination of these observations on the highly coordinated postural and locomotor performance that can be generated and controlled by the spinal circuitry along with the proprioceptive and cutaneous input demonstrates that a major neural component of automaticity lies within the spinal circuitry that processes complex sensory input and executes motor output controls in real time.

4.3. **Sensory Control.** A third origin of automaticity relies in the various forms of sensory information that is constantly available, though dynamically changing particularly from vision, hearing, proprioception and cutaneous input, to the spinal cord and brain. The importance of sensory information for this control has been demonstrated in rats that have been paralyzed from the mid thoracic region. After a few weeks of recovery from injury, the animals could step forward and backward and gradually change angles of stepping on a treadmill belt (Shah et al., 2012), as well as varying degrees of loading and speeds of stepping (Edgerton et al., 1991). Further, SCI rats were also capable of modulating the firing patterns of flexor and extensor muscles to

accommodate the changing speed and weight bearing while stepping on a treadmill (Gad et al., 2013a). Similar observations were made in human subjects stepping on a treadmill with body weight support and variable load and speed (Harkema et al., 1997).

These results demonstrate that mainly the combination of proprioception and cutaneous inputs derived from the limbs can serve as the sole source of control for all motor pools and muscles needed to perform very complex movements.

4.4. **Propriospinal System as an Interface between the Brain and the Spinal Cord.** The spinal cord contains interconnecting propriospinal neurons and related axons, which are known overall as the propriospinal system (PSS; Jankowska et al., 1974). The PSS extends along the whole spinal cord, connecting ventral and dorsal horns, as well as cervical and lumbar enlargements, and provides bilateral projections to the left and right sides of the cord (Reed et al., 2009, Brockett et al., 2013).

Propriospinal neurons are numerically predominant in the spinal cord (Chung et al., 1984) and have an extremely heterogeneous morphology (Saywell et al., 2011). Moreover, during development, they are exposed to such a variety of extracellular guidance cues (Jacobi et al., 2014) that minimize specific connectivity, thus providing a stochastic feature to the whole process of network formation. Indeed, on par with realistic neuronal circuitry simulation based solely on the proximity among cells (van Ooyen et al., 2014), during spinal cord development, a plethora of interneurons establish a great number of synaptic connections by simply following the anatomical overlapping of their axons and dendrites (Li et al., 2007). The PSS can function as an interface between cortical, subcortical and spinal neuronal networks. Indeed, propriospinal neurons can interconnect multiple spinal segments along the length of the spinal cord via their axons and dendrites (Skinner et al., 1979; Menétrey et al., 1985; Courtine et al., 2008; van den Brand et al., 2012). Among these, the majority of unmyelinated propriospinal axons are located in the

dorsolateral funiculus, while in the dorsal funiculi are found a large number of descending myelinated propriospinal fibers (Chung et al., 1987; Chung and Coggeshall, 1988).

At lumbar level, this highly-recurrent diffuse network functionally interfaces with CPG neurons (Cowley and Schmidt, 1997; Cazalets 2005). Here, PSS functioning can be assimilated to cortical neuronal networks with a balanced ratio of excitation/inhibition (Shew et al., 2011). Indeed, just like in cortical networks, spontaneous activity of propriospinal networks might rhythmically emerge as irregular, isolated population bursts that synaptically spread through the whole network, without the need for a specific wiring (Streit et al., 2001). This activity might synchronize anatomically dispersed neuronal ensembles (Penn et al., 2016) and can be described as a neuronal avalanche, namely a sequence of events initiated by exciting a network node which, in turn, triggers a subsequent cascade of excitation of nearby nodes (Larremore et al., 2012). Furthermore, feedforward inputs to the PSS can amplify small fluctuations into large population avalanches (Murphy and Miller, 2009; Benayoun et al., 2010), as demonstrated by modeling studies, where excitation and inhibition in a network of thousands of neurons has been closely balanced, generating an irregular synchronous bursting activity (Friedman and Landsberg, 2013).

Experimentally, the activity of the PSS can be recorded in the dorsal spinal cord in the form of traveling electrical waves (Bayev and Kostyuk, 1981; Noga et al., 1995; Cuellar et al., 2009; Saltiel et al., 2016). These waves can also be recorded at rest (Cuellar et al., 2009), suggesting that the propriospinal network continuously produces a stable background pattern, reverberating the excitation along the whole spinal cord (Eblen-Zajjur and Sandkühler, 1997). Also in vivo multiple recordings from spinal interneurons demonstrated that some units are tonically active even at rest, but become modulated only during locomotion (Berg et al., 2007). Thus, the background activity of propriospinal networks represents a continuous source of subthreshold facilitatory input acting on spinal CPGs (Li and Moult, 2012; Warp et al., 2012). Indeed, spontaneous tonic discharges have been recently recorded (Husch et al., 2015) from a class of excitatory spinal interneurons that couple locomotor circuits on both sides of the spinal cord (Crone et al., 2008).

Background excitatory synaptic potentials might keep CPG excitability near the triggering threshold and thus make the CPG more responsive to voluntary inputs for locomotor control, but also to afferent phasic inputs, especially of proprioceptive nature.

From a functional point of view, the PSS provides a mechanism for intersegmental coupling and coordination of motor pools within and among multiple spinal segments that control the lower limbs, and even trunk musculature during quadrupedal locomotion (Skinner et al., 1979; Rovainen, 1985; Krutki and Mrówczyński, 2004; Juvin et al., 2005; Courtine et al., 2008; Shah et al., 2013; Beliez et al., 2015). For example, human PSS contributes to the rhythmic coordination of the upper and lower limbs during locomotion (Dietz et al., 2001) and mediates some inter-limb neurological responses, such as modulation of the H-reflex amplitude during phasic voluntary contractions of arm muscles (Mazevet and Pierrot-Deseilligny, 1994).

PSS is also involved in the physiological control of the locomotor activity. Indeed, in addition to the direct cortico-motoneuronal control, an indirect descending pathway establishes synaptic relays within the PSS (Kostyuk and Vasilenko, 1978; Pierrot-Deseilligny and Marchand-Pauvert, 2002; Cowley et al., 2010). Then, once a volitional movement is selected, the synaptic relays within the PSS can amplify and prolong the descending command throughout the lumbosacral segments of the spinal cord (Kostyuk and, Vasilenko, 1978; Noga et al., 1995; Roche et al 2012).

Since the PSS presents a significant level of redundancy and plasticity, it has been linked to some functional recoveries after severe experimental lesions of the spinal cord (de Leon 1998a, b; Courtine et al., 2008; Shah et al., 2013; Filli et al., 2014), as well as to an aberrant intersegmental connectivity along the level of injury. For instance, the PSS might play a role in upper limb reflexes after stimulating nerves on their lower extremity, in subjects with chronic cervical lesions (Calancie, 1991; Calancie et al., 2002). In addition, the PSS generates the propriospinal

myoclonus, namely thoraco-abdominal spontaneous muscle jerks that propagate rostrally to upper intercostal muscles and to abdominal muscles (Chokroverty et al., 1992).

Moreover, after a spinal lesion, descending cortico-spinal pathways are more or less compromised and unable to activate motor patterns with the sufficient supraspinally-derived voluntary stimuli. At the same time, a compromised cortico-spinal connection perturbs the descending drive towards the PSS. The resulting muscular aryflexia and hypotonia characterizing the spinal shock phase following an acute injury, might also originate from the sudden lack of descending input, which would physiologically modulate the PSS. In turn, to account for the loss of descending inputs, the PSS undergoes a series of plastic rearrangements that can further alter its excitability (reviewed by Flynn et al., 2011).

At the same time, the PSS might also be affected by some phenomena of dendrite regression, secondary to the stress of injury (Magariños and McEwen, 1995; Chen et al., 2008), while the expression of several genes with putative roles in synaptic plasticity are downregulated following SCI (Siebert et al., 2010), at the expenses of synaptic efficacy.

For all these reasons, a spinal lesion may reduce PSS basal rhythmicity and, in turn, the possibility for sprouted descending connections to re-establish the local propriospinal circuitry (Bareyre et al., 2004). A lower level of PSS activity may contribute to a lower level of CPG excitability, which would reduce the probability of residual inputs to facilitate locomotor patterns.

Nevertheless, PSS anatomically and functionally survives even after a complete transection of the spinal cord (Faganel and Dimitrijevic, 1982; Conta and Stelzner, 2004) and can thus support functional recovery following a severe lesion, when propriospinal neuron excitability is modulated towards physiological values (Courtine et al., 2008; Cowley et al., 2015).

4.5. **Propriospinal "stepping strip" that can facilitate stepping.** Shik and colleagues in a series of experiments on mesencephalic cats described a "stepping strip" extending through the dorsal lateral funiculus (DLF) from the cervical to lumbar level (Kazennikov et al., 1983a). It has

been suggested that the "stepping strip" is a continuation of pontomedullary locomotor strip (Kazennikov et al., 1983b). Stimulation of the "stepping strip" at 60 Hz can evoke stepping movements initially in the ipsilateral limb, and with increased intensity of stimulation, in the contralateral hindlimb and forelimbs as well. Using local lesions of DLF at different levels of the spinal cord, they found that stimulation of the DLF can elicit stepping only when at least 8 to 12 segments were intact (Kazennikov et al., 1983b). Based on these findings, it was suggested that propriospinal neurons must be activated to facilitate stepping during stimulation of the "stepping strip" (Kazennikov et al., 1990). Interestingly, stepping could be induced during DLF stimulation at thoracic level even after damage of DLF at cervical and upper lumbar levels, suggesting an indirect mechanism of activation of the locomotor circuitry (Kazennikov and Shik 1988). Indeed, it was found that the neurons responding to DLF stimulation were localized at a border between lateral and ventral funiculus (Kazennikov et al., 1985).

Shik (1997) hypothesized that stimulation of the "stepping strip" distinctively excites the spinal neurons that project to the locomotor network, by sending their axons to the VLF, and for this reason are termed V neuron (**Figure 1**). Critical for such a hypothesis could be experiments with verification of V neurons and with demonstration of their direct influence on locomotor network.

5. Strategies and Mechanisms for Electrically Neuromodulating Spinal Motor Function.

At present, individuals with a complete paralysis due to a severe SCI are considered to have virtually no potential of functional recovery after several months post-injury. However, this dogma is challenged by animal and human experiments demonstrating the recovery of sensory-motor and autonomic functions with electrical spinal cord stimulation (SCS; Gad et al., 2013b; Gerasimenko et al., 2015; Gad et al., 2015). These same observations prioritize the need to understand the mechanisms of the neuromodulatory strategies that are so far largely based on

modeling, eventually corroborated by experimental studies (Struijk et al., 1993; Capogrosso et al., 2013). In turn, these theoretical studies were mainly conceived from the assumption that neural networks respond to electrical stimulation solely by inducing action potentials, and that the biophysical properties of the axons follow Ohms law, i.e., the larger axons have the lowest excitatory thresholds. Nevertheless, recent experimental results challenge these assumptions, indicating that control of neural networks in the injured system may be equally relevant in the uninjured system (Gerasimenko et al., 2006; Bergquist et al., 2011; Sayenko et al., 2015).

Given that the term neuromodulation is used to refer to a wide range of neural phenomena, in the present manuscript we use this term to indicate a change in the functional state of excitability of a neuron or combination of neurons within neuronal networks.

There also seems to be largely similar mechanisms in the different methods of neuromodulation of spinal networks. For example, transcranial magnetic stimulation is a tool used to noninvasively stimulate the human brain and spinal cord (Barker et al., 1985; Hallet 2000, 2007; Gerasimenko 2010). Transcutaneous electrical spinal cord stimulation (tSCS) is another non-invasive technique for engaging locomotor-related circuitries in human. This method utilizes unique painless stimulation waveforms, which are transmitted via electrodes placed on the skin over the spine and presumably travel through DRs to activate the spinal circuitry **(Figure 2)**. Observations from these experiments are consistent with the concept of specific modulation of the networks projecting to distinct combinations of interneurons coordinating the motor pools' recruitment during a step cycle. A third neuromodulatory intervention which shows considerable potential in recovering function after paralysis is pharmacological (Pearson and Rossignol 1991; Rossignol et al., 2001; Musienko et al., 2011). Although there are undoubtedly unique features of each of these techniques, the main difference appears to be which neurons, axons and networks are more readily modulated. The focus of the present review is on the basic biophysical properties of membranes, axons, dendrites, cells and neuronal networks that underlie neuromodulatory

interventions. We propose that the main topics of neuromodulation of the spinal cord are the identification of the mechanisms that drive responses.

In the following sections, we have examined some of the elements that are important in understanding the mechanisms of electrical neuromodulation of spinal neuronal networks and their interaction with supraspinal and peripheral sensory inputs. One crucial question to address is: What sub-cellular, cellular, networks components of the neural networks respond to the numerous combinations of neuromodulatory parameters used?

5.1. **Dorsal Roots (DRs)**. Electrical SCS, with either transcutaneous, epidural or intraspinal electrodes, facilitates functional standing and walking in individuals with a chronic SCI. In many cases, this effect has been almost exclusively ascribed to the direct modulation of posterior roots (Struijk et al., 1993; Murg et al., 2000; Rattay et al., 2000; Danner et al., 2011; Capogrosso et al., 2013; Minassian et al., 2016).

DR activation during epidural electrical stimulation has been effectively proven by antidromic potentials recorded from peripheral nerves (Su et al., 1992). On par, also the antidromically driven cutaneous vasodilation provides an indirect proof of DR involvement (Linderoth et al., 1989), although in this latter case, also the activation of sympathetic efferents plays an active role (Croom et al., 1997).

Afferent inputs, as the ones generated by posterior root stimulation, reach the locomotor networks (Hultborn et al., 1998; Rybak et al., 2006; Bui and Brownstone, 2015), as clearly demonstrated by epochs of locomotor patterns elicited in vitro by the selective electrical stimulation of single or multiple DRs, using tight suction electrodes (Marchetti et al., 2001a; Strauss and Lev-Tov, 2003; Taccola, 2011; Dose et al., 2016a, b).

Nevertheless, electrical SCS does not only activate DRs. Indeed, the epidural stimulation technology currently used to facilitate locomotion and standing after lesion comes partly from the field of neuropathic pain management, which however aims at minimizing DR stimulation (Molnar

and Barolat, 2014). This is fundamentally antithetical to the purpose of finding the best simulation pattern to generate posture and locomotion (Sayenko et al., 2014, Rejc et al., 2015).

Further evidence that electrical SCS recruits other structures apart from DRs comes from previous reports, where epidural SCS at low amplitude applied to higher thoracic vertebrae antidromically activated ascending fibers in the dorsal columns, with the appearance of DR potentials from the underlying DRs. On the other hand, at higher intensities, also the descending motor tracts were activated, generating responses, from the lumbar ventral roots and from hindlimb muscles, which did not change after dorsal lumbar rhizotomy (Haghighi et al., 1994).

A clear indication of the involvement of other targets of SCS in the spinal cord comes from the measurement of intraspinal current density during epidural stimulation in isolated human cadaver cords, demonstrating that, despite a rapid current decrease away from electrode location, a substantial amount of applied current inevitably passes through the entire spinal cord (Swiontek et al., 1976). Although this study cannot explain what neural structures are excited, this observation provides insights on the shape and distribution of the electrical field generated by electrical SCS of the spinal cord, showing that many neural structures are directly impacted by the electrical field: axons, synapses, neuronal cell bodies, glial cells and cerebrospinal fluid.

Among these, electrical SCS mainly recruits type-A myelinated fibers and axons. (Ranck, 1975; Holsheimer, 2002). Nevertheless, when axons are oriented in the same direction as the field, they become polarized and their synaptic extremities, once depolarized, can modulate the integration of incoming synaptic inputs (Jankowska, 2017). For example, polarizing currents, passing across the cat spinal cord in a dorsal-ventral direction, increased synaptic excitatory potentials elicited in motoneurons by afferent stimulation (Eccles et al., 1962). According to this selectivity provided by fibers' orientation within spinal networks, both excitatory and inhibitory synapses can be equally depolarized. Nevertheless, the physiological contribution of excitatory inputs prevails at the level of the rhythmogenic core of the CPG (Grillner, 2006) and, thus, the net effect would be an increased excitability of the whole network, with the consequence that even weak stimuli (e.g.

afferent), can activate locomotor patterns, especially cutaneous and proprioceptive input, as well as ascending (Etlin et al., 2010; Gad et al., 2013a) and descending input.

5.2. **Longitudinal spinal fibers of the posterior column.** Stimulation of the residual, longitudinal axons of the spinal cord below injury might facilitate spinal locomotor networks. Nevertheless, activation of longitudinal pathways, ascending and descending, is quite controversial. Indeed, some theoretical studies indicate that the threshold for activating DRs through electrical SCS is lower than the one required to activate longitudinal pathways (Danner et al., 2011). However, electrical SCS does seem to mainly recruit longitudinal pathways running along the posterior column fibers, according to additional computational studies that consider fibers' curved trajectory, inhomogeneity and anisotropy of the conductive media they traverse, and their orientation relative to the placement of the stimulation leads (Coburn, 1985; Struijk et al., 1993). Moreover, the neuromodulatory effect of electrical SCS in alleviating neuropathic pain, without inducing any uncomfortable motor reflexes, has been mainly ascribed to the selective activation of longitudinal dorsal spinal pathways, with a minimal recruitment of DRs (Molnar and Barolat, 2014).

Similarly, stimulation of residual, longitudinal fibers below injury is considered as the main mechanism for electrical SCS to modulate spasticity (Gybels and van Roost, 1985; Waltz, 1998; Minassian et al., 2012), which also corresponds to an improved locomotor performance in persons with a partial injury (Hofstoetter et al., 2014).

It is still possible to activate descending fibers, by modifying the stimulation settings applied to the spinal cord. For example, this could be done by modifying the electrode geometry utilizing a tripole with a central cathode or by longitudinally aligning the electrical field with the spinal cord, that is, by reducing the distance between the anode and cathode (Holsheimer and Wesselink, 1997). Due to this partial selectivity, it seems likely that electrical SCS protocols used for motor recovery after SCI would inevitably recruit other residual descending fibers. Among these, electrical SCS

should activate the descending fibers, with a motor significance, running along the postero-lateral tract, such as the lateral corticospinal tract and the rubrospinal tract. In post mortem samples collected from SCI survivors, the preserved continuity of a portion of lateral and posterior white matter was widely reported (Kakulas, 1984), even in lesions diagnosed as 'clinically' complete (Kakulas, 1988).

5.3. **Propriospinal network.** Activation of propriospinal neurons, elicited by both descending commands of voluntary movement attempts and electrical stimulation of the more rostral spinal segments, can be propagated caudal to a spinal lesion and activate the locomotor networks below the lesion (Yakovenko et al., 2007). In fact, in addition to the direct activation of the descending propriospinal tract projecting to postural and locomotor networks, SCS facilitates locomotion also through a nonspecific increase in the overall excitability of a wide range of spinal networks, which allow other inputs to actually initiate and control the movement, thus bringing to the enabling "concept", namely enabling spinal circuitries to process proprioceptive and descending supra-spinal input. These other inputs are generated by the remaining, or alternatively reorganizing, supraspinal descending input, as well as by the extensive proprioceptive and cutaneous input triggered by movements. Indeed, relatively prolonged periods of SCS at low intensity proved to enable the spinal components that had been electrically non-responsive for over a year. Nevertheless, it is not determined whether the restoration of functional supraspinal-spinal connectivity can be strictly attributed to propriospinal networks. Still, it is clear that the activation patterns necessary to perform a wide range of highly coordinated motor tasks can be restored by an increase in the net excitability levels of one or more types of spinal networks (Shah et al., 2012; 2013; Gad et al., 2013b; Gerasimenko et al., 2015). This net increase in excitability of the postural and locomotor networks augments the probability of complementary supraspinal and peripherally derived sensory inputs to exceed the threshold for the motor pools to generate movement, whether it is intentional (supraspinally) or more "automatically" derived from proprioceptive and

cutaneous inputs. This modulatory strategy enables the locomotor networks to generate highly coordinated and complex movements because spinal networks can accurately process constantly changing volleys of afferent inputs and generate the motor pattern "intended" by that sensory ensemble.

From this point of view, the highly diffused divergence of sensory fibers to large populations of spinal neurons on multiple spinal segments, provides a comprehensive mechanism for monitoring the kinetics and kinematics of micro and macro mechanical events, which enables highly systemic levels of control (Gerasimenko et al., 2015). For instance, when we stand, virtually all sensorimotor systems are activated and highly coordinated. As a consequence, a dynamic and minimally assisted standing posture of a subject with compromised sensory feedback and motor control of the trunk and lower limbs may be a more dynamic and task-specific experience (Sayenko et al. 2010, 2012) than even locomotor training. Indeed, a sudden postural perturbation triggers multiple attempts to recover balance, which can result in an extensive source of compelling descending inputs and in a higher modulation frequency compared to inputs evoked by stereotyped stepping on a treadmill, with passive weight bearing.

5.4. **Electrical stimulation modulates the chemical environment of the spinal cord.** Neurotransmitter and neuromodulator release from neurons (Raiteri, 2006) and glia (Tawfik et al., 2010) is induced by electrical stimulation. Indeed, some examples of electrical SCS (30-90 min) modifying the concentrations of neurotransmitters and neuromodulators in the spinal cord, are glycine (Simpson et al., 1991), GABA (Linderoth et al., 1994), serotonin (Linderoth et al., 1992; Franck et al., 1993; Song et al., 2009) and catecholamine levels (Levin and, Hubschmann, 1980; Liu et al., 2008).

On the other hand, the application of several exogenous pharmacological agents was able to activate locomotor patterns and can provide a rather variegated neural modulatory effect on spinal segments, to largely control standing and stepping (Douglas et al., 1993; de Leon et al., 1999;

Rossignol et al., 2001; reviewed by Alford et al., 2003; Gerasimenko et al., 2007; Ichiyama et al., 2008; Fouad et al., 2010; Musienko et al., 2011; Wei et al., 2014). As mentioned above, the locomotor patterns can be activated by many and different substances, and this scenario is further complicated by experiments showing that a specific pharmacological blockage of distinct receptor subtypes was able to halt the hindlimb stepping induced by epidural stimulation, although the same specific pharmacological block was readily bypassed simply by the passive movement of forelimbs in a step like motion (Gerasimenko et al., 2009). This is a clear demonstration that the same motor task can be generated by different and independent receptor systems. Nevertheless, in higher primates, including man, it has been harder to evoke similar patterns with the sole application of neurochemicals (Fedirchuk et al., 1998). Pharmacological facilitation of locomotion in individuals with an incomplete spinal injury was obtained through pharmacological cocktails, such as clonidine + cyproheptadine. Consequent improvements in walking abilities were assessed both as an increased maximal belt speed at which individuals manage treadmill stepping associated with more phasic kinematic and EMG patterns, as well as a reduced spasticity and an ability for some of them to functionally ambulate overground (Fung et al., 1990; Norman et al., 1998). Moreover, the combination of serotoninergic and dopaminergic agents (buspirone + levodopa + cardidopa) is currently under clinical investigation (NCT01484184, clinicaltrials.gov). In addition, the cocktails with the most clinical interest for facilitating locomotion often include pharmacological agents, such as clonidine and cyproheptadine, relatively non-selective for a single receptor subtype (Alexander et al., 2015). This might possibly indicate that either the receptor targets have not been completely identified or that a wider range of receptors needs to be activated in the spinal cord.

Nevertheless, the systemic administration of neurochemicals seems to be less effective than electrical SCS. This might be the case for several reasons. First of all, electrical SCS is not single-agent selective, but simultaneously facilitates the release of a great variety of neurotransmitters and neuromodulators because of the different synapses encountered by the electrical field in the

spinal cord. Secondly, electrical SCS induces a distinct increase of transmitters specifically at the level of the synaptic milieu of multiple network sites. Thirdly, as opposed to the stable extracellular concentrations obtained with the addition of exogenous agents, release induced by phasic electrical SCS can be patterned (Hentall et al., 2006) and may be able to exploit mechanisms of synaptic potentiation, also limiting fatigue or receptor desensitization.

Through this orchestrated tuning of multiple neurotransmitters and neuromodulators, each one with its specific release site, electrical SCS might mimic more accurately the physiological changes in the chemical environment of the spinal cord during locomotion than the exogenous application of a relatively simple cocktail of pharmaceutical agents.

However, a large number of animal studies suggest the need for a thorough examination of the potential of different combinations of inhibitory and excitatory receptor systems, to provide even more evidence on the efficacy of combining a pharmacological approach with the neural modulatory strategies that use electrical stimulation. This path seems to be only at the beginning, although in vitro studies suggest that pharmacological neuromodulation of spinal locomotor circuits is much more variegated than tested to date in preclinical models.

5.5. **Other targets.** Although localized far from the dorsal stimulation site a wide range of spinal interneurons can be reached by electrical stimulation (Kjaerulff et al., 1994; Cazalets et al., 1995; Kjaerulff and Kiehn, 1996; Cowley and Schmidt, 1997; Kremer and Lev-Tov, 1997), and their membranes can be progressively depolarized by electrical fields without triggering action potentials. Nevertheless, spinal interneurons can still provide a higher level of network excitability that can facilitate or enable a rhythmic pattern when reached by further excitation from proprioception or by a voluntary attempt to perform a specific motor task.

While electrical SCS delivered at lower intensities can engage the spinal circuitry through DRs, which generally have the lower activation thresholds, SCS at higher levels of stimulation can directly recruit motoneurons, and their excitation may be mainly associated with the activation of

longitudinally oriented fiber systems in the dorsal column (Hunter and Ashby, 1994). Furthermore, high voltage stimulation of the lower lumbar cord can be used for assessing ventral root functionality, for the direct activation of motor fibres as they exit the spinal cord (Roy et al., 2012). It is worth noting that DR activation at high stimulation intensities is inevitable and should be considered when discussing potential mechanisms and targeted neural structures during SCS.

Electrical stimulation can also recruit glial cells (Tawfik et al., 2010; reviewed by Vedam-Mai et al., 2012). Among these, astrocytes represent a numerous component within the spinal cord, each of them tightly connected to one another by gap junctions to form an extended network (Fellin, 2009). Although glial cells are traditionally considered non-excitable, i.e., unable to generate action potentials, their depolarization is coupled with variations in their intracellular calcium concentrations (Kim and Rioult, 1994). Thus, calcium waves propagate rapidly within the astrocytary network (Newman and Zahs, 1997; Tawfik et al., 2010; Fleischer et al., 2015), also in response to electrical SCS. Propagation of calcium waves regulates synaptic transmission along the neuronal network, mainly through three mechanisms: the neurotransmitter reuptake (Conti et al., 1998; Oliet et al., 2001; Pascual et al., 2005), the buffering of extracellular ionic concentrations (Carmignoto and Haydon, 2012) and the release of gliotransmitters (Liang et al., 2006, Jourdain et al., 2007, Panatier et al., 2011, Kang et al., 2013; Tang et al., 2014). For example, electrical stimulation of astrocytes releases adenosine (Caciagli et al., 1988) and, in turn, endogenous adenosine of glial origin (Acton and Miles, 2015) modulates rhythmic motor patterns (Dale and Gilday, 1996).

Other neural factors can contribute to facilitating the locomotor rhythm. In particular, electrical SCS inevitably spreads to the spinal canal, where the cerebrospinal fluid is contained. This is characterized by an electrolytic composition that makes it significantly conducive at body temperature (Baumann et al., 1997). Electric fields distributed through the cerebrospinal fluid might reach the ventrolateral laminae adjacent to the central canal (Hoppenstein, 1975), even of segments rostral and caudal to the stimulation site. Noteworthy, around the central canal are

localized a class of interneurons crucial for the expression of the locomotor pattern (Huang et al., 2000; Tillakaratne, 2014; Duru, 2015, Jalalvand et al., 2016).

6. Subthreshold electrical stimulation.

At rest, the membrane of neurons is electrically polarized as a consequence of the unbalanced concentration of ions across the membrane, which acts as a selective barrier. These variations generate a membrane potential that is affected by any electrical field able to reduce (depolarize) or increase (hyperpolarize) its magnitude (Kuffler and Nicholls, 1976).

In excitable cells, depolarization and hyperpolarization correspond to two opposite shifts of the membrane potential, bringing it closer (or farther, respectively) to the threshold for triggering an action potential. However, even small depolarizations, namely the ones unable to reach the threshold for triggering an action potential (i.e. subthreshold), can affect the biophysical properties of neuronal membrane and modulate synaptic transmission (Katz and Miledi, 1967; Martin and Ringham, 1975).

Electrical SCS delivered at intensities unable to trigger any motor action potentials interacts with the ongoing network activity (Ozen et al., 2010). The efficacy of network recruitment using subthreshold electrical pulses is not due to a mere summation of weak stimuli, but also exploits distinct and probably significantly underestimated mechanisms that do not parallel those of "threshold" stimulation. As a matter of fact, networks are more sensitive to subthreshold electrical stimuli than single neurons, since weak electric fields can actually synchronize the neurons composing a circuit (Francis et al., 2003; Selverston et al., 2009).

Furthermore, subthreshold impulses might selectively activate discrete interneuronal populations, potentially different from the ones recruited by a threshold stimulation. As a matter of fact, the sensitivity to subthreshold electric fields is defined in part by cell morphology (Radman et al., 2009). Likewise, subthreshold electrical stimuli might also flexibly reconfigure the functional

coupling among the elements of the circuit and modulate distinct pattern regimes (Berzhanskaya et al., 2013).

Subthreshold electrical stimulation might also contribute to amplify spontaneous voltage fluctuations of neuronal membranes, which, eventually, can also affect the tonic activity of the propriospinal network and the integration of sensory inputs. The combination of all these subthreshold contributions might exploit phenomena of spike timing-dependent plasticity to bring some elements of the spinal locomotor network to threshold (Dan and Poo, 2004).

As a consequence, circuit excitability is modulated in a subthreshold manner by small electrical fields. In turn, the small fields produced by network activity can modulate excitability of neighbor cells, even those not synaptically connected to the firing neurons that produce the electrical fields, or those that are not spiking at the moment (Francis et al., 2003).

Nevertheless, constitutively non-spiking interneurons, with the ability of sensing and transmitting any changes of the local electrical field, have been predominantly identified in invertebrates, in part because they are technically more accessible for microelectrode recordings from different sites of the same interneuron or from a related motoneuron (Pearson and Fourtner, 1975; Burrows and Siegler, 1978; Burrows, 1980; Dickinson et al., 1981; Wilson, 1981; DiCaprio, 2004; Smarandache-Wellmann et al., 2013, Berg et al., 2015). Networks of non-spiking interneurons in invertebrates were reported to generate a graded modulation of synaptic neurotransmitter release in response to slight changes in their membrane potential (Mendelson, 1971). The possibility to convert a small depolarization of the presynaptic terminal into a proportional amount of transmitter released, as opposed to the stereotyped all-or-none response of transmission based solely on action potentials, should provide an efficient means to finely modulate the activity of even a subset of axonal or dendritic branches of neurons.

As crucial elements of invertebrate CPGs, non-spiking interneurons convey numerous incoming input, resulting in a high background synaptic noise (Pearson and Fourtner, 1975). For their

unique properties, non-spiking neurons represent decisional nodes of neuronal networks, as they are interposed between the source of rhythmic activity and motoneurons, thus filtering or amplifying the patterned CPG output (Pearson and Fourtner, 1975; Burrows, 1980).

The presence of neurons that do not produce any spikes might represent a ubiquitous principle of CNS functioning also in mammals. There are in fact many examples of graded release in mammals in specific cells of the retina and olfactory bulb (Hartveit, 1999; Charpak et al., 2001; Pan et al., 2001; Sterling and Matthews, 2005; Snellman et al., 2011), nevertheless non-spiking interneurons in mammalian spinal cord have seldom been reported so far (King and Lopez-Garcia, 1994; Darbon et al., 2004). Regardless of the presence or absence of non-spiking interneurons in mammal SNC, a similar graded modulation of network activity can be played also by spiking neurons, as a titrated slight depolarization of their presynaptic terminals determines a graded increase in neurotransmitter release (Katz and Miledi, 1967; Martin and Ringham, 1975; Graubard et al., 1980). Indeed, the resting membrane potential recorded immediately before an invasion of action potentials modulates neurotransmitter release (Awatramani et al., 2005). In more detail, a subthreshold depolarizing electrical input at presynaptic level might augment neurotransmitter release, only if occurring soon after an adequate releasing input (Dudel et al., 1984). Such potentiation of the release induced by a weak depolarization of the presynaptic terminal does not seem to depend upon variations in intracellular calcium (Dudel et al., 1984). Rather, it might derive from conformational changes of membrane proteins affecting the exocytotic machinery (Castro and Urban, 2009; Huang and Trussell, 2011).

In summary, in the neuromotor system, a mechanism based on digital input (action potentials) suits well the rapidity and reliability required to impart commands to start or stop gait. On the other hand, a continuum of analogue input (subthreshold depolarizations) from multiple sensory stimuli

and propriospinal sources, and its integration in real time would be advantageous to finely modulate outgoing locomotor patterns.

In this scenario, diffused subthreshold electrical stimulation exploits the properties of analogue modulation at cellular level. The net effect would be to facilitate the intrinsic rhythmogenicity of locomotor networks, which can now activate a wide range of physiological patterns, even in response to a weak triggering input.

7. Activity-dependent plasticity.

In spite of the complexity of the spinal cord (from molecules to synapses, cells, networks and systems), there appears to be a common underlying mechanism, which allows a relatively simple state of neuromodulation to enable ambulatory animals and humans with SCI to recover sensory motor functions. For example, the application of the same common stimulating parameters, consisting in a tonic stimulation at the same stereotyped frequency and intensity, generates very complex movements (Ichiyama et al., 2005).

It is also evident that some of these "plastic" events can occur very acutely in response to the first application of a single burst of tonic stimulation, even if additional changes occur after exposure to repetitive stimulating periods within a single training session, as well as further adaptive events occurring over a period of even months (Gad et al., 2013b).

While the role of plasticity is far from clear, we use the term "plasticity" to embrace the reconfiguration of networks, the ancillary recruitment of other rhythmogenic sources as well as the exploitation of silent or newly sprouted connections, with the understanding that we know little about the mechanisms of any of these adaptive phenomena. The sensory-motor activity can drive all these events by generating peripheral afferent inputs that support and refine movements with feedback and feedforward loops in real time (Gerasimenko et al., 2017).

7.1 **Electrically enabling non-responsive spinal sensory-motor networks.** All data collected to date in our laboratory have been consistent with the hypothesis that, following a severe SCI, the baseline level of spinal network excitability in many cases is substantially reduced (Harkema et al., 2011; Angeli et al., 2014; Gerasimenko et al., 2015; Grahn et al., 2017). Thus, the basic concept underlying neuromodulation is that our tonic electrical stimulation and/or pharmacological modulation moves this baseline excitability level closer to the motor threshold of the networks generating the sensory-motor and autonomic functions of interest (Gerasimenko et al., 2015). This changes the physiological state of the spinal circuitry below the lesion thus requiring smaller levels of excitation from cutaneous and proprioceptive input from descending motor pathways (Harkema et al., 2011; Grahn et al., 2017). These two conditions (elevation of the baseline excitability level combined with adding relatively small amounts of sensory excitation and\or supraspinal input) allow the subject to generate a movement because the level of excitability can now be elevated above motor threshold (Angeli et al., 2014; Rejc et al., 2015; Grahn et al., 2017). Thus, spinal cord networks can be converted from a non-responsive state to one that can generate and conduct action potentials when the membranes are sufficiently excited. Thus, the final component of the neural modulatory strategy is to engage the networks that have been elevated to a level that exceeds the motor threshold of the appropriate motor pools with the appropriate timing that will generate a well-coordinated motor task, such as stepping, standing or reaching, for an improved trunk control. This engagement of the networks with elevated excitability provides the means for the networks to relearn how to translate proprioceptive and cutaneous input during motor tasks, to learn the necessary timing among a given set of synapses through which sensory information is translated to a motor event. When the performance of these motor tasks is practiced periodically, extensive sensory-motor learning occurs within and among the networks that become engaged and the improved function in the presence of neuromodulation in one training session persists to the next training session. This persistence reflects the learning and memory capability within the spinal networks. This combined series of events provides the

basis of the effectiveness of rehabilitation. For example, there would be little to no progression in improvement if there was not some persistent effect, i.e. memory of the events that occurred in the previous training session. The crucial point is that the spinal networks need to be engaged in a motor task that generates cutaneous and proprioceptive input that can drive the reorganization of the synaptic efficacies of selected combinations of interneurons and motoneurons to generate a coordinated movement.

A relatively common observation during the process of improving motor function with neuromodulation is that the level of excitation that must be provided for the spinal networks to reach motor threshold is gradually reduced (Shah et al., 2012). This was demonstrated in subjects with complete paralysis receiving transcutaneous eSCS once a week for eight weeks, with the motor task being the generation of rhythmic stepping in an unloaded condition (Gerasimenko et al., 2015). At the end of the study there was a significant increase in the range of movements that could be generated during the step-like cycle when the subject attempted a step either in the presence or absence of any stimulation. But the most important observation in this case was the absence of any significant difference in the voluntarily generated movements with or without stimulation. Thus, it suggests that both the supraspinal and spinal networks had reorganized sufficiently to become equally effective with a voluntary effort alone compared to a voluntary effort generated in the presence of electrical neuromodulation. A similar phenomenon was demonstrated in rats with a complete SCI that were trained to step sideways, i.e. significantly lower stimulation intensity was needed at the end of 28 training sessions (Shah et al., 2012). Further, within a single day of testing, when either quipazine and/or strychnine were administered to a spinal rat, the intensity of stimulation needed to induce bipedal stepping was lower than when neither were administered.

To gain some mechanistic insight into the characteristics of spinal networks that are being modulated by electrical stimulation, there has been an extensive focus on the effect of different intensities of stimulation on the characteristics of the simultaneous spinally evoked potentials in

multiple muscles. The characteristics of these potentials are highly dependent on multiple factors, particularly on the intensity of stimulation. Evoked potentials have been characterized as early, middle and late responses (ER, MR, LR, respectively, Gerasimenko et al., 2006). ER can occur only at high stimulation intensities and it is likely to be the result of the direct recruitment of motoneurons or ventral roots. The presence of a time-linked MR over all stimulation intensities in the flexor and extensor muscles has some component consistent with a monosynaptic reflex. On the other hand, the LRs almost certainly reflect combinations of polysynaptic responses generated through spinal interneuron networks. These LRs can be much more readily generated in the presence of different pharmacological cocktails (Gad et al., 2013a, Gad et al., 2015) or of chronic subthreshold stimulation (Gad et al., 2013b). The lowered dependence on the time-linked MR and increased LRs during chronic subthreshold stimulation suggests that the spinal networks are not being **induced** to generate a movement, but are placed in a state of readiness to **enable** movements based on the appropriate proprioceptive information of supraspinal commands.

7.2. **Reconnectivity of supraspinal-spinal networks via transformation of electrically non-responsive to functionally competent cellular elements.** First the study of Harkema and colleagues (2011) on one motor complete paralyzed subject followed by the study of Angeli et al. (2014) on three additional individuals with chronic complete motor paralysis demonstrated clear evidence of the ability to recover joint-specific, coordinated voluntary movements in the presence of epidural stimulation. The results in the three individuals who were tested after implantation, but before repetitive training suggest that descending connections to the spinal cord circuitry emerged as a result of stimulation of networks well below the spinal lesion transforming cellular components within the more proximal lesioned segments from electrically non-responsive to responsive. Unlike in the first subject in which this observation occurred after almost 7 months of daily stimulation sessions with training, the latter three subjects regained the supraspinal-spinal connectivity within only a few stimulation sessions. Such a rapid transformation makes it highly

unlikely that the mechanism for reconnectivity can be attributable to a significant degree of axonal growth. Also, even when this reconnectivity emerged, it could be observed in the presence of a critical level of stimulation. Daily exercises using epidural stimulation in conjunction with standing and voluntary activity resulted in the generation of higher forces during volitional movements and lower stimulation voltages to reach the motor thresholds. Interestingly, the participants were able to more readily generate flexion compared to extension in the lower limbs (Angeli et al., 2014). Although these results demonstrate that the spinal circuitries below the lesion have a potential that exceeds what has been reported previously, critical questions to address are 1) To what degree is activity-based training necessary or beneficial to recover voluntary motor control? and 2) What are the critical training parameters for regaining more effective voluntary motor control? While there is little information available to answer these two questions as to how they pertain to electrical or pharmacological neuromodulation, there is abundant evidence of plasticity within the sensory-motor networks within brain and spinal networks in response to training alone. There is little clarity, however, on a conceptual principle that defines the degree of specificity among different sensory-motor tasks necessary to gain some cross-over effects among different tasks. This important topic, however, is well beyond the scope of this review.

In considering the questions noted above, however, several points are appropriate to keep in mind. Significant levels of cortical reorganization are common in humans after SCI (Oni-Orisan et al., 2016). Mapping studies using transcranial magnetic stimulation reveal an expansion of cortical sensorimotor areas representing muscles above the level of lesion in individuals with tetraplegia (Levy et al., 1990) and enhanced excitability of motor pathways targeting muscles rostral to the level of a spinal lesion in those with paraplegia (Topka et al., 1991). Cortical reorganization after dorsal column lesion is not limited to the primary somatosensory area, but also extends to the secondary somatosensory cortex and parietal ventral area (Tandon et al., 2009). Multiple combinations of adaptive network reorganizations undoubtedly occur and some of these changes are likely to lead to some recovery of motor control. It seems probable that functional

reorganization of cortico-brainstem-spinal, corticospinal and spinal networks will define the degree and quality of the newly acquired voluntary function. Given the extensive functional reorganization that can occur within and between the brain and spinal networks, two points seem inevitable. First, given the massive loss of connectivity with a severe SCI it is highly improbable that the connections that re-emerged in the cases noted above can be attributed to the same connections that were present before the lesion. Secondly, the level of functionality that develops as a result of the newly formed connections is likely to be reflected in the level of synergism of the reorganization of the networks within and between the brain and spinal cord.

The fact that regaining voluntary motor control can occur within a few sessions (Angeli et al., 2014, Gerasimenko et al., 2015), for years after SCI, indicates a persistence of the potential of taking advantage of brain-spinal plasticity that not only has not been previously realized, but has been steadfastly denied as a possibility.

8. Possible interpretation of the voluntary recovery induced by eEmc.

Based on our current state of understanding, efficacy of eEmc can be attributed to either the potentiation or reactivation of cellular components that survived the lesion, but which are sufficiently damaged and disabled in their potential to reinstate a functional supraspinal-spinal connectome. Once some functional connection has been restored, eEmc seems to further enhance the functional level by amplifying and remodeling this connectome (**Figure 3**). This might be induced via sprouting of the few remaining fibers that are spared by the damage but that are in an insufficient number to recruit an appropriate quantity of post lesional targets (Calancie et al., 1999; Asensio-Pinilla et al., 2009). A greater number of synaptic contacts with sub-lesional targets might be established, which will consequently increase the number of voluntarily recruited networks.

Also, eEmc might bring the exiguous descending axons, spared by the lesion but unable to conduct impulses (Shuman et al., 1997; Nashmi and Fehlings, 2001), to a functional state that

enables them to conduct action potentials to spinal networks below the lesion. Electrical stimulation of residual descending fibers over a greater period of time might promote remyelination (Ishibashi et al., 2006; Wake et al., 2011) and re-establish conduction in fibers that were spared by the initial trauma but apparently became unable to conduct impulses (Kakulas, 1999). To this regard, electrical stimulation of the corticospinal tract induced activity-dependent proliferation and differentiation of oligodendrocyte progenitor cells (Li et al., 2010) and the formation of myelin in mixed neuronal and oligodendrocyte cultures (Gary et al., 2012). Notably, a protracted electrical stimulation of the spinal cord using transcutaneous electrodes, improved the neurological outcomes of persons with demyelinating disorders (Dooley et al., 1978).

Moreover, the reduced descending inputs following a lesion, combined with subsequent disuse due to paralysis, may depress synapses among residual descending and propriospinal fibers, as well as MNs. Synaptic depression due to the presence of silent synapses (Malinow and Malenka, 2002) has been identified in some neurological disorders (Shevtsova and Leitch, 2012; Wan et al., 2011; Kerchner et al., 1999), but not yet in SCIs.

At pre-synaptic levels, eEmc might modulate density and properties of ionic channels in the network, such as transient I_A K^+ currents (Watanabe et al., 2002) and Ca^{2+} activated K^+ channels (Nanou et al., 2013). Moreover, it might facilitate variations in synaptic excitability, by acting on Na^+ channels (Ganguly et al., 2000), I_h current (Mellor et al., 2002) and slow-activating K^+ channels (Li et al., 2004), or, again, it might limit the release, from postsynaptic terminals, of retrograde factors with an inhibitory significance (endocannabinoids, Sjöström et al., 2003).

In addition, electrical SCS increases cerebral spinal blood flow (Kanno et al., 1989; Linderoth et al., 1995; Liu et al., 2008) and, thus, its prompt adoption is proposed for rescuing *sleeping neurons* located in the penumbra zone of cortical ischemia (Visocchi et al., 1994). A similar effect might occur also at spinal level, but only if around the chronic spinal lesion are localized some impaired but spared neurons that would benefit from the increased perfusion.

In addition, impulses that travel along residual axons may project to electrically non-responsive neurons below or within the lesion. After a SCI, several changes occur in intrinsic electrophysiological properties of motoneurons, such as the depth of after-hyperpolarization of action potentials and the amplitude of segmental or descending excitatory post-synaptic potentials (Petruska et al., 2007). Concurrently, an increased activation of intrinsic persistent inward currents (PICs; ElBasiouny et al., 2010) and a downregulation of the potassium-chloride co-transporter-2 (KCC2; Boulenguez et al., 2010) can change motoneuronal responses to sensory stimuli. Moreover, an upregulation of glycinergic receptors depresses motoneurons, as demonstrated by facilitation of stepping in chronic paraplegic animals using prolonged full weight-bearing after administrating the glycinergic inhibitor, strychnine (de Leon et al., 1999).

Furthermore, eEmc might affect basic and active membrane biophysical properties of motoneurons (Button et al., 2008) or the expression of mGluR receptors (Karmarkar and Buonomano, 2002). Moreover, even the different kinetics of post synaptic NMDA receptors, linked to a variation in NR2A/NR2B subunits expression, must be considered (Tang et al., 1999).

Finally, awakening silent synapses may require coordinated pre- and postsynaptic modifications, e.g., incorporation of new AMPA receptors at postsynaptic site and presynaptic modification in release machinery (Voronin and Cherubini, 2004).

The spinal cord owns smart abilities, such as learning new motor tasks, forget them after a lesion or disuse and remember them again after an intense task specific training, that were considered, until more recently, to be a prerogative solely of the brain (Edgerton, 2004, 2001; Jindrich et al., 2009). In the brain, information storage and refinement of neuronal circuits occurs through the phenomenon of Hebbian synaptic plasticity, which pairs stimulation of pre- and post- synaptic terminals (Voronin and Cherubini, 2004). The timing with which pre- and post- synaptic impulses follow one another can modify synaptic efficacy in a dependent manner, i.e. spike-timing-dependent plasticity (Caporale and Dan, 2008; Dan and Poo, 2004). This principle is in

accordance with observations in both cortical and hippocampal neurons (Levy and Steward, 1983), also reproduced by modeling studies (Song et al., 2000). Moreover, in individuals with a chronic incomplete SCI, spike timing-dependent plasticity of spared corticospinal-motoneuronal synapse provides a mechanism to improve motor functions of upper limbs (Bunday and Perez, 2012).

Based on spike-timing-dependent facilitation, paired stimulation of multiple inputs, converging onto MNs with different frequencies and latencies, may be crucial in recruiting different motoneuronal pools. This is in line with the observation that direct stimulation of the spinal cord with different frequencies facilitates different voluntary motor tasks following SCI (Harkema et al., 2011; Gerasimenko et al., 2015; Shah et al., 2016).

9. Synergism of neuromodulation and proprioception.

Afferent inputs projecting to the postural and locomotor networks are the primary contributors in facilitating standing and stepping. Indeed, assisted stepping evokes afferent inputs, which allow the recovery of locomotion in subjects with spared residual connections crossing the lesion (Wernig et al., 1995; Harkema et al., 1997). Likewise, afferent electrical stimulation generates brief episodes of stepping in humans (Selionov et al., 2009) and a more robust locomotor behavior in animals with a complete spinal transection (Alluin et al., 2015). Indeed, electrical and pharmacological interventions modulate the physiological feedback, which can enable the proprioceptive-mechanical input generated during gait to initiate and sustain a wide range of temporally precise sensory ensembles. These ensembles can activate the appropriate motor pools in real time to achieve stable posture and locomotion (Musienko et al., 2012a; 2012b). Nevertheless, motor output and locomotion were not necessarily induced without any afferent input, i.e. in the absence of any treadmill activity, by electrical SCS alone, even at a relatively high stimulation strength, i.e., well above motor threshold (Ichiyama et al., 2005). On the other hand, treadmill alone is not able to replicate the same facilitatory effect without eEmc in paralyzed

stepping rats, mice and humans (Ichiyama et al., 2005, Fong 2005, Rejc et al., 2017). Thus, proprioception and electrical SCS synergizes to facilitate standing and stepping.

These findings raise the question on whether this wide range of stimulating sources project to similar interneuronal networks and motor pools. We recently began to address this question by comparing the kinematics and EMG patterns of lower limbs during rhythmic stepping in a gravity position. More specifically, we compared these features when the locomotor behavior was initiated and sustained in response to electrical SCS alone, as well as to the voluntary generation of stepping without stimulation and their combination (Gerasimenko et al., 2016). Interestingly, the final net kinematics and EMG patterns were remarkably similar among the three modes of activation. Nevertheless, these results cannot be univocally interpreted as an activation of either the same interneuronal networks projecting to the motor pools or of a defined final output from a motor pool. This observation implies that there may be "pods" of networks with some selectivity in the relative dominance of the type of motor units recruited.

10. Conclusion.

Conceptual cores of the automaticity of movement are 1. Central pattern generation, 2. Brainstem origins of the control of movement, 3. The dominating effect of all sources of sensory input, with the focus in this review, being on proprioception and cutaneous input to the spinal cord, and 4. The propriospinal system, which serves as the interface between the brain and spinal cord. From numerous observations from animal experiments and more recently from human subjects, the question becomes, what experimental strategies can be used that will enable us to take advantage of the automaticity in order to regain significant levels of function following severe paralysis. A more detailed understanding of the subcellular, cellular and systemic level networks that can be modulated is needed. The more recent observations in response to modulatory techniques also points in the direction of the importance of subthreshold modulation as an extremely important source of control of motor function, not only in the injured state, but also in

the uninjured neuromotor system. Concepts associated with neuromuscular plasticity represent a fundamental component of the mechanisms that underlie the recovery of not only relatively automatic movements, such as stepping and standing, but also in the recovery of voluntary control of movements of the upper limb. This observation illustrates the importance of using neuromodulation at subthreshold levels of excitability of spinal networks that are less dependent on the fundamental concept of central pattern generation, which seems to play a dominant role in the control of lower limbs. The new and important question to address given the recovery of supraspinal-spinal connectivity after a motor complete injury with the aid of neuromodulation and training is, how to optimize a synergistic reorganization of supraspinal and spinal networks in order to regain the highest level of function.

Author Disclosure Statement

VRE, YG, and PG researchers on the study team hold shareholder interest in NeuroRecovery Technologies and hold certain inventorship rights on intellectual property licensed by the Regents of the University of California to NeuroRecovery Technologies and its subsidiaries.

person	level of injury	degree of injury (ASIA scale)	mode of electrical stimulation	Site (vertebrae)	stimulating protocol (frequency, amplitude, pulse width)	outcomes	refs
#1	C_7-T_1	B	16-electrode epidural array	T_{11}-L_1	15 - 40Hz, 0.5 - 10V, 210 or 450µs	Independent standing (max 4.25 min), locomotor-like EMG patterns in the legs while stepping on the treadmill with body weight support and manual assistance, volitional movements of both legs, autonomic gains.	Harkema et al., 2011
#2	T_5-T_6	A		T_{11}-T_{12}	25 - 40Hz, 0.5-9V, 250, 330 or 400µs	Locomotor-like EMG patterns in the legs while stepping on the treadmill with body weight support and manual assistance, volitional movements of both legs with graded levels of force in response to a verbal command.	Angeli et al., 2014
#3	C_6-C_7	B					
#4	T_5	A					
#5	T_3-T_4	B	two round transcutaneous electrodes (2.5 cm)	T_{11} + Co_1	30Hz + 5Hz (10kHz modulated), 80 - 180mA, 1000µs	Volitional leg oscillations in a gravity-neutral position.	Gerasimenko et al., 2015
#6	C_5-C_6	B					
#7	C_6	B					
#8	C_7	B					
#9	T_3-T_4	B					
#10	T_6	A	16-electrode epidural array	T_{11}-L_1	15, 25 and 40 Hz, 1.5 - 5.5V, 210 µs	Volitional control of task-specific muscle activity, volitional control of rhythmic muscle activity to produce steplike movements while side-lying, independent standing and while in a vertical position with body weight partially supported, voluntary control of steplike movements and rhythmic muscle activity.	Grahn et al., 2017

Table 1. Parameters of each stimulating procedure and their outcomes for different individuals with a spinal cord injury.
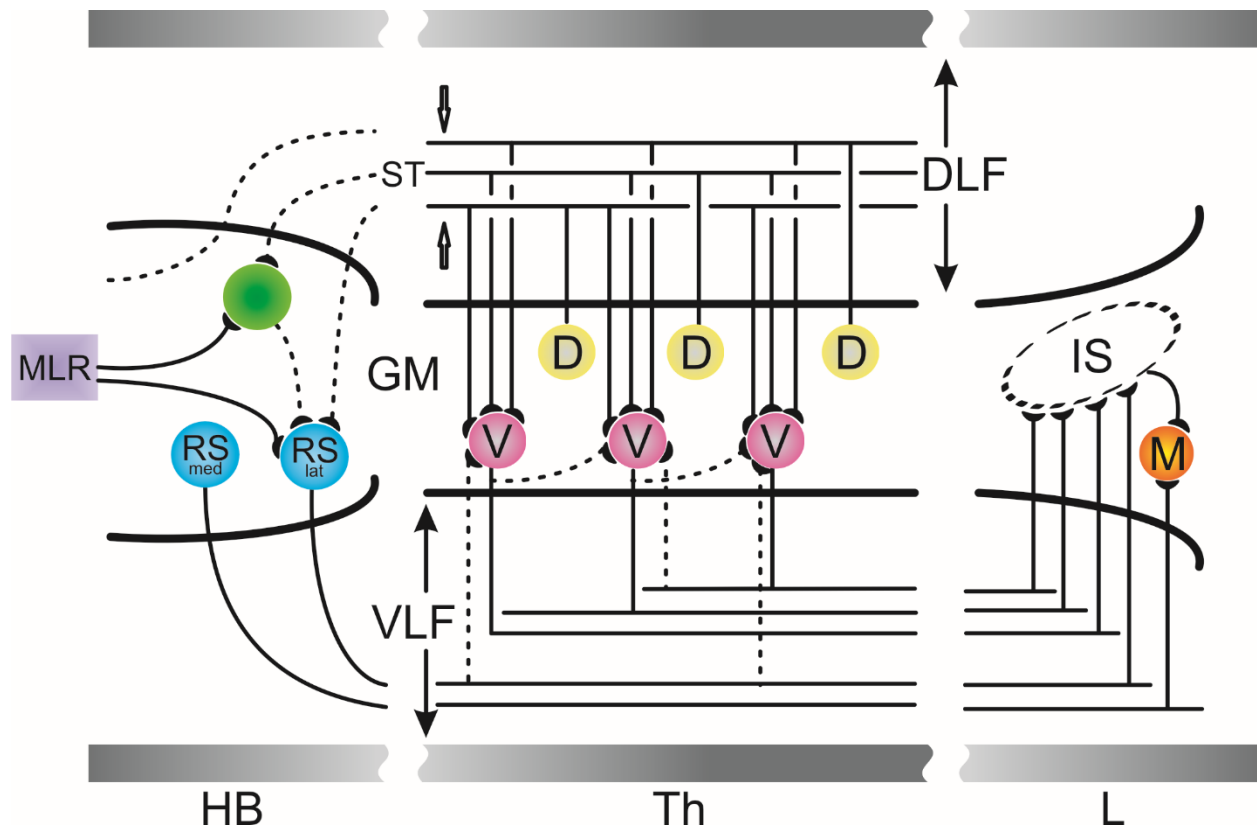
Figure 1. Wiring diagram suggesting the role of propriospinal and reticulospinal systems in initiation of stepping.

Spinal cord includes the dorsal and ventral parts of the lateral funiculus (DLF and VLF) and gray matter (GM). The spinal neurons that send their axons to DLF are termed D neurons, while V neurons send their axons to VLF. MLR, mesencephalic "locomotor region"; HB, hindbrain; thoracic (Th) and lumbar (L) segments of the spinal cord.; IS, interneurons assembling stepping; M, motoneurons; RS, reticulospinal neurons; St, stepping strip (*modified from Shik, Motor Control, 1997*).
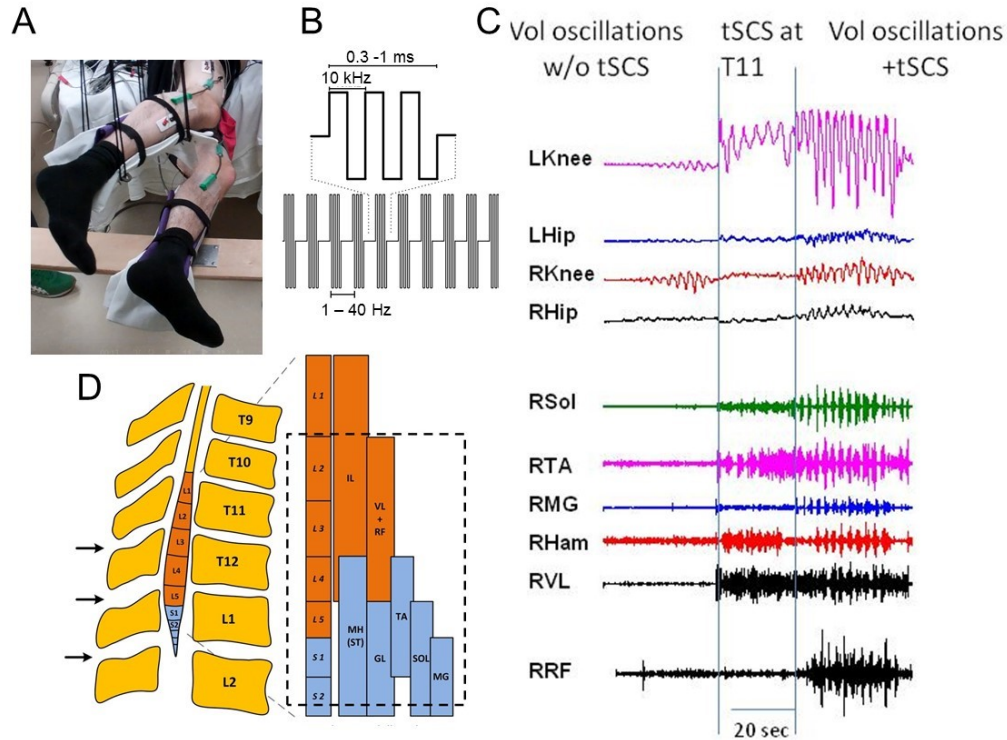
Figure 2. Facilitation of stepping-like volitional oscillations using non-invasive transcutaneous electrical spinal cord stimulation in SCI subject.

(A) Position of the participant in the gravity-neutral apparatus. (B) Biphasic electrical stimulation was delivered using unique waveforms consisting of 0.3-1.0 ms bursts filled by 10 kHz frequency that were administered at 5-40 Hz. (C) EMG activity of right soleus (RSol), right tibialis anterior (RTA), right medial gastrocnemius (RMG), right hamstrings (RHam), right vastus lateralis (RVL), right rectus femoris (RRF) and angular displacement in the knee and hip joints of both legs during leg oscillations with a voluntary effort alone (Vol), stimulation at T11 (Stim), and Vol+Stim are shown. (D) Schematics demonstrating the approximate location of transcutaneous electrodes above the lumbosacral enlargement, in relation to the location of the motor pools based on Kendall et al. (1993) and Sharrard (1964).

A

descending input

propriospinal network

CPG   CPG

loc. CPG

CPG

CPG

motoneurons

afferent input

locomotor pattern

B

descending input

propriospinal network

CPG   CPG

loc. CPG

CPG

CPG

motoneurons

afferent input

C

descending input

propriospinal network

sub-threshold electrical stimulation

CPG   CPG

loc. CPG

CPG

CPG

motoneurons

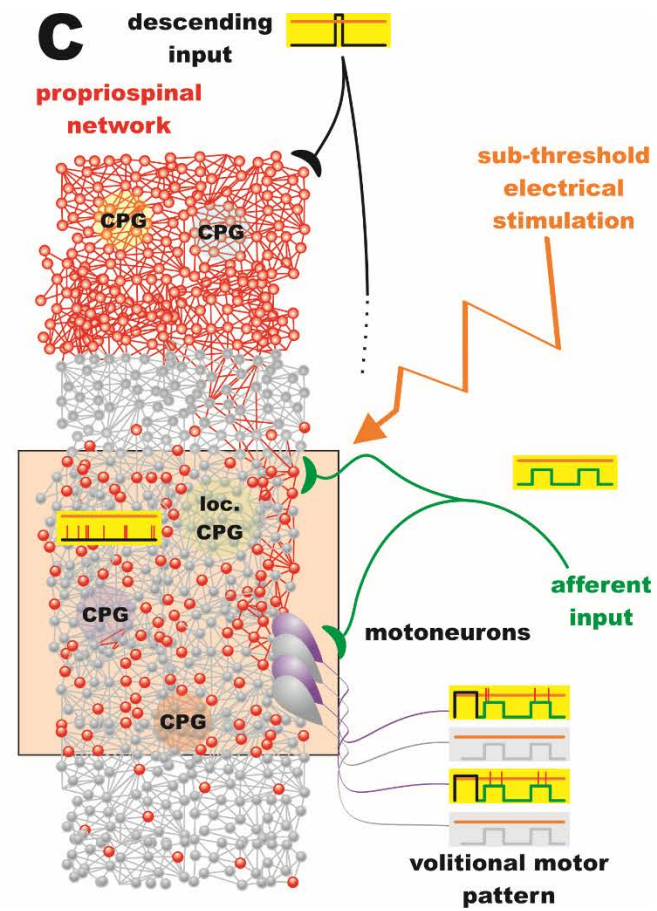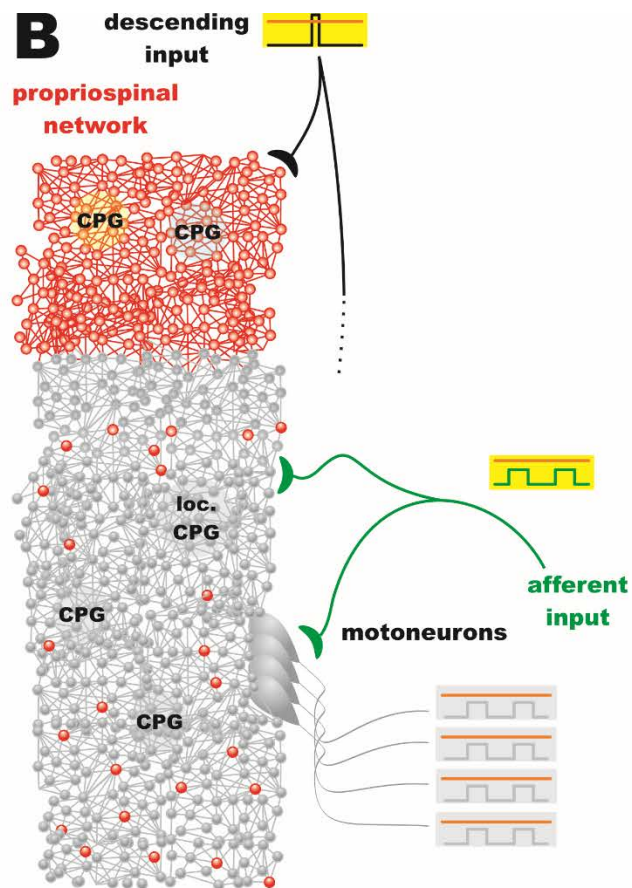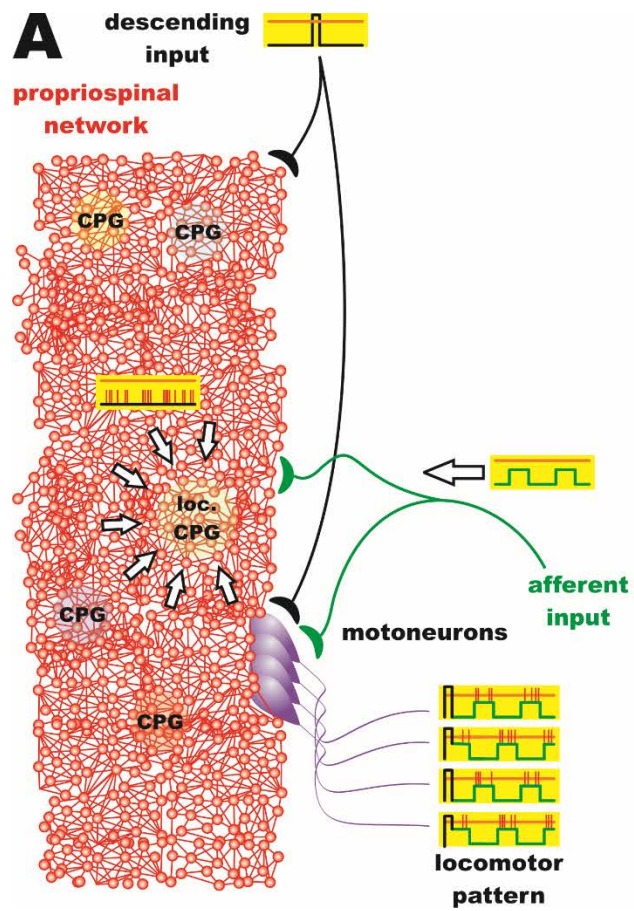afferent input

volitional motor pattern

Figure 3. Neuromodulatory mechanisms for the recovery of volitional control after SCI (simplified depiction).

This cartoon illustrates some of the proposed targets and mechanisms of neuromodulation of the spinal cord, as discussed in the body of the present review.

Physiologically (A), a plethora of propriospinal neurons (red dots) establishes a diffused dynamic network of synaptic contacts along the grey matter of the entire thoracolumbar spinal cord.

CPGs responsible for the genesis and the control of different motor tasks are represented by circumscribed areas of the networks as functional subgroups of interneurons that project in a continuously changing pattern toward different combinations of motor pools.

Fibers descending from supraspinal centers (top black lines) reach the propriospinal network and eventually to the spinal motoneurons (purple). Descending volitional command is represented by a single depolarizing input that reaches the motor threshold for network activation (yellow box with black line).

Afferent input from the periphery alone (green line) can reach the motor pools via the interneuronal network systems noted above, which is capable of conveying subthreshold and suprathreshold phasic output (yellow box with green line).

For example, during locomotion asynchronous discharges of subthreshold and suprathreshold input (yellow box with red lines) converges (white arrows) onto interneuronal networks with CPG qualities (highly ordered activation of networks that process proprioceptive input in real time) with sufficient precision to control movements as complex as locomotion (locoCPG; pale yellow circle). The locomotor CPG uses the subthreshold background noise from the propriospinal network and the subthreshold phasic rhythm from afferents to organize rhythmic and alternated patterns (locomotor pattern). The locomotor pattern passes the threshold in order to sequentially activate motoneuronal pools (purple lines) and thus muscles in a highly time-dependent action pattern of muscles (not shown).

For the sake of simplicity, we only represented the motor pools on one side, but the output from the interneuronal networks having CPG qualities is however to be considered bilateral.

Following a spinal lesion (B), the descending pathway directed to motor neurons is interrupted, while the propriospinal network below lesion mostly appears to be functionally silent and afferent input reduced because of damage and paralysis. Thus, the locomotor CPG does not receive an adequate amount of subthreshold input, hence the inability to voluntarily evoke motor patterns.

An innovative treatment (C), which pairs an appropriate subthreshold multi-site electrical stimulation of the thoracolumbar spinal cord with a specific motor training, can reactivate part of the sublesional elements of the propriospinal network, thus restoring the subthreshold background activity that, although reduced in frequency due to the more exiguous network extension, can still reach the CPG (yellow box with red lines).

Although the direct descending fibers remain interrupted, descending input can now reach motoneurons through the polysynaptic pattern of propriospinal connections now transformed from electrically non-responsive to responsive. The descending volitional command, although with reduced amplitude and increased latency, can be processed by the spinal networks so that well-coordinated patterns of muscular activation can be generated.

Graphical abstract
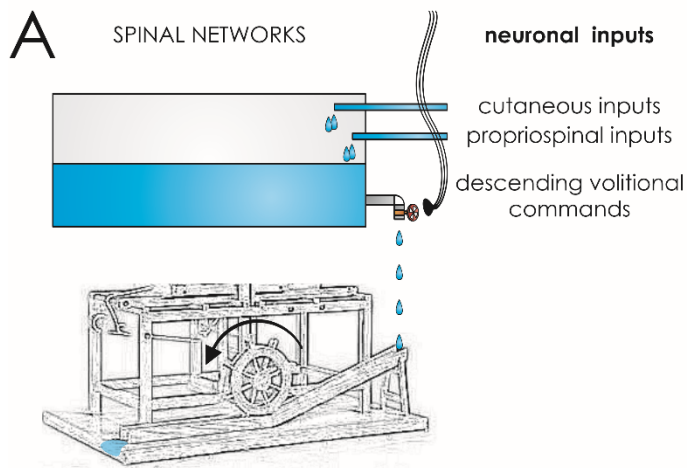
Conceptual depiction of how changes in the excitability of spinal networks and neuromodulation after a spinal lesion plays an important role in the control of movement.

A, In the uninjured state spinal networks (reservoir) maintain a level of excitability that is defined by cutaneous and propriospinal inputs from the periphery and all descending motor input. Input from one or more of these sources has the potential to trigger (open the faucet) and control a wide range of movement patterns (the rotation of the blades in Leonardo da Vinci's hydraulic engine).
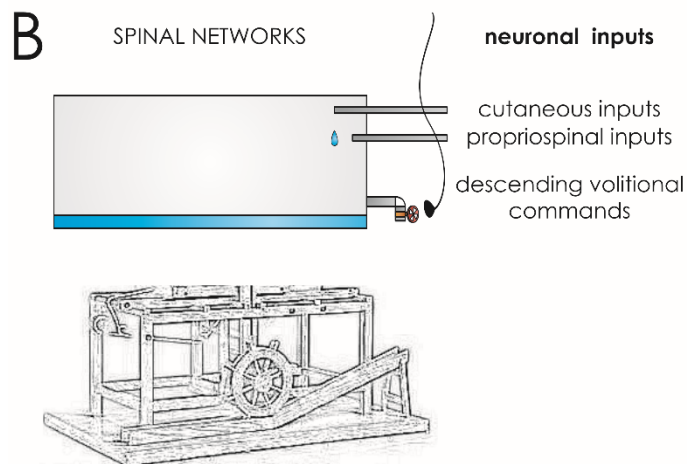
B, After a spinal lesion, the resting level of excitability of spinal networks descends further below the motor threshold necessary to activate the pattern, albeit sometimes spared descending commands and some types of sensory input could still be able to trigger some generally uncoordinated movements.
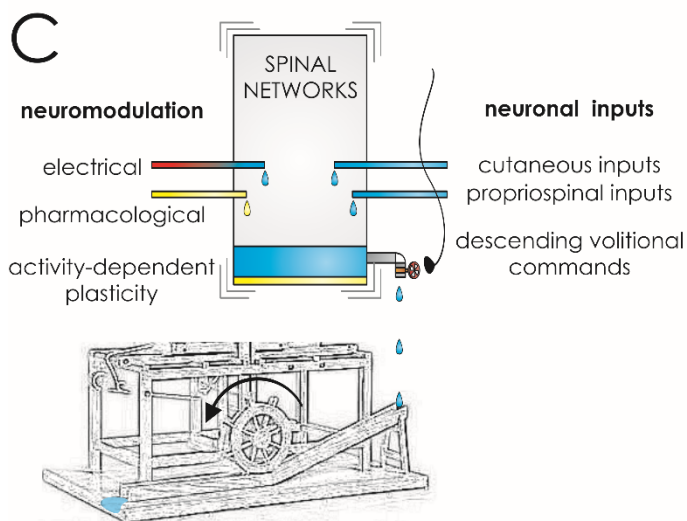
C, A rehabilitative intervention aimed at recovering excitability of spinal networks consists of restoring (amplifying) peripheral input through electrical neuromodulation directed to the spinal cord and the action of pharmacological agents and training (patterned proprioceptive input). Moreover, repetitive training promotes phenomena of activity dependent plasticity that reshapes the spinal networks, by elevating excitability sufficient to reach the threshold (note that the blue areas in B and C are the same). Albeit exiguous, the spared voluntary contributions may be able to trigger the movement of actuators downstream.

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