Progress in Neurobiology 160 (2018) 64–81

Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Review article

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

G. Taccola[a,b], D. Sayenko[a], P. Gad[a], Y. Gerasimenko[a,c], V.R. Edgerton[a,d,e,f,g,h,*]

[a] Department of Integrative Biology and Physiology, University of California, Los Angeles, CA 90095 USA
[b] Neuroscience Department, International School for Advanced Studies (SISSA), Bonomea 265, Trieste, Italy
[c] Pavlov Institute of Physiology, St. Petersburg 199034, Russia
[d] Department of Neurobiology, University of California, Los Angeles, CA 90095 USA
[e] Department of Neurosurgery, University of California, Los Angeles, CA 90095 USA
[f] Brain Research Institute, University of California, Los Angeles, CA 90095 USA
[g] The Centre for Neuroscience and Regenerative Medicine, Faculty of Science, University of Technology Sydney, Ultimo, 2007 NSW, Australia
[h] Institut Guttmann, Hospital de Neurorehabilitació, Institut Universitari adscrit a la Universitat Autònoma de Barcelona, Barcelona, 08916 Badalona, Spain

ARTICLE INFO

Article history:
Received 9 March 2017
Received in revised form 9 October 2017
Accepted 21 October 2017
Available online 2 November 2017

Keywords:
Neuromodulation
Electrical stimulation
Spinal networks
Motor training

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.

Contents

Abbreviations: CPG, central pattern generator; DLF, dorsal lateral funiculus; DR, dorsal root; eEmc, electrical Enabling motor control; ER, early response; MR, middle response; LR, late response; SCI, spinal cord injury; SCS, spinal cord stimulation; tSCS, transcutaneous electrical spinal cord stimulation.

* Corresponding author at: Department of Integrative Biology and Physiology, University of California, Los Angeles, Terasaki Life Sciences Building 61 Charles E. Young Drive East, Los Angeles, CA, 90095-1527, USA.
E-mail address: vre@ucla.edu (V.R. Edgerton).

https://doi.org/10.1016/j.pneurobio.2017.10.004

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 became motor incomplete 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 multiple 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., 2001; Strauss and Lev-Tov, 2003; Taccola, 2011; Dose et al., 2013; Dose and Taccola, 2016) and pharmacological agents (Cazalets et al., 1992; Houssaini et al., 1993; Kiehn and Kjaerulff, 1996; Marchetti and Nistri, 2001; 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.

Table 1
Parameters of each stimulating procedure and their outcomes for different individuals with a spinal cord injury.

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	15–40 Hz, 0.5–10 V, 210 or 450 μs	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}	25–40 Hz, 0.5–9 V, 250, 330 or 400 μs	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	30 Hz + 5 Hz (10 kHz modulated), 80–180 mA, 1000 μs	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, 1.5–5.5 V, 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)

4.3. Sensory control

A third origin of automaticity relies in the various forms of sensory information that is constantly available, though dynamically changing sources 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 et al., 1998a, 1998b; 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, in subjects with chronic cervical lesions, (Calancie, 1991; Calancie et al., 2002) the PSS might play a role in upper limb reflexes after stimulating nerves on their lower extremity. 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 (Fig. 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, 2015; Gerasimenko 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

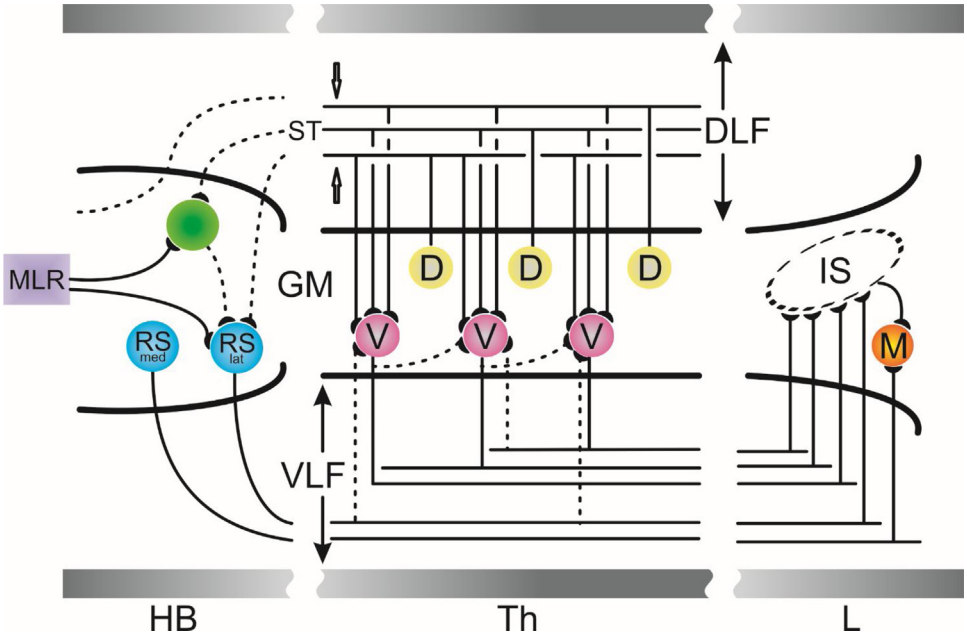

Fig. 1. Wiring diagram suggesting the role of propriospinal and reticulospinal systems in initiation of stepping.
Spinal cord includes the dorsal and ventral parts of the lateral funiculus (DLF and VLF) and gray matter (GM). The spinal neurons that send their axons to DLF are termed D neurons, while 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).

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; Hallett, 2000, 2007; Gerasimenko et al., 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 (Fig. 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., 2001; Strauss and Lev-Tov, 2003; Taccola, 2011; Dose et al., 2016; Dose and Taccola, 2016).

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

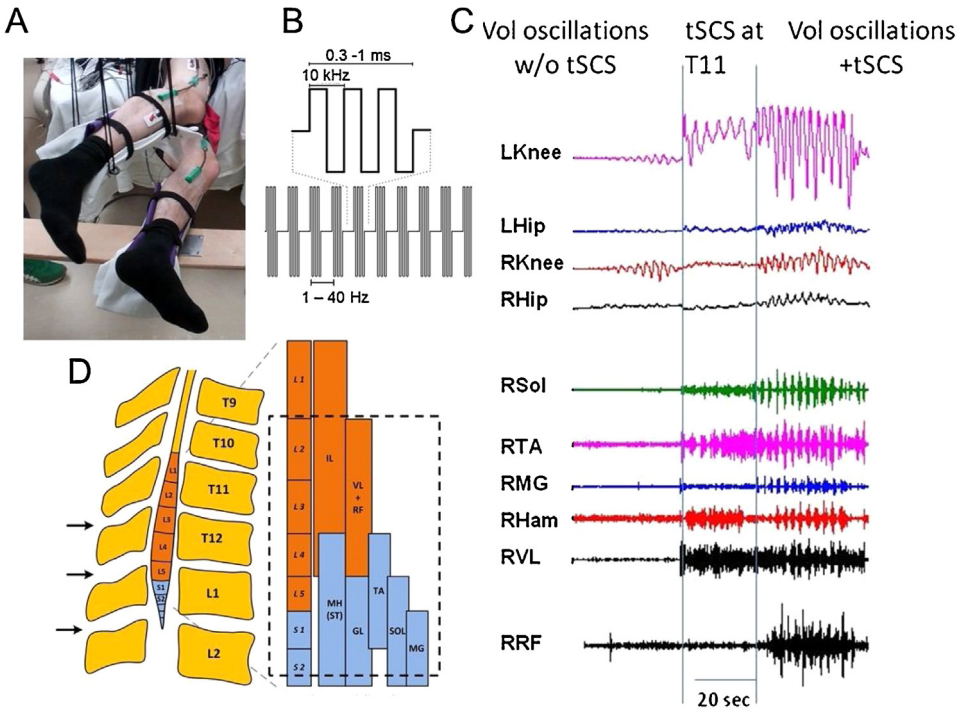

Fig. 2. Facilitation of stepping-like volitional oscillations using non-invasive transcutaneous electrical spinal cord stimulation in SCI subject.
(A) Position of the participant in the gravity-neutral apparatus. (B) Biphasic electrical stimulation was delivered using unique waveforms consisting of 0.3–1.0 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).

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 et al., 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 et al., 2014; Duru et al., 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, 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, 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., 2016b).

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, 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 et al. (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

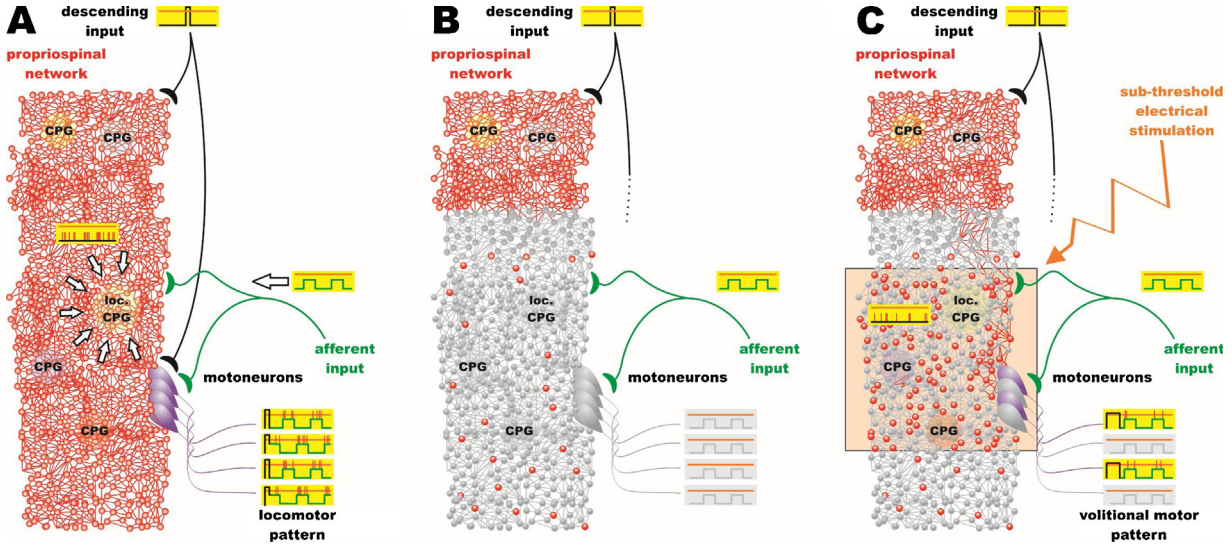

Fig. 3. Neuromodulatory mechanisms for the recovery of volitional control after SCI (simplified depiction).
This cartoon illustrates some of the proposed targets and mechanisms of neuromodulation of the spinal cord, as discussed in the body of the present review.
Physiologically (A), a plethora of propriospinal 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 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 actition 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.

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 (Fig. 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 (8) 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 et al., 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 et al., 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., 2016a). 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.

Acknowledgments

We are indebted to Prof Allen Selverston for his highly constructive criticism of an early version of this review. GT is also grateful to Dr. Elisa Ius for her excellent assistance in preparing the manuscript.

GT is supported by funding from the European Union’s Horizon 2020 research and innovation program under the Marie Sklodowska-Curie (grant agreement No 661452). This review is funded in part by NIH R01EB007615, the Christopher & Dana Reeve Foundation, Broccoli Foundation, WalkAbout Foundation and Russian Foundation for Fundamental Research (Grant No. 16-29-08173-ofi-m).

References

Acton, D., Miles, G.B., 2015. Stimulation of glia reveals modulation of mammalian spinal motor networks by adenosine. PLoS One 10, e0134488.
Alexander, S.P., Davenport, A.P., Kelly, E., Marrion, N., Peters, J.A., Benson, H.E., Faccenda, E., Pawson, A.J., Sharman, J.L., Southan, C., Davies, J.A., 2015. CGTP Collaborators C. The Concise Guide to Pharmacology 2015/16: G protein-coupled receptors. Br. J. Pharmacol. 172, 5744–5869.
Alford, S., Schwartz, E., Viana di Prisco, G., 2003. The pharmacology of vertebrate spinal central pattern generators. Neuroscientist 9, 217–228.
Alluin, O., Delivet-Mongrain, H., Rossignol, S., 2015. Inducing hindlimb locomotor recovery in adult rat after complete thoracic spinal cord section using repeated treadmill training with perineal stimulation only. J. Neurophysiol. 114, 1931–1946.
Angeli, C.A., Edgerton, V.R., Gerasimenko, Y.P., Harkema, S.J., 2014. Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans. Brain 137, 1394–1409.
Asensio-Pinilla, E., Udina, E., Jaramillo, J., Navarro, X., 2009. Electrical stimulation combined with exercise increase axonal regeneration after peripheral nerve injury. Exp. Neurol. 219, 258–265.
Atsuta, Y., Garcia-Rill, E., Skinner, R.D., 1990. Characteristics of electrically induced locomotion in rat in vitro brain stem-spinal cord preparation. J. Neurophysiol. 64, 727–735.
Awatramani, G.B., Price, G.D., Trussell, L.O., 2005. Modulation of transmitter release by presynaptic resting potential and background calcium levels. Neuron 48, 109–121.
Bareyre, F.M., Kerschensteiner, M., Raineteau, O., Mettenleiter, T.C., Weinmann, O., Schwab, M.E., 2004. The injured spinal cord spontaneously forms a new intraspinal circuit in adult rats. Nat. Neurosci. 7, 269–277.
Barker, A.T., Jalinous, R., Freeston, I.L., 1985. Non-invasive magnetic stimulation of human motor cortex. Lancet 1, 1106–1107.
Baumann, S.B., Wozny, D.R., Kelly, S.K., Meno, F.M., 1997. The electrical conductivity of human cerebrospinal fluid at body temperature. IEEE Trans. Biomed. Eng. 44, 220–223.
Bayev, K.V., Kostyuk, P.G., 1981. Primary afferent depolarization evoked by the activity of spinal scratching generator. Neuroscience 6, 205–215.
Beliez, L., Barrière, G., Bertrand, S.S., Cazalets, J.R., 2015. Origin of thoracic spinal network activity during locomotor-like activity in the neonatal rat. J. Neurosci. 35, 6117–6130.
Benayoun, M., Cowan, J.D., van Drongelen, W., Wallace, E., 2010. Avalanches in a stochastic model of spiking neurons. PLoS Comput. Biol. 6, e1000846.
Berg, R.W., Alaburda, A., Hounsgaard, J., 2007. Balanced inhibition and excitation drive spike activity in spinal half-centers. Science 315, 390–393.
Berg, E.M., Hooper, S.L., Schmidt, J., Büschges, A., 2015. A leg-local neural mechanism mediates the decision to search in stick insects. Curr. Biol. 25, 2012–2017.
Bergquist, A.J., Clair, J.M., Lagerquist, O., Mang, C.S., Okuma, Y., Collins, D.F., 2011. Neuromuscular electrical stimulation: implications of the electrically evoked sensory volley. Eur. J. Appl. Physiol. 111, 2409–2426.
Berzhanskaya, J., Chernyy, N., Gluckman, B.J., Schiff, S.J., Ascoli, G.A., 2013. Modulation of hippocampal rhythms by subthreshold electric fields and network topology. J. Comput. Neurosci. 34, 369–389.

Boulenguez, P., Liabeuf, S., Bos, R., Bras, H., Jean-Xavier, C., Brocard, C., Stil, A., Darbon, P., Cattaert, D., Delpire, E., Marsala, M., Vinay, L., 2010. Down-regulation of the potassium-chloride cotransporter KCC2 contributes to spasticity after spinal cord injury. Nat. Med. 16, 302–307.
Bracci, E., Beato, M., Nistri, A., 1998. Extracellular K+ induces locomotor-like patterns in the rat spinal cord in vitro: comparison with NMDA or 5-HT induced activity. J. Neurophysiol. 79, 2643–2652.
Brockett, E.G., Seenan, P.G., Bannatyne, B.A., Maxwell, D.J., 2013. Ascending and descending propriospinal pathways between lumbar and cervical segments in the rat: evidence for a substantial ascending excitatory pathway. Neuroscience 240, 83–97.
Bui, T.V., Brownstone, R.M., 2015. Sensory-evoked perturbations of locomotor activity by sparse sensory input: a computational study. J. Neurophysiol. 113, 2824–2839.
Bunday, K.L., Perez, M.A., 2012. Motor recovery after spinal cord injury enhanced by strengthening corticospinal synaptic transmission. Curr. Biol. 22, 2355–2361.
Burrows, M., Siegler, M.V., 1978. Graded synaptic transmission between local interneurones and motor neurons in the metathoracic ganglion of the locust. J. Physiol. 285, 231–255.
Burrows, M., 1980. The control of sets of motoneurones by local interneurones in the locust. J. Physiol. 298, 213–233.
Butt, S.J., Kiehn, O., 2003. Functional identification of interneurons responsible for left-right coordination of hindlimbs in mammals. Neuron 38, 953–963.
Caciagli, F., Ciccarelli, R., Di Iorio, P., Ballerini, P., Tacconelli, L., 1988. Cultures of glial cells release purines under field electrical stimulation: the possible ionic mechanisms. Pharmacol. Res. Commun. 20, 935–947.
Calancie, B., Alexeeva, N., Broton, J.G., Suys, S., Hall, A., Klose, K.J., 1999. Distribution and latency of muscle responses to transcranial magnetic stimulation of motor cortex after spinal cord injury in humans. J. Neurotrauma 16, 49–67.
Calancie, B., Molano, M.R., Broton, J.G., 2002. Interlimb reflexes and synaptic plasticity become evident months after human spinal cord injury. Brain 125, 1150–1161.
Calancie, B., 1991. Interlimb reflexes following cervical spinal cord injury in man. Exp. Brain Res. 85, 458–469.
Capogrosso, M., Wenger, N., Raspopovic, S., Musienko, P., Beauparlant, J., Bassi Luciani, L., Courtine, G., Micera, S., 2013. 2013 A computational model for epidural electrical stimulation of spinal sensorimotor circuits. J. Neurosci. 33, 19326–19340.
Caporale, N., Dan, Y., 2008. Spike timing-dependent plasticity: a Hebbian learning rule. Annu. Rev. Neurosci. 31, 25–46.
Carmignoto, G., Haydon, P.G., 2012. Astrocyte calcium signaling and epilepsy. Glia 60, 1227–1233.
Castro, J.B., Urban, N.N., 2009. Subthreshold glutamate release from mitral cell dendrites. J. Neurosci. 29, 7023–7030.
Cazalets, J.R., Sqalli-Houssaini, Y., Clarac, F., 1992. Activation of the central pattern generators for locomotion by serotonin and excitatory amino acids in neonatal rat. J. Physiol. 455, 187–204.
Cazalets, J.R., Borde, M., Clarac, F., 1995. Localization and organization of the central pattern generator for hindlimb locomotion in newborn rat. J. Neurosci. 15, 4943–4951.
Cazalets, J.R., 2005. Metachronal propagation of motoneurone burst activation in isolated spinal cord of newborn rat. J. Physiol. 568, 583–597.
Charpak, S., Mertz, J., Beaurepaire, E., Moreaux, L., Delaney, K., 2001. Odor-evoked calcium signals in dendrites of rat mitral cells. Proc. Natl. Acad. Sci. U. S. A. 98, 1230–1234.
Chen, Y., Dubé, C.M., Rice, C.J., Baram, T.Z., 2008. Rapid loss of dendritic spines after stress involves derangement of spine dynamics by corticotropin-releasing hormone. J. Neurosci. 28, 2903–2911.
Chokroverty, S., Walters, A., Zimmerman, T., Picone, M., 1992. Propriospinal myoclonus: a neurophysiologic analysis. Neurology 42, 1591–1595.
Chung, K., Coggeshall, R.E., 1988. Propriospinal fibers in the white matter of the cat sacral spinal cord. J. Comp. Neurol. 269, 612–617.
Chung, K., Kevetter, G.A., Willis, W.D., Coggeshall, R.E., 1984. An estimate of the ratio of propriospinal to long tract neurons in the sacral spinal cord of the rat. Neurosci. Lett. 44, 173–177.
Chung, K., Langford, L.A., Coggeshall, R.E., 1987. Primary afferent and propriospinal fibers in the rat dorsal and dorsolateral funiculi. J. Comp. Neurol. 263, 68–75.
Coburn, B., 1985. A theoretical study of epidural electrical stimulation of the spinal cord—Part II: effects on long myelinated fibers. IEEE Trans. Biomed. Eng. 32, 978–986.
Conta, A.C., Stelzner, D.J., 2004. Differential vulnerability of propriospinal tract neurons to spinal cord contusion injury. J. Comp. Neurol. 479, 347–359.
Conti, F., DeBiasi, S., Minelli, A., Rothstein, J.D., Melone, M., 1998. EAAC1, a high-affinity glutamate tranporter, is localized to astrocytes and gabaergic neurons besides pyramidal cells in the rat cerebral cortex. Cereb. Cortex 8, 108–116.
Courtine, G., Song, B., Roy, R.R., Zhong, H., Herrmann, J.E., Ao, Y., Qi, J., Edgerton, V.R., Sofroniew, M.V., 2008. Recovery of supraspinal control of stepping via indirect propriospinal relay connections after spinal cord injury. Nat. Med. 14, 69–74.
Cowley, K.C., Schmidt, B.J., 1997. Regional distribution of the locomotor pattern-generating network in the neonatal rat spinal cord. J. Neurophysiol. 77, 247–259.
Cowley, K.C., Zaporozhets, E., Schmidt, B.J., 2010. Propriospinal transmission of the locomotor command signal in the neonatal rat. Ann. N. Y. Acad. Sci. 1198, 42–53.
Cowley, K.C., MacNeil, B.J., Chopek, J.W., Sutherland, S., Schmidt, B.J., 2015. Neurochemical excitation of thoracic propriospinal neurons improves hindlimb stepping in adult rats with spinal cord lesions. Exp. Neurol. 264, 174–187.
Crone, S.A., Quinlan, K.A., Zagoraiou, L., Droho, S., Restrepo, C.E., Lundfald, L., Endo, T., Setlak, J., Jessell, T.M., Kiehn, O., Sharma, K., 2008. Genetic ablation of V2a ipsilateral interneurons disrupts left-right locomotor coordination in mammalian spinal cord. Neuron 60, 70–83.
Croom, J.E., Foreman, R.D., Chandler, M.J., Barron, K.W., 1997. Cutaneous vasodilation during dorsal column stimulation is mediated by dorsal roots and CGRP. Am. J. Physiol. 272, H950–H957.
Cuellar, C.A., Tapia, J.A., Juárez, V., Quevedo, J., Linares, P., Martínez, L., Manjarrez, E., 2009. Propagation of sinusoidal electrical waves along the spinal cord during a fictive motor task. J. Neurosci. 29, 798–810.
Dale, N., Gilday, D., 1996. Regulation of rhythmic movements by purinergic neurotransmitters in frog embryos. Nature 383, 259–263.
Dan, Y., Poo, M.M., 2004. Spike timing-dependent plasticity of neural circuits. Neuron 44, 23–30.
Danner, S.M., Hofstoetter, U.S., Ladenbauer, J., Rattay, F., Minassian, K., 2011. Can the human lumbar posterior columns be stimulated by transcutaneous spinal cord stimulation? A modeling study. Artif. Organs 35, 257–262.
Darbon, P., Yvon, C., Legrand, J.C., Streit, J., 2004. INaP underlies intrinsic spiking and rhythm generation in networks of cultured rat spinal cord neurons. Eur. J. Neurosci. 20, 976–988.
de Leon, R.D., Hodgson, J.A., Roy, R.R., Edgerton, V.R., 1998a. Locomotor capacity attributable to step training versus spontaneous recovery after spinalization in adult cats. J. Neurophysiol. 79, 1329–1340.
de Leon, R.D., Hodgsonm, J.A., Roy, R.R., Edgerton, V.R., 1998b. Full weight-bearing hindlimb standing following stand training in the adult spinal cat. J. Neurophysiol. 80, 83–91.
de Leon, R.D., Tamaki, H., Hodgson, J.A., Roy, R.R., Edgerton, V.R., 1999. Hindlimb locomotor and postural training modulates glycinergic inhibition in the spinal cord of the adult spinal cat. J. Neurophysiol. 82, 359–369.
DiCaprio, R.A., 2004. Information transfer rate of nonspiking afferent neurons in the crab. J. Neurophysiol. 92, 302–310.
Dickinson, P.S., Nagy, F., Moulins, M., 1981. Interganglionic communication by spiking and nonspiking fibers in same neuron. J. Neurophysiol. 45, 1125–1138.
Dietz, V., Fouad, K., Bastiaanse, C.M., 2001. Neuronal coordination of arm and leg movements during human locomotion. Eur. J. Neurosci. 14, 1906–1914.
Dimitrijevic, M.R., Faganel, J., Lehmkuhl, D., Sherwood, A., 1983. Motor control in man after partial or complete spinal cord injury. Adv. Neurol. 39, 915–926.
Dimitrijevic, M.R., Dimitrijevic, M.M., Faganel, J., Sherwood, A.M., 1984. Suprasegmentally induced motor unit activity in paralyzed muscles of patients with established spinal cord injury. Ann. Neurol. 16, 216–221.
Dooley, D.M., Sharkey, J., Keller, W., Kasprak, M., 1978. Treatment of demyelinating and degenerative diseases by electro stimulation of the spinal cord. Med. Prog. Technol. 6, 1–14.
Dose, F., Taccola, G., 2016. Two distinct stimulus frequencies delivered simultaneously at low intensity generate robust locomotor patterns. Neuromodulation 19, 563–575.
Dose, F., Menosso, R., Taccola, G., 2013. Rat locomotor spinal circuits in vitro are activated by electrical stimulation with noisy waveforms sampled from human gait. Physiol. Rep. 1, e00025.
Dose, F., Deumens, R., Forget, P., Taccola, G., 2016. Staggered multi-site low-frequency electrostimulation effectively induces locomotor patterns in the isolated rat spinal cord. Spinal Cord 54, 93–101.
Douglas, J.R., Noga, B.R., Dai, X., Jordan, L.M., 1993. The effects of intrathecal administration of excitatory amino acid agonists and antagonists on the initiation of locomotion in the adult cat. J. Neurosci. 13, 990–1000.
Dudel, J., 1984. Control of quantal transmitter release at frog's motor nerve terminals. II. Modulation by de- or hyperpolarizing pulses. Pflugers Arch. 402, 235–243.
Duru, P.O., Tillakaratne, N.J., Kim, J.A., Zhong, H., Stauber, S.M., Pham, T.T., Xiao, M.S., Edgerton, V.R., Roy, R.R., 2015. Spinal neuronal activation during locomotor-like activity enabled by epidural stimulation and 5-hydroxytryptamine agonists in spinal rats. J. Neurosci. Res. 93, 1229–1239.
Eblen-Zajjur, A.A., Sandkühler, J., 1997. Synchronicity of nociceptive and non-nociceptive adjacent neurons in the spinal dorsal horn of the rat: stimulus-induced plasticity. Neuroscience 76, 39–54.
Eccles, J.C., Kostyuk, P.G., Schmidt, R.F., 1962. The effect of electric polarization of the spinal cord on central afferent fibres and on their excitatory synaptic action. J. Physiol. 162, 138–150.
Edgerton, V.R., de Guzman, C.P., Gregor, R.J., Roy, R.R., Hodgson, J.A., Lovely, R.G., 1991. Trainability of the spinal cord to generate hindlimb stepping patterns in adult spinalized cats. In: Shimamura, M., Grillner, S., Edgerton, V.R. (Eds.), Neurobiological Basis of Human Locomotion. Japan Scientific Societies Press.
Edgerton, V.R., de Leon, R.D., Harkema, S.J., Hodgson, J.A., London, N., Reinkensmeyer, D.J., Roy, R.R., Talmadge, R.J., Tillakaratne, N.J., Timoszyk, W., Tobin, A., 2001. Retraining the injured spinal cord. J. Physiol. 533, 15–22.
Edgerton, V.R., Tillakaratne, N.J., Bigbee, A.J., de Leon, R.D., Roy, R.R., 2004. Plasticity of the spinal neural circuitry after injury. Annu. Rev. Neurosci. 27, 145–167.
ElBasiouny, S.M., Schuster, J.E., Heckman, C.J., 2010. Persistent inward currents in spinal motoneurons: important for normal function but potentially harmful after spinal cord injury and in amyotrophic lateral sclerosis. Clin. Neurophysiol. 121, 1669–1679.
Etlin, A., Blivis, D., Ben-Zwi, M., Lev-Tov, A., 2010. Long and short multifunicular projections of sacral eurons are activated by sensory input to produce locomotor activity in the absence of supraspinal control. J. Neurosci. 30, 10324–10336.

Faganel, J., Dimitrijevic, M.R., 1982. Study of propriospinal interneuron system in man. Cutaneous exteroceptive conditioning of stretch reflexes. J. Neurol. Sci. 56, 155–172.
Fawcett, J.W., Curt, A., Steeves, J.D., Coleman, W.P., Tuszynski, M.H., Lammertse, D., Bartlett, P.F., Blight, A.R., Dietz, V., Ditunno, J., Dobkin, B.H., Havton, L.A., Ellaway, P.H., Fehlings, M.G., Privat, A., Grossman, R., Guest, J.D., Kleitman, N., Nakamura, M., Gaviria, M., Short, D., 2007. Guidelines for the conduct of clinical trials for spinal cord injury as developed by the ICCP panel: spontaneous recovery after spinal cord injury and statistical power needed for therapeutic clinical trials. Spinal Cord 45, 190–205.
Fedirchuk, B., Nielsen, J., Petersen, N., Hultborn, H., 1998. Pharmacologically evoked fictive motor patterns in the acutely spinalized marmoset monkey (Callithrix jacchus). Exp. Brain. Res. 122, 351–361.
Fellin, T., 2009. Communication between neurons and astrocytes: relevance to the modulation of synaptic and network activity. J. Neurochem. 108, 533–544.
Filli, L., Engmann, A.K., Zörner, B., Weinmann, O., Moraitis, T., Gullo, M., Kasper, H., Schneider, R., Schwab, M.E., 2014. Bridging the gap: a reticulo-propriospinal detour bypassing an incomplete spinal cord injury. J. Neurosci. 34, 13399–13410.
Fisher, C.G., Noonan, V.K., Smith, D.E., Wing, P.C., Dvorak, M.F., Kwon, B.K., 2005. Motor recovery, functional status, and health-related quality of life in patients with complete spinal cord injuries. Spine (Phila Pa 1976) 30, 2200–2207.
Fleischer, W., Theiss, S., Slotta, J., Holland, C., Schnitzler, A., 2015. High-frequency voltage oscillations in cultured astrocytes. Physiol. Rep. 3, e12400.
Flynn, J.R., Graham, B.A., Galea, M.P., Callister, R.J., 2011. The role of propriospinal interneurons in recovery from spinal cord injury. Neuropharmacology 60, 809–822.
Fong, A.J., Cai, L.L., Otoshi, C.K., Reinkensmeyer, D.J., Burdick, J.W., Roy, R.R., Edgerton, V.R., 2005. Spinal cord-transected mice learn to step in response to quipazine treatment and robotic training. J. Neurosci. 747.
Fouad, K., Rank, M.M., Vavrek, R., Murray, K.C., Sanelli, L., Bennett, D.J., 2010. Locomotion after spinal cord injury depends on constitutive activity in serotonin receptors. J. Neurophysiol. 104, 2975–2984.
Francis, J.T., Gluckman, B.J., Schiff, S.J., 2003. Sensitivity of neurons to weak electric fields. J. Neurosci. 23, 7255–7261.
Franck, J., Brodin, E., Fried, G., 1993. Differential release of endogenous 5-hydroxytryptamine, substance P, and neurokinin A from rat ventral spinal cord in response to electrical stimulation. J. Neurochem. 61, 704–711.
Friedman, E.J., Landsberg, A.S., 2013. Hierarchical networks, power laws, and neuronal avalanches. Chaos 23, 013135.
Fung, J., Stewart, J.E., Barbeau, H., 1990. The combined effects of clonidine and cyproheptadine with interactive training on the modulation of locomotion in spinal cord injured subjects. J. Neurol. Sci. 100, 85–93.
Gad, P., Lavrov, I., Shah, P., Zhong, H., Roy, R.R., Edgerton, V.R., Gerasimenko, Y., 2013a. Neuromodulation of motor-evoked potentials during stepping in spinal rats. J. Neurophysiol. 110, 1311–1322.
Gad, P., Choe, J., Shah, P., Garcia-Alias, G., Rath, M., Gerasimenko, Y., Zhong, H., Roy, R. R., Edgerton, V.R., 2013b. Sub-threshold spinal cord stimulation facilitates spontaneous motor activity in spinal rats. J. Neuroeng. Rehabil. 10, 108.
Gad, P., Roy, R.R., Choe, J., Creagmile, J., Zhong, H., Gerasimenko, Y., Edgerton, V.R., 2015. Electrophysiological biomarkers of neuromodulatory strategies to recover motor function after spinal cord injury. J. Neurophysiol. 113, 3386–3396.
Ganguly, K., Kiss, L., Poo, M., 2000. Enhancement of presynaptic neuronal excitability by correlated presynaptic and postsynaptic spiking. Nat. Neurosci. 3, 1018–1026.
Gary, D.S., Malone, M., Capestany, P., Houdayer, T., McDonald, J.W., 2012. Electrical stimulation promotes the survival of oligodendrocytes in mixed cortical cultures. J. Neurosci. Res. 90, 72–83.
Gerasimenko, Y.P., Lavrov, I.A., Courtine, G., Ichiyama, R.M., Dy, C.J., Zhong, H., Roy, R. R., Edgerton, V.R., 2006. Spinal cord reflexes induced by epidural spinal cord stimulation in normal awake rats. J. Neurosci. Methods 157, 253–263.
Gerasimenko, Y.P., Ichiyama, R.M., Lavrov, I.A., Courtine, G., Cai, L., Zhong, H., Roy, R. R., Edgerton, V.R., 2007. Epidural spinal cord stimulation plus quipazine administration enable stepping in complete spinal adult rats. J. Neurophysiol. 98, 2525–2536.
Gerasimenko, Y., Musienko, P., Bogacheva, I., Moshonkina, T., Savochin, A., Lavrov, I., Roy, R.R., Edgerton, V.R., 2009. Propriospinal bypass of the serotonergic system that can facilitate stepping. J. Neurosci. 29, 5681–5689.
Gerasimenko, Y., Gorodnichev, R., Machueva, E., Pivovarova, E., Semyenov, D., Savochin, A., Roy, R.R., Edgerton, V.R., 2010. Novel and direct access to the human locomotor spinal circuitry. J. Neurosci. 30, 3700–3708.
Gerasimenko, Y.P., Lu, D.C., Modaber, M., Zdunowski, S., Gad, P., Sayenko, D.G., Morikawa, E., Haakana, P., Ferguson, A.R., Roy, R.R., Edgerton, V.R., 2015. Noninvasive reactivation of motor descending control after paralysis. J. Neurotrauma 32, 1968–1980.
Gerasimenko, Y., Gad, P., Sayenko, D., McKinney, Z., Gorodnichev, R., Puhov, A., Moshonkina, T., Savochin, A., Selionov, V., Shigueva, T., Tomilovskaya, E., Kozlovskaya, I., Edgerton, V.R., 2016a. Integration of sensory, spinal, and volitional descending inputs in regulation of human locomotion. J. Neurophysiol. 116, 98–105.
Gerasimenko, Y., Sayenko, D., Gad, P., Liu, C.T., Tillakaratne, N.J., Roy, R.R., Kozlovskaya, I., Edgerton, V.R., 2016b. Feed-forwardness of spinal networks in posture and locomotion. Neuroscientist 2017 (23), 441–453.
Gosgnach, S., Lanuza, G.M., Butt, S.J., Saueressig, H., Zhang, Y., Velasquez, T., Riethmacher, D., Callaway, E.M., Kiehn, O., Goulding, M., 2006. V1 spinal neurons regulate the speed of vertebrate locomotor outputs. Nature 440, 215–219.
Grahn, P.J., Lavrov, I.A., Sayenko, D.G., Van Straaten, M.G., Gill, M.L., Strommen, J.A., Calvert, J.S., Drubach, D.I., Beck, L.A., Linde, M.B., Thoreson, A.R., Lopez, C., Mendez, A.A., Gad, P.N., Gerasimenko, Y.P., Edgerton, V.R., Zhao, K.D., Lee, K.H., 2017. Enabling task-specific volitional motor functions via spinal cord neuromodulation in a human with paraplegia. Mayo Clin. Proc. 92, 544–554.
Graubard, K., Raper, J.A., Hartline, D.K., 1980. Graded synaptic transmission between spiking neurons. Proc. Natl. Acad. Sci. U. S. A. 77, 3733–3735.
Grillner, S., Rossignol, S., 1978. On the initiation of the swing phase of locomotion in chronic spinal cats. Brain Res. 146, 269–277.
Grillner, S., Zangger, P., 1975. How detailed is the central pattern generation for locomotion? Brain Res. 88, 367–371.
Grillner, S., 2006. Biological pattern generation: the cellular and computational logic of networks in motion. Neuron 52, 751–766.
Gybels, J., van Roost, D., 1985. Spinal cord stimulation for the modification of dystonic and hyperkinetic conditions: a critical review. In: Eccles, J., Dimitrijevic Karger, M.R. (Eds.), Recent achievements in restorative neurology. Vol. 1. Upper motor neuron functions and dysfunctions. Karger, Basel, pp. 58–70.
Haghighi, S.S., York, D.H., Gaines, R.W., Oro, J.J., 1994. Monitoring of motor tracts with spinal cord stimulation. Spine (Phila Pa 1976) 19, 1518–1524.
Hallett, M., 2000. Transcranial magnetic stimulation and the human brain. Nature 406, 147–150.
Hallett, M., 2007. Transcranial magnetic stimulation: a primer. Neuron 55, 187–199.
Harkema, S.J., Hurley, S.L., Patel, U.K., Requejo, P.S., Dobkin, B.H., Edgerton, V.R., 1997. Human lumbosacral spinal cord interprets loading during stepping. J. Neurophysiol. 77, 797–811.
Harkema, S., Gerasimenko, Y., Hodes, J., Burdick, J., Angeli, C., Chen, Y., Ferreira, C., Willhite, A., Rejc, E., Grossman, R.G., Edgerton, V.R., 2011. Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: a case study. Lancet 377, 1938–1947.
Hartveit, E., 1999. Reciprocal synaptic interactions between rod bipolar cells and amacrine cells in the rat retina. J. Neurophysiol. 81, 2923–2936.
Hentall, I.D., Pinzon, A., Noga, B.R., 2006. Spatial and temporal patterns of serotonin release in the rat's lumbar spinal cord following electrical stimulation of the nucleus raphe magnus. Neuroscience 142, 893–903.
Hofstoetter, U.S., McKay, W.B., Tansey, K.E., Mayr, W., Kern, H., Minassian, K., 2014. Modification of spasticity by transcutaneous spinal cord stimulation in individuals with incomplete spinal cord injury. J. Spinal Cord Med. 37, 202–211.
Holsheimer, J., Wesselink, W.A., 1997. Optimum electrode geometry for spinal cord stimulation: the narrow bipole and tripole. Med. Biol. Eng. Comput. 35, 493–497.
Holsheimer, J., 2002. Which neuronal elements are activated directly by spinal cord stimulation. Neuromodulation 5, 25–31.
Hoppenstein, R., 1975. Electrical stimulation of the ventral and dorsal columns of the spinal cord for relief of chronic intractable pain: preliminary report. Surg. Neurol. 4, 187–194.
Houssaini, Y.S., Cazalets, J.R., Martini, F., Clarac, F., 1993. Induction of fictive locomotion by sulphur-containing amino acids in an in vitro newborn rat preparation. Eur. J. Neurosci. 5, 1226–1232.
Huang, H., Trussell, L.O., 2011. KCNQ5 channels control resting properties and release probability of a synapse. Nat. Neurosci. 14, 840–847.
Huang, A., Noga, B.R., Carr, P.A., Fedirchuk, B., Jordan, L.M., 2000. Spinal cholinergic neurons activated during locomotion: localization and electrophysiological characterization. J. Neurophysiol. 83, 3537–3547.
Hultborn, H., Conway, B.A., Gossard, J.P., Brownstone, R., Fedirchuk, B., Schomburg, E.D., Enríquez-Denton, M., Perreault, M.C., 1998. How do we approach the locomotor network in the mammalian spinal cord? Ann. N. Y. Acad. Sci. 860, 70–82.
Hunter, J.P., Ashby, P., 1994. Segmental effects of epidural spinal cord stimulation in humans. J. Physiol. 474, 407–419.
Husch, A., Dietz, S.B., Hong, D.N., Harris-Warrick, R.M., 2015. Adult spinal V2a interneurons show increased excitability and serotonin-dependent bistability. J. Neurophysiol. 113, 1124–1134.
Ichiyama, R.M., Gerasimenko, Y.P., Zhong, H., Roy, R.R., Edgerton, V.R., 2005. Hindlimb stepping movements in complete spinal rats induced by epidural spinal cord stimulation. Neurosci. Lett. 383, 339–344.
Ichiyama, R.M., Gerasimenko, Y., Jindrich, D.L., Zhong, H., Roy, R.R., Edgerton, V.R., 2008. Dose dependence of the 5-HT agonist quipazine in facilitating spinal stepping in the rat with epidural stimulation. Neurosci. Lett. 438, 281–285.
Ishibashi, T., Dakin, K.A., Stevens, B., Lee, P.R., Kozlov, S.V., Stewart, C.L., Fields, R.D., 2006. Astrocytes promote myelination in response to electrical impulses. Neuron 49, 823–832.
Jacobi, A., Schmalz, A., Bareyre, F.M., 2014. Abundant expression of guidance and synaptogenic molecules in the injured spinal cord. PLoS One 9, e88449.
Jalalvand, E., Robertson, B., Wallén, P., Grillner, S., 2016. Ciliated neurons lining the central canal sense both fluid movement and pH through ASIC3. Nat. Commun. 7, 10002.
Jankowska, E., Lundberg, A., Roberts, W.J., Stuart, D., 1974. A long propriospinal system with direct effect on motoneurones and on interneurones in the cat lumbosacral cord. Exp. Brain Res. 21, 169–194.
Jankowska, E., 2017. Spinal control of motor outputs by intrinsic and externally induced electric field potentials. J. Neurophysiol. 118, 1221–1234.
Jindrich, D.L., Joseph, M.S., Otoshi, C.K., Wei, R.Y., Zhong, H., Roy, R.R., Tillakaratne, N. J., Edgerton, V.R., 2009. Spinal learning in the adult mouse using the Horridge paradigm. J. Neurosci. Methods 182, 250–254.

Jourdain, P., Bergersen, L.H., Bhaukaurally, K., Bezzi, P., Santello, M., Domercq, M., Matute, C., Tonello, F., Gundersen, V., Volterra, A., 2007. Glutamate exocytosis from astrocytes controls synaptic strength. Nat. Neurosci. 10, 331–339.
Juvin, L., Simmers, J., Morin, D., 2005. Propriospinal circuitry underlying interlimb coordination in mammalian quadrupedal locomotion. J. Neurosci. 25, 6025–6035.
Kakulas, B.A., 1984. Pathology of spinal injuries. Cent. Nerv. Syst. Trauma 1, 117–129.
Kakulas, A., 1988. The applied neurobiology of human spinal cord injury: a review. Paraplegia 26, 371–379.
Kakulas, B.A., 1999. A review of the neuropathology of human spinal cord injury with emphasis on special features. J. Spinal Cord Med. 22, 119–124.
Kang, N., Peng, H., Yu, Y., Stanton, P.K., Guilarte, T.R., Kang, J., 2013. Astrocytes release D-serine by a large vesicle. Neuroscience 240, 243–257.
Kanno, T., Kamel, Y., Yokoyama, T., Shoda, M., Tanji, H., Nomura, M., 1989. Effects of dorsal column spinal cord stimulation (DCS) on reversibility of neuronal function–experience of treatment for vegetative states. Pacing Clin. Electrophysiol. 12, 733–738.
Karmarkar, U.R., Buonomano, D.V., 2002. A model of spike-timing dependent plasticity: one or two coincidence detectors? J. Neurophysiol. 88, 507–513.
Katz, B., Miledi, R., 1967. A study of synaptic transmission in the absence of nerve impulses. J. Physiol. 192, 407–436.
Kazennikov, O.V., Shik, M.L., 1988. Propagation of the activity along the stepping strip of the spinal cord in the cat. Neurophysiology 20, 763–769.
Kazennikov, O.V., Shik, M.L., Iakovleva, G.V., 1983a. Responses of neurons of the upper cervical segments of the spinal cord in the cat to stimulation of the locomotor region of the brain stem with different frequencies. Neurophysiology 15, 355–361.
Kazennikov, O.V., Shik, M.L., Iakovleva, G.V., 1983b. Stepping movements caused by stimulation of the cat spinal cord dorsolateral funiculus. Biull. Eksp. Biol. Med. 96, 8–10.
Kazennikov, O., Shik, M., Yakovleva, G., 1985. Synaptic responses of propriospinal neurons to stimulation of the stepping strip of the dorsolateral funiculus in cats. Neurophysiology 17, 195–202.
Kazennikov, O.V., Shik, M.L., Ioffe, M.E., 1990. The origin of the fibers of the dorsal portion of the lateral funiculus of the spinal cord necessary for evoking stepping movements in the cat. Zh Vyssh Nerv Deiat Im I P Pavlova 40, 165–168.
Kendall, F.P., McCreary, E.K., Provance, P.G., 1993. Muscles, testing and function. Md Williams & Wilkins.
Kerchner, G.A., Li, P., Zhuo, M., 1999. Speaking out of turn: a role for silent synapses in pain. IUBMB Life 48, 251–256.
Kiehn, O., Kjaerulff, O., 1996. Spatiotemporal characteristics of 5-HT and dopamine-induced rhythmic hindlimb activity in the in vitro neonatal rat. J. Neurophysiol. 75, 1472–1482.
Kim, W.T., Rioult, M.G., Cornell-Bell, A.H., 1994. Glutamate-induced calcium signaling in astrocytes. Glia 11, 173–184.
King, A.E., Lopez-Garcia, J.A., 1994. Intracellular analysis of cutaneous afferent-induced excitation and inhibition in rat dorsal horn neurones in vitro. J. Neurosci. Methods 52, 61–68.
Kirshblum, S., Millis, S., McKinley, W., Tulsky, D., 2004. Late neurologic recovery after traumatic spinal cord injury. Arch. Phys. Med. Rehabil. 85, 1811–1817.
Kjaerulff, O., Kiehn, O., 1996. Distribution of networks generating and coordinating locomotor activity in the neonatal rat spinal cord in vitro: a lesion study. J. Neurosci. 16, 5777–5794.
Kjaerulff, O., Barajon, I., Kiehn, O., 1994. Sulphorhodamine-labelled cells in the neonatal rat spinal cord following chemically induced locomotor activity in vitro. J. Physiol. 478, 265–273.
Kostyuk, P.G., Vasilenko, D.A., 1978. Propriospinal neurones as a relay system for transmission of cortico-spinal influences. J. Physiol. (Paris) 74, 247–250.
Kremer, E., Lev-Tov, A., 1997. Localization of the spinal network associated with generation of hindlimb locomotion in the neonatal rat and organization of its transverse coupling system. J. Neurophysiol. 77, 1155–1170.
Krutki, P., Mrówczyński, W., 2004. Convergence of forelimb afferent actions on C7-Th1 propriospinal neurones bilaterally projecting to sacral segments of the cat spinal cord. Arch. Ital. Biol. 142, 47–58.
Kuffler, S.W., Nicholls, J.G., 1976. From neuron to brain: a cellular approach to the function of the nervous system. Sinauer Associates, Sunderland, MA.
Kullander, K., Butt, S.J., Lebret, J.M., Lundfald, L., Restrepo, C.E., Rydström, A., Klein, R., Kiehn, O., 2003. Role of EphA4 and EphrinB3 in local neuronal circuits that control walking. Science 299, 1889–1892.
Kwan, A.C., Dietz, S.B., Webb, W.W., Harris-Warrick, R.M., 2009. Activity of Hb9 interneurons during fictive locomotion in mouse spinal cord. J. Neurosci. 29, 11601–11613.
Lanuza, G.M., Gosgnach, S., Pierani, A., Jessell, T.M., Goulding, M., 2004. Genetic identification of spinal interneurons that coordinate left-right locomotor activity necessary for walking movements. Neuron 42, 375–386.
Larremore, D.B., Carpenter, M.Y., Ott, E., Restrepo, J.G., 2012. Statistical properties of avalanches in networks. Phys. Rev. E Stat. Nonlin Soft Matter Phys. 85, 066131.
Levin, B.E., Hubschmann, O.R., 1980. Dorsal column stimulation: Effect on human cerebrospinal fluid and plasma catecholamines. Neurology 30, 65–71.
Levy, W.B., Steward, O., 1983. Temporal contiguity requirements for long-term associative potentiation/depression in the hippocampus. Neuroscience 8, 791–797.
Levy, W.J. Jr., Amassian, V.E., Traad, M., Cadwell, J., 1990. Focal magnetic coil stimulation reveals motor cortical system reorganized in humans after traumatic quadriplegia. Brain Res. 510, 130–134.
Li, W.C., Moult, P.R., 2012. The control of locomotor frequency by excitation and inhibition. J. Neurosci. 32, 6220–6230.
Li, C.Y., Lu, J.T., Wu, C.P., Duan, S.M., Poo, M.M., 2004. Bidirectional modification of presynaptic neuronal excitability accompanying spike timing-dependent synaptic plasticity. Neuron 41, 257–268.
Li, W.C., Cooke, T., Sautois, B., Soffe, S.R., Borisyuk, R., Roberts, A., 2007. Axon and dendrite geography predict the specificity of synaptic connections in a functioning spinal cord network. Neural Dev. 2, 17.
Li, Q., Brus-Ramer, M., Martin, J.H., McDonald, J.W., 2010. Electrical stimulation of the medullary pyramid promotes proliferation and differentiation of oligodendrocyte progenitor cells in the corticospinal tract of the adult rat. Neurosci. Lett. 479, 128–133.
Liang, S.L., Carlson, G.C., Coulter, D.A., 2006. Dynamic regulation of synaptic GABA release by the glutamate-glutamine cycle in hippocampal area CA1. J. Neurosci. 26, 8537–8548.
Linderoth, B., Fedorcsak, I., Meyerson, B.A., 1989. Is vasodilatation following dorsal column stimulation mediated by antidromic activation of small diameter afferents? Acta Neurochir. Suppl. (Wien) 46, 99–101.
Linderoth, B., Gazelius, B., Franck, J., Brodin, E., 1992. Dorsal column stimulation induces release of serotonin and substance P in the cat dorsal horn. Neurosurgery 31, 289–296.
Linderoth, B., Stiller, C.O., Gunasekera, L., O'Connor, W.T., Ungerstedt, U., Brodin, E., 1994. Gamma-aminobutyric acid is released in the dorsal horn by electrical spinal cord stimulation: an in vivo microdialysis study in the rat. Neurosurgery 34, 484–489.
Linderoth, B., Gherardini, G., Ren, B., Lundeberg, T., 1995. Preemptive spinal cord stimulation reduces ischemia in an animal model of vasospasm. Neurosurgery 37, 266–271.
Liu, J.T., Tan, W.C., Liao, W.J., 2008. Effects of electrical cervical spinal cord stimulation on cerebral blood perfusion, cerebrospinal fluid catecholamine levels, and oxidative stress in comatose patients. Acta Neurochir. Suppl. 101, 71–76.
Lovely, R.G., Gregor, R.J., Roy, R.R., Edgerton, V.R., 1986. Effects of training on the recovery of full-weight-bearing stepping in the adult spinal cat. Exp. Neurol. 92, 421–435.
Magariños, A.M., McEwen, B.S., 1995. Stress-induced atrophy of apical dendrites of hippocampal CA3c neurons: comparison of stressors. Neuroscience 69, 83–88.
Magnuson, D.S., Trinder, T.C., 1997. Locomotor rhythm evoked by ventrolateral funiculus stimulation in the neonatal rat spinal cord in vitro. J. Neurophysiol. 77, 200–206.
Malinow, R., Malenka, R.C., 2002. AMPA receptor trafficking and synaptic plasticity. Annu. Rev. Neurosci. 25, 103–126.
Marchetti, C., Nistri, A., 2001. Neuronal bursting induced by NK3 receptor activation in the neonatal rat spinal cord in vitro. J. Neurophysiol. 86, 2939–2950.
Marchetti, C., Beato, M., Nistri, A., 2001. Alternating rhythmic activity induced by dorsal root stimulation in the neonatal rat spinal cord in vitro. J. Physiol. 530, 105–112.
Marino, R.J., Ditunno Jr, J.F., Donovan, W.H., Maynard, F. Jr., 1999. Neurologic recovery after traumatic spinal cord injury: data from the Model Spinal Cord Injury Systems. Arch. Phys. Med. Rehabil. 80, 1391–1396.
Martin, A.R., Ringham, G.L., 1975. Synaptic transfer at a vertebrate central nervous system synapse. J. Physiol. 251, 409–426.
Mazevet, D., Pierrot-Deseilligny, E., 1994. Pattern of descending excitation of presumed propriospinal neurones at the onset of voluntary movement in humans. Acta Physiol. Scand. 150, 27–38.
Mellor, J., Nicoll, R.A., Schmitz, D., 2002. Mediation of hippocampal mossy fiber long-term potentiation by presynaptic Ih channels. Science 295, 143–147.
Menétrey, D., de Pommery, J., Roudier, F., 1985. Propriospinal fibers reaching the lumbar enlargement in the rat. Neurosci. Lett. 58, 257–261.
Mendelson, M., 1971. Oscillator neurons in crustacean ganglia. Science 171, 1170–1173.
Minassian, K., Hofstoetter, U., Tansey, K., Mayr, W., 2012. Neuromodulation of lower limb motor control in restorative neurology. Clin. Neurol. Neurosurg. 114, 489–497.
Minassian, K., Hofstoetter, U.S., Danner, S.M., Mayr, W., Bruce, J.A., McKay, W.B., Tansey, K.E., 2016. Spinal rhythm generation by step-induced feedback and transcutaneous posterior root stimulation in complete spinal cord-injured individuals. Neurorehabil. Neural Repair 30, 233–243.
Molnar, G., Barolat, G., 2014. Principles of cord activation during spinal cord stimulation. Neuromodulation 17, 12–21.
Mori, S., Shik, M.L., Yagodnitsyn, A.S., 1977. Role of pontine tegmentum for locomotor control in mesencephalic cat. J. Neurophysiol. 40, 284–295.
Mori, S., Nishimura, H., Kurakami, C., Yamamura, T., Aoki, M., 1978. Controlled locomotion in the mesencephalic cat: distribution of facilitatory and inhibitory regions within pontine tegmentum. J. Neurophysiol. 41, 1580–1591.
Mori, S., Sakamoto, T., Ohta, Y., Takakusaki, K., Matsuyama, K., 1989. Site-specific postural and locomotor changes evoked in awake, freely moving intact cats by stimulating the brainstem. Brain Res. 505, 66–74.
Murg, M., Binder, H., Dimitrijevic, M.R., 2000. Epidural electric stimulation of posterior structures of the human lumbar spinal cord: 1. muscle twitches – a functional method to define the site of stimulation. Spinal Cord 38, 394–402.
Murphy, B.K., Miller, K.D., 2009. Balanced amplification: a new mechanism of selective amplification of neural activity patterns. Neuron 61, 635–648.
Musienko, P., van den Brand, R., Märzendorfer, O., Roy, R.R., Gerasimenko, Y., Edgerton, V.R., Courtine, G., 2011. Controlling specific locomotor behaviors

through multidimensional monoaminergic modulation of spinal circuitries. J. Neurosci. 31, 9264–9278.
Musienko, P., Courtine, G., Tibbs, J.E., Kilimnik, V., Savochin, A., Garfinkel, A., Roy, R. R., Edgerton, V.R., Gerasimenko, Y., 2012a. Somatosensory control of balance during locomotion in decerebrated cat. J. Neurophysiol. 107, 2072–2082.
Musienko, P.E., Zelenin, P.V., Lyalka, V.F., Gerasimenko, Y.P., Orlovsky, G.N., Deliagina, T.G., 2012b. Spinal and supraspinal control of the direction of stepping during locomotion. J. Neurosci. 32, 17442–17453.
Nanou, E., Alpert, M.H., Alford, S., El Manira, A., 2013. Differential regulation of synaptic transmission by pre- and postsynaptic SK channels in the spinal locomotor network. J. Neurophysiol. 109, 3051–3059.
Nashmi, R., Fehlings, M.G., 2001. Changes in axonal physiology and morphology after chronic compressive injury of the rat thoracic spinal cord. Neuroscience 104, 235–251.
Newman, E.A., Zahs, K.R., 1997. Calcium waves in retinal glial cells. Science 275, 844–847.
Noga, B.R., Fortier, P.A., Kriellaars, D.J., Dai, X., Detillieux, G.R., Jordan, L.M., 1995. Field potential mapping of neurons in the lumbar spinal cord activated following stimulation of the mesencephalic locomotor region. J. Neurosci. 15, 2203–2217.
Norman, K.E., Pépin, A., Barbeau, H., 1998. Effects of drugs on walking after spinal cord injury. Spinal Cord 36, 699–715.
Oliet, S.H., Piet, R., Poulain, D.A., 2001. Control of glutamate clearance and synaptic efficacy by glial coverage of neurons. Science 292, 923–926.
Oni-Orisan, A., Kaushal, M., Li, W., Leschke, J., Ward, B.D., Vedantam, A., Kalinosky, B., Budde, M.D., Schmit, B.D., Li, S.J., Muqeet, V., Kurpad, S.N., 2016. Alterations in cortical sensorimotor connectivity following complete cervical spinal cord injury: a prospective resting-state fMRI study. PLoS One 11 (3), e0150351.
Orlovskiĭ, G.N., Severin, F.V., Shik, M.L., 1966. Locomotion induced by stimulation of the mesencephalon. Dokl Akad Nauk SSSR 169, 1223–1226.
Ozen, S., Sirota, A., Belluscio, M.A., Anastassiou, C.A., Stark, E., Koch, C., Buzsáki, G., 2010. Transcranial electric stimulation entrains cortical neuronal populations in rats. J. Neurosci. 30, 11476–11485.
Pan, Z.H., Hu, H.J., Perring, P., Andrade, R., 2001. T-type Ca(2+) channels mediate neurotransmitter release in retinal bipolar cells. Neuron 32, 89–98.
Panatier, A., Vallée, J., Haber, M., Murai, K.K., Lacaille, J.C., Robitaille, R., 2011. Astrocytes are endogenous regulators of basal transmission at central synapses. Cell 146, 785–798.
Pascual, O., Casper, K.B., Kubera, C., Zhang, J., Revilla-Sanchez, R., Sul, J.Y., Takano, H., Moss, S.J., McCarthy, K., Haydon, P.G., 2005. Astrocytic purinergic signaling coordinates synaptic networks. Science 310, 113–116.
Pearson, K.G., Fourtner, C.R., 1975. Nonspiking interneurons in walking system of the cockroach. J. Neurophysiol. 38, 33–52.
Pearson, K.G., Rossignol, S., 1991. Fictive motor patterns in chronic spinal cats. J. Neurophysiol. 66, 1874–1887.
Penn, Y., Segal, M., Moses, E., 2016. Network synchronization in hippocampal neurons. Proc. Natl. Acad. Sci. U. S. A. 113, 3341–3346.
Petruska, J.C., Ichiyama, R.M., Jindrich, D.L., Crown, E.D., Tansey, K.E., Roy, R.R., Edgerton, V.R., Mendell, L.M., 2007. Changes in motoneuron properties and synaptic inputs related to step training after spinal cord transection in rats. J. Neurosci. 27, 4460–4471.
Pierani, A., Moran-Rivard, L., Sunshine, M.J., Littman, D.R., Goulding, M., Jessell, T.M., 2001. Control of interneuron fate in the developing spinal cord by the progenitor homeodomain protein Dbx1. Neuron 29, 367–384.
Pierrot-Deseilligny, E., Marchand-Pauvert, V., 2002. A cervical propriospinal system in man. Adv. Exp. Med. Biol. 508, 273–279.
Radman, T., Ramos, R.L., Brumberg, J.C., Bikson, M., 2009. Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation in vitro. Brain Stimul. 2, 215–228.
Raiteri, M., 2006. Functional pharmacology in human brain. Pharmacol. Rev. 58, 162–193.
Ranck Jr, J.B., 1975. Which elements are excited in electrical stimulation of mammalian central nervous system: a review. Brain Res. 98, 417–440.
Rattay, F., Minassian, K., Dimitrijevic, M.R., 2000. Epidural electrical stimulation of posterior structures of the human lumbosacral cord: 2. quantitative analysis by computer modeling. Spinal Cord 38, 473–489.
Reed, W.R., Shum-Siu, A., Whelan, A., Onifer, S.M., Magnuson, D.S., 2009. Anterograde labeling of ventrolateral funiculus pathways with spinal enlargement connections in the adult rat spinal cord. Brain Res. 1302, 76–84.
Rejc, E., Angeli, C., Harkema, S., 2015. Effects of lumbosacral spinal cord epidural stimulation for standing after chronic complete paralysis in humans. PLoS One 10, e0133998.
Rejc, E., Angeli, C.A., Bryant, N., Harkema, S.J., 2017. Effects of stand and step training with epidural stimulation on motor function for standing in chronic complete paraplegics. J. Neurotrauma 34, 1787–1802.
Roche, N., Lackmy, A., Achache, V., Bussel, B., Katz, R., 2012. Effects of anodal tDCS on lumbar propriospinal system in healthy subjects. Clin. Neurophysiol. 123, 1027–1034.
Rossignol, S., Giroux, N., Chau, C., Marcoux, J., Brustein, E., Reader, T.A., 2001. Pharmacological aids to locomotor training after spinal injury in the cat. J. Physiol. 533, 65–74.
Rovainen, C.M., 1985. Effects of groups of propriospinal interneurons on fictive swimming in the isolated spinal cord of the lamprey. J. Neurophysiol. 54, 959–977.
Roy, F.D., Gibson, G., Stein, R.B., 2012. Effect of percutaneous stimulation at different spinal levels on the activation of sensory and motor roots. Exp. Brain Res. 223, 281–289.
Rybak, I.A., Stecina, K., Shevtsova, N.A., McCrea, D.A., 2006. Modelling spinal circuitry involved in locomotor pattern generation: insights from the effects of afferent stimulation. J. Physiol. 577, 641–658.
Saltiel, P., d'Avella, A., Wyler-Duda, K., Bizzi, E., 2016. Synergy temporal sequences and topography in the spinal cord: evidence for a traveling wave in frog locomotion. Brain Struct. Funct. 221, 3869–3890.
Sayenko, D.G., Alekhina, M.I., Masani, K., Vette, A., Obata, H., Popovic, M., Nakazawa, K., 2010. Positive effect of balance training with visual feedback on standing balance abilities in people with incomplete spinal cord injury. Spinal Cord 48, 886–893.
Sayenko, D.G., Masani, K., Vette, A.H., Alekhina, M.I., Popovic, M.R., Nakazawa, K., 2012. Effects of balance training with visual feedback during mechanically unperturbed standing on postural corrective responses. Gait Posture 35, 339–344.
Sayenko, D.G., Angeli, C., Harkema, S.J., Edgerton, V.R., Gerasimenko, Y.P., 2014. Neuromodulation of evoked muscle potentials induced by epidural spinal-cord stimulation in paralyzed individuals. J. Neurophysiol. 111, 1088–1099.
Sayenko, D.G., Nguyen, R., Hirabayashi, T., Popovic, M.R., Masani, K., 2015. Method to reduce muscle fatigue during transcutaneous neuromuscular electrical stimulation in major knee and ankle muscle groups. Neurorehabil. Neural. Repair 29, 722–733.
Saywell, S.A., Ford, T.W., Meehan, C.F., Todd, A.J., Kirkwood, P.A., 2011. Electrophysiological and morphological characterization of propriospinal interneurons in the thoracic spinal cord. J. Neurophysiol. 105, 806–826.
Selionov, V.A., Ivanenko, Y.P., Solopova, I.A., Gurfinkel, V.S., 2009. Tonic central and sensory stimuli facilitate involuntary air-stepping in humans. J. Neurophysiol. 101, 2847–2858.
Selverston, A.I., Szücs, A., Huerta, R., Pinto, R., Reyes, M., 2009. Neural mechanisms underlying the generation of the lobster gastric mill motor pattern. Front. Neural Circuits 3, 12.
Shah, P.K., Gerasimenko, Y., Shyu, A., Lavrov, I., Zhong, H., Roy, R.R., Edgerton, V.R., 2012. Variability in step training enhances locomotor recovery after a spinal cord injury. Eur. J. Neurosci. 36, 2054–2062.
Shah, P.K., Garcia-Alias, G., Choe, J., Gad, P., Gerasimenko, Y., Tillakaratne, N., Zhong, H., Roy, R.R., Edgerton, V.R., 2013. Use of quadrupedal step training to re-engage spinal interneuronal networks and improve locomotor function after spinal cord injury. Brain 136, 3362–3377.
Shah, P.K., Sureddi, S., Alam, M., Zhong, H., Roy, R.R., Edgerton, V.R., Gerasimenko, Y., 2016. Unique spatiotemporal neuromodulation of the lumbosacral circuitry shapes locomotor success after spinal cord injury. J. Neurotrauma 33, 1709–1723.
Sharrard, W.J., 1964. The segmental innervation of the lower limb muscles in man. Ann. R. Coll. Surg. Engl. 35, 106–122.
Sherwood, A.M., Dimitrijevic, M.R., McKay, W.B., 1992. Evidence of subclinical brain influence in clinically complete spinal cord injury: discomplete SCI. J. Neurol. Sci. 110, 90–98.
Shevtsova, O., Leitch, B., 2012. Selective loss of AMPA receptor subunits at inhibitory neuron synapses in the cerebellum of the ataxic stargazer mouse. Brain Res. 1427, 54–64.
Shew, W.L., Yang, H., Yu, S., Roy, R., Plenz, D., 2011. Information capacity and transmission are maximized in balanced cortical networks with neuronal avalanches. J. Neurosci. 31, 55–63.
Shik, M., 1997. Recognizing propriospinal and reticulospinal systems of initiation of stepping. Motor Control 1, 310–313.
Shuman, S.L., Bresnahan, J.C., Beattie, M.S., 1997. Apoptosis of microglia and oligodendrocytes after spinal cord contusion in rats. J. Neurosci. Res. 50, 798–808.
Siebert, J.R., Middelton, F.A., Stelzner, D.J., 2010. Intrinsic response of thoracic propriospinal neurons to axotomy. BMC Neurosci. 11, 69.
Simpson Jr., R.K., Robertson, C.S., Goodman, J.C., Halter, J.A., 1991. Recovery of amino acid neurotransmitters from the spinal cord during posterior epidural stimulation: a preliminary study. J. Am. Paraplegia Soc. 14, 3–8.
Sjöström, P.J., Turrigiano, G.G., Nelson, S.B., 2003. Neocortical LTD via coincident activation of presynaptic NMDA and cannabinoid receptors. Neuron 39, 641–654.
Skinner, R.D., Coulter, J.D., Adams, R.J., Remmel, R.S., 1979. 1979Cells of origin of long descending propriospinal fibers connecting the spinal enlargements in cat and monkey determined by horseradish peroxidase and electrophysiological techniques. J. Comp. Neurol. 188, 443–454.
Smarandache-Wellmann, C., Weller, C., Wright Jr., T.M., Mulloney, B., 2013. Five types of nonspiking interneurons in local pattern-generating circuits of the crayfish swimmeret system. J. Neurophysiol. 110, 344–357.
Snellman, J., Mehta, B., Babai, N., Bartoletti, T.M., Akmentin, W., Francis, A., Matthews, G., Thoreson, W., Zenisek, D., 2011. Acute destruction of the synaptic ribbon reveals a role for the ribbon in vesicle priming. Nat. Neurosci. 14, 1135–1141.
Song, S., Miller, K.D., Abbott, L.F., 2000. Competitive Hebbian learning through spike-timing-dependent synaptic plasticity. Nat. Neurosci. 3, 919–926.
Song, Z., Ultenius, C., Meyerson, B.A., Linderoth, B., 2009. Pain relief by spinal cord stimulation involves serotonergic mechanisms: an experimental study in a rat model of mononeuropathy. Pain 147, 241–248.

Spiess, M.R., Müller, R.M., Rupp, R., Schuld, C., EM-SCI Study Group, van Hedel, H.J., 2009. Conversion in ASIA impairment scale during the first year after traumatic spinal cord injury. J. Neurotrauma 26, 2027–2036.
Sterling, P., Matthews, G., 2005. Structure and function of ribbon synapses. Trends Neurosci. 28, 20–29.
Strauss, I., Lev-Tov, A., 2003. Neural pathways between sacrocaudal afferents and lumbar pattern generators in neonatal rats. J. Neurophysiol. 89, 773–784.
Streit, J., Tscherter, A., Heuschkel, M.O., Renaud, P., 2001. The generation of rhythmic activity in dissociated cultures of rat spinal cord. Eur. J. Neurosci. 14, 191–202.
Struijk, J.J., Holsheimer, J., Boom, H.B., 1993. Excitation of dorsal root fibers in spinal cord stimulation: a theoretical study. IEEE Trans. Biomed. Eng. 40, 632–639.
Su, C.F., Haghighi, S.S., Oro, J.J., Gaines, R.W., 1992. 1992 Backfiring in spinal cord monitoring High thoracic spinal cord stimulation evokes sciatic response by antidromic sensory pathway conduction, not motor tract conduction. Spine (Phila Pa 1976) 17, 504–508.
Swiontek, T.J., Sances Jr., A., Larson, S.J., Ackmann, J.J., Cusick, J.F., Meyer, G.A., Millar, E.A., 1976. Spinal cord implant studies. IEEE Trans. Biomed. Eng. 23, 307–312.
Taccola, G., Nistri, A., 2006. Fictive locomotor patterns generated by tetraethylammonium application to the neonatal rat spinal cord in vitro. Neuroscience 137, 659–670.
Taccola, G., 2011. The locomotor central pattern generator of the rat spinal cord in vitro is optimally activated by noisy dorsal root waveforms. J. Neurophysiol. 106, 872–884.
Tandon, S., Kambi, N., Lazar, L., Mohammed, H., Jain, N., 2009. Large-scale expansion of the face representation in somatosensory areas of the lateral sulcus after spinal cord injuries in monkeys. J. Neurosci. 29, 12009–12019.
Tang, Y.P., Shimizu, E., Dube, G.R., Rampon, C., Kerchner, G.A., Zhuo, M., Liu, G., Tsien, J.Z., 1999. Genetic enhancement of learning and memory in mice. Nature 401, 63–69.
Tang, F., Lane, S., Korsak, A., Paton, J.F., Gourine, A.V., Kasparov, S., Teschemacher, A. G., 2014. Lactate-mediated glia-neuronal signalling in the mammalian brain. Nat. Commun. 5, 3284.
Tawfik, V.L., Chang, S.Y., Hitti, F.L., Roberts, D.W., Leiter, J.C., Jovanovic, S., Lee, K.H., 2010. Deep brain stimulation results in local glutamate and adenosine release: investigation into the role of astrocytes. Neurosurgery 67, 367–375.
Tillakaratne, N.J., Duru, P., Fujino, H., Zhong, H., Xiao, M.S., Edgerton, V.R., Roy, R.R., 2014. Identification of interneurons activated at different inclines during treadmill locomotion in adult rats. J Neurosci. Res. 92, 1714–1722.
Topka, H., Cohen, L.G., Cole, R.A., Hallett, M., 1991. Reorganization of corticospinal pathways following spinal cord injury. Neurology 41, 1276–1283.
Vedam-Mai, V., van Battum, E.Y., Kamphuis, W., Feenstra, M.G., Denys, D., Reynolds, B.A., Okun, M.S., Hol, E.M., 2012. Deep brain stimulation and the role of astrocytes. Mol. Psychiatry 17, 124–131.
Visocchi, M., Cioni, B., Pentimalli, L., Meglio, M., 1994. Increase of cerebral blood flow and improvement of brain motor control following spinal cord stimulation in ischemic spastic hemiparesis. Stereotact. Funct. Neurosurg. 62, 103–107.
Voronin, L.L., Cherubini, E., 2004. 'Deaf, mute and whispering' silent synapses: their role in synaptic plasticity. J. Physiol. 557, 3–12.
van Ooyen, A., Carnell, A., de Ridder, S., Tarigan, B., Mansvelder, H.D., Bijma, F., de Gunst, M., van Pelt, J., 2014. Independently outgrowing neurons and geometry-based synapse formation produce networks with realistic synaptic connectivity. PLoS One 9, e85858.
van den Brand, R., Heutschi, J., Barraud, Q., DiGiovanna, J., Bartholdi, K., Huerlimann, M., Friedli, L., Vollenweider, I., Moraud, E.M., Duis, S., Dominici, N., Micera, S., Musienko, P., Courtine, G., 2012. Restoring voluntary control of locomotion after paralyzing spinal cord injury. Science 336, 1182–1185.
Wake, H., Lee, P.R., Fields, R.D., 2011. Control of local protein synthesis and initial events in myelination by action potentials. Science 333, 1647–1651.
Waltz, J.M., 1998. Chronic stimulation for motor disorders. In: Gindelberg, P.L., Tasker, R.R. (Eds.), Text Book for Stereotactic and Functional Neurosurgery. McGraw-Hill, NewYork, pp. 1087–1099.
Wan, Y., Feng, G., Calakos, N., 2011. Sapap3 deletion causes mGluR5-dependent silencing of AMPAR synapses. J. Neurosci. 31, 16685–16691.
Warp, E., Agarwal, G., Wyart, C., Friedmann, D., Oldfield, C.S., Conner, A., Del Bene, F., Arrenberg, A.B., Baier, H., Isacoff, E.Y., 2012. Emergence of patterned activity in the developing zebrafish spinal cord. Curr. Biol. 22, 93–102.
Watanabe, S., Hoffman, D.A., Migliore, M., Johnston, D., 2002. Dendritic K+ channels contribute to spike-timing dependent long-term potentiation in hippocampal pyramidal neurons. Proc. Natl. Acad. Sci. U. S. A. 99, 8366–8371.
Waters, R.L., Yakura, J.S., Adkins, R.H., Sie, I., 1992. Recovery following complete paraplegia. Arch. Phys. Med. Rehabil. 73, 784–789.
Wei, K., Glaser, J.I., Deng, L., Thompson, C.K., Stevenson, I.H., Wang, Q., Hornby, T.G., Heckman, C.J., Kording, K.P., 2014. Serotonin affects movement gain control in the spinal cord. J. Neurosci. 34, 12690–12700.
Wernig, A., Müller, S., Nanassy, A., Cagol, E., 1995. Laufband therapy based on 'rules of spinal locomotion' is effective in spinal cord injured persons. Eur. J. Neurosci. 7, 823–829.
Wilson, J.M., Blagovechtchenski, E., Brownstone, R.M., 2010. Genetically defined inhibitory neurons in the mouse spinal cord dorsal horn: a possible source of rhythmic inhibition of motoneurons during fictive locomotion. J. Neurosci. 30, 1137–1148.
Wilson, J.A., 1981. Unique, identifiable local nonspiking interneurons in the locust mesothoracic ganglion. J. Neurobiol. 12, 353–366.
Yakovenko, S., Kowalczewski, J., Prochazka, A., 2007. Intraspinal stimulation caudal to spinal cord transections in rats. Testing the propriospinal hypothesis. J. Neurophysiol. 97, 2570–2574.
Zhong, G., Sharma, K., Harris-Warrick, R.M., 2011. Frequency-dependent recruitment of V2a interneurons during fictive locomotion in the mouse spinal cord. Nat. Commun. 2, 274.