Spinal Cord Plasticity and Neuromodulation After SCI

Stefano Piazza and Jaime Ibáñez

Abstract Over the past several decades, it has been shown that the spinal cord exhibits significant adaptive plasticity during development and throughout life. This is normally a positive phenomenon, allowing the spinal cord to develop fundamental functions and learn novel behaviours. However, after a spinal cord injury, the pathways controlling the behaviours mediated by the spinal cord are interrupted and maladaptive plasticity can take place. The traditional approach to rehabilitation after spinal cord injury is to apply physical training exercises improving the overall condition and functioning of the patient, and thus to indirectly promote neural recovery. Emerging neuromodulation therapies that complement physical therapy have been proposed to directly stimulate and modify specific impaired neural pathways and thereby produce a more satisfactory functional state. This chapter presents an overview of these new treatment approaches.

1 Introduction

The term neuroplasticity refers to the changes or adaptations of the nervous system in response to endogenous or exogenous stimuli. Historically, the nervous system's neuroplastic properties were attributed solely to supraspinal structures and the spinal cord (SC) was seen as a hardwired neural structure with the capability only of reacting quickly and in a predictable manner to external and descending stimuli. According to this view, complex motor skills acquired through intensive practice (such as walking, dancing, or playing a musical instrument) are achieved by modulating only the supraspinal control of the unchanging SC.

This view that nervous system plasticity was limited exclusively to supraspinal structures endured despite the publication of studies showing long-term SC changes resulting from pathological situations or conditioning paradigms [29, 105, 115].

S. Piazza (✉) · J. Ibáñez
Cajal Institute, Spanish National Research Council, Madrid, Spain
e-mail: to.stefano.piazza@gmail.com

J. Ibáñez
e-mail: jaime.ibanez@gmail.com

J.L. Pons et al. (eds.), *Emerging Therapies in Neurorehabilitation II*,
Biosystems & Biorobotics 10, DOI 10.1007/978-3-319-24901-8_6

During recent decades, numerous studies have revealed a better understanding and characterization of the modification of the SC as it learns new behaviours, as well as an understanding of how this process contributes to the adaptation of the SC after a neurological lesion.

At present, novel targeted neuromodulation techniques are being explored and developed to take advantage of the SC's plasticity to support and enhance motor recovery after a lesion. These rehabilitation approaches are especially relevant for people with spinal cord injury (SCI). In such cases, regaining basic functions (such as locomotion) may be empowered by modifying specific neural circuits and behaviours located in the SC that in turn may generalize to more complex and coordinated motor capabilities.

This chapter presents a general overview of new neurorehabilitation techniques that are targeted to improve lower limb function (mainly gait function) in people with SCI. The overall goal of these neurorehabilitation strategies is to induce focalized changes in the SC that result in better function after treatment. Experiments that generate modulation from descending supraspinal and peripheral pathways are considered. The first section of the chapter summarizes the main functional and neurophysiological impacts of a lesion in the SC, and describes the approaches that are currently being integrated in the rehabilitation interventions for people with SCI to improve locomotion. The next section describes the current understanding of the plastic properties of the SC that result from learning or injury or in experimental settings. Finally, the last section covers some of the most important approaches published during recent years describing rehabilitation using targeted neuromodulation strategies to improve gait function in individuals with SCI.

2 SCI: Impact, Neurophysiological Consequences and Current Therapies for Functional Recovery

SCI leads to a partial or complete interruption of the neural pathways between the brain and parts of the SC and the peripheral nervous system. Such disruption causes alterations in the sensori-motor and autonomic systems controlled by pathways at the lesion level or below. It causes an array of functional, structural, and neurochemical/molecular changes at multiple levels of the somatosensory core [36]. SCI-related dysfunctions affect cardiovascular, gastrointestinal, genitourinary, musculoskeletal, respiratory, skin, endocrinologic, and hematologic systems, as well as mobility and other voluntary functions. These dysfunctions can contribute to diminished autonomy and functional abilities which often cannot be completely restored with rehabilitation [110].

Many SCI-related dysfunctions, such as spasms, spasticity or neurologic pain, are caused by processes of maladaptive spinal plasticity [46]. After injury, the influence of the brain on SC functions is at least partially reduced leading to an altered supraspinal-spinal interaction [36]. The associated symptoms and signs of SCI are

collectively called the 'upper motor neuron syndrome' and are classified as positive or negative. Positive symptoms and signs include muscular hyperactivity causing spasticity, hypertonia, hyperreflexia, clonus, spasms, and muscles coactivation. Negative symptoms include muscle weakness, loss of dexterity and fatigue [34].

In addition to traditional physical and occupational therapy, the most accepted approaches over the past few decades for the rehabilitation of SC function have been mainly based on functional training of the patient to recover function-specific spinal cord activation patterns. Current gait-rehabilitation strategies are based on a large body of evidence demonstrating that the adult mammalian spinal cord has a remarkable capacity for activity-dependent plasticity when trained to walk on a treadmill [9]. Over the past 30 years, the impact of treadmill walking on locomotion has been widely studied in animal models of SCI [65, 81, 107] and in people with SCI [1, 33, 68, 75, 83]. Locomotion in spinalized cats following treadmill training has been shown to be comparable to that in healthy cats and superior to that in spinalized cats without training [10, 30]. Comparable treadmill training in humans with complete or incomplete SCI has also been evaluated [31, 47, 48, 61, 134, 135]. Both in animal models and in humans with SCI, treadmill training-dependent improvement after the lesion persists over subsequent months and appears to mainly be due to activity-dependent plasticity in the SC [38, 54, 136, 143]. This conclusion is based on the induced synchronized patterns of afferent, efferent, and interneuronal activity produced during locomotor training [38, 72, 106].

These traditional approaches to rehabilitation from SCI might be improved upon with the use of other complementary technologies such as advanced neurorobotic or neuroprosthetic systems. Current therapies may have the potential to include complementary methods that target changes to specific neural pathways. Such targeted neuromodulation requires determining the properties of the impaired state and the desired neural changes that will produce improvement in the functional outcome of the person with spinal cord damage. To achieve this requires an understanding of the plastic behaviour of the SC.

3 Plasticity in the Spinal Cord

During the past several decades, an increasing number of studies have demonstrated unequivocally that changes in the SC and the corticospinal tract (CST) can occur throughout life as a result of normal development of the individual, in the process of learning new behaviors or following an injury [84, 100, 136].

Several studies have described significant differences in the the pattern and strengths of corticospinal and spinal connections during post-natal development and in maturity [78, 85]. Development encompasses important changes in spinal connections including elimination of transient terminations and growth to new targets. This refinement in the spinal neural connections is driven by supraspinal descending activity and by afferent feedback arising from sensory receptors located in the limbs [85, 136]. The motor control functions of the corticospinal system are not expressed

until development of connectional specificity with spinal cord neurons and the formation of the cortical motor map is complete. This is especially significant in humans, where only reduced motor capacities in the SC are present immediately after birth in order to carry out the most basic survival behaviours (e.g., flexion withdrawal and feeding-related behaviours) [97].

In the adult, SC plasticity has also been demonstrated during learning and acquisition of new motor skills [10, 122, 138]. For example, professional ballet dancers have smaller soleus H-reflexes (muscles' reaction to stimulation of the sensory fibres) than those in non-dancers or even other elite athletes, suggesting an increased cortical control of lower-limb muscles in the former group [101]. Adult SC plasticity is also seen in the progressive adaptation of the soleus H-reflex in healthy subjects as a result of daily training of a non-automated motor task such as backward walking [111], or in the decrease of soleus H-reflex amplitude associated with skill acquisition in a cycling task with sudden impedance perturbations [89]. Since H-reflexes are largely monosynaptic and are spinally mediated, the changes observed in these studies appear to represent plasticity within the SC.

Finally, long-term plastic changes in the SC also occur as a result of injury or disease. It is well established that the damage or alteration of supraspinal descending modulatory activity due to a SC injury or disease in the mature individual often causes maladaptive changes leading to increased reflexes, appearance of mass reflexes, and spasticity [42, 64, 108, 138].

All this evidence of a spatially and temporally distributed plasticity in the CNS including the SC leads to an understanding of the SC as playing a more complex role than traditionally thought. Rather than operating as a hard-wired executor of descending influence from the brain, the SC is capable of task-induced plasticity, Wolpaw [137] describes a state of *negotiated equilibrium* in which the SC and supraspinal descending activity maintain spinal neurons and synapses in a state that successfully serves all the incorporated behaviours. Learning new skills (i.e., new SC behaviours) implies incorporation of finely tuned muscle contractions in response to concurrent sensory inputs. As described by Wolpaw and colleagues [123, 137], this process involves modulation of supraspinal signals descending from the brain, to adjust spinal pathways to a constantly and reiteratively revised state of *negotiated equilibrium* that accommodates newly acquired skills and those learned previously. For this to happen, ubiquitous activity-dependent plasticity in the CNS is essential [144].

The study of the mechanisms of SC plasticity offers unique opportunities to answer basic neurological questions regarding behaviour, learning, and the consequences of injury, and at the same time offers new opportunities for rehabilitation after injury in humans. The principal advantage of focusing on the SC to study plasticity in the CNS is the relative simplicity of its structure and behaviours (especially in the case of spinal reflexes) and the methods available to access and condition them either through multisensory afferents or through descending pathways. Plasticity produced by sensory inputs in the isolated spinal cord has been shown to produce short- and long-term effects (for a review see [143]). Thus both changes in simple reflex arcs (*e.g.* the flexion withdrawal reflexes and the proprioceptive reflexes) [80] as well as

in functional tasks such as by training spinalized animals on a treadmill [10, 116] have been revealed.

Since the SC connects directly to motor behaviour, it is easier to link learning processes with visible behavioural changes. The study of SC plasticity is also of significant clinical relevance. The impact of lesions at different levels of the neuromotor system may severely impair functionally relevant capacities such as locomotion. The appropriate engagement and guidance of spinal cord plasticity could play a major role in restoring useful function after spinal cord injuries, stroke or other trauma or disease.

The SC integrates nondeclarative memory [10] (i.e., memory that does not require conscious thought). In particular, four principal learning mechanisms can be identified, which are at the basis of the currently available spinal neuromodulation protocols: habituation, sensitization, classical conditioning and operant/instrumental conditioning. Since these capacities are intrinsic to the SC, we will present examples studied in the isolated SC, where supraspinal input is absent. When the SC is not in complete isolation, the conditioning input may originate from the brain, and additionally the brain will be influenced by afferents from the lower structures.

3.1 Habituation

Habituation is one of the simplest form of learning, and is considered a prerequisite for more complex behaviours. Habituation is defined as a behavioural response decrement that results from repeated stimulation and does not involve sensory adaptation/sensory fatigue or motor fatigue [104]. Due to this mechanism, non-relevant stimuli are filtered out, allowing the CNS to focus on the important ones [104]. The first observations of the phenomenon of habituation in the SC of spinally transected dogs [113], cats [39, 125], and rats [103] indicated that the SC could learn from repeated activity, and demonstrated a form of spinal memory that manifested itself behaviourally. The absence of observable sensory receptor adaptation in the periphery, or changes in the neuromuscular junction, suggested that the memory for stimulus training history resided in spinal interneuronal synapses [46].

Habituation effects are stronger if the conditioning stimulation is delivered with constant and moderate intensity [35], and at fixed frequencies [58]. Despite extensive study of the effects of habituation on the SC, the neural mechanisms driving this phenomenon are still not completely understood [104].

3.2 Sensitization

In contrast to habituation, exposure to a single intense or noxious stimulus has the capacity to increase subsequent responsiveness to a variety of inputs. This is known as sensitization [6]. Sensitization is an essential warning mechanism that helps protect

an organism from environmental dangers. It manifests itself both in the peripheral and central nervous systems. Sensitization is the reduction in threshold and increase in responsiveness of the peripheral ends of nociceptor neurons that occurs when these are exposed to inflammatory mediators or damaged tissues [77]. Central sensitization is an enhancement in the functional status of neurons and circuits caused by increases in membrane excitability, synaptic efficacy, or a reduced inhibition. The net effect is a state of facilitation, potentiation or amplification in which previously subthreshold inputs generate exaggerated neural output [77]. Sensitization may produce increased spontaneous activity, a reduction in the threshold for activation by peripheral stimuli, and increased responses to suprathreshold stimulation. Moreover, sensitized cells may also increase sensitivity to neural inputs which normally are not considered part of the neuron's receptive field. For example, when central sensitization is observed in nociceptive pathways, spinal neurons can become sensitive to input such as large low-threshold mechanoreceptor myelinated fibers to produce Aβ fiber-mediated pain [145].

In the presence of prolonged nociceptive stimulation, for example after an injury, peripheral and central sensitization produce pain hypersensitivity, a defense mechanism to protect the damaged tissue. This effect may last even when the tissue is healed, in the form of neuropathic pain. This type of pain represents an obstacle to rehabilitation and a form of maladaptive plasticity that reduces spinal learning [46]. Descending brain pathways can exert a protective effect limiting central sensitization [57]. However, the alteration or interruption of supraspinal input following SCI leaves SC plasticity uncontrolled and often leads to the manifestation of neuropathic pain [77].

3.3 Classical Conditioning

Spinal neurons are responsive to classical (Pavlovian) conditioning protocols. In classical conditioning, after the repeated paired delivery of a conditioned (CS) and an unconditioned stimulus (US), the relationship between the two stimuli is encoded and learned by the spinal interneurons. For example in an isolated spinal cord, when weak thigh stimulation (CS) and strong plantar foot stimulation (US) are presented in paired succession, the thigh stimulation ends by modulating the flexion withdrawal reflex [49].

Simple hind-limb motor responses to cutaneous or electrical stimulation are enhanced in animals with completely transected spinal cords, for example in spinalized cats with the modulation of flexion reflex by pairing saphenous nerve stimulation (CS) with superficial peroneal nerve stimulation (US) [40, 67], by stimulating superficial peroneal sensory nerve (CS) with a stronger electrical stimulus to the ankle skin (US) of the same leg [8], or in spinal dogs when mechanical or electric stimulation of the tail is combined with shock to the left hind paw [115].

3.4 Operant Conditioning

Instrumental conditioning, also known as operant conditioning, is a more sophisticated form of learning than those discussed thus far. It requires the acquisition of a behaviour in response to a conditioning stimulus. Evidence that the isolated SC is sensitive to operant conditioning was provided by [28] and [69] by training spinally transected rats with a paradigm that consists in the delivery of a nociceptive stimulation on the hind paw, when the leg was fully extended. After the training, the rats learned to maintain their leg in a flexed position, displaying an increase in the duration of a flexion reflex response that minimizes net shock exposure [28]. The same effect was not present if the SC was anesthetized with lidocaine, or if a lesion in the sciatic nerve prevented the afferent information from reaching the SC, indicating that the process of acquisition of an operant response depends on spinal cord neurons [28].

The characteristics of the conditioning stimulus are critical for learning to occur, in particular the intensity of the stimulation and the accuracy in the instant of delivery. [55] showed that if stimulus intensity is too weak, habituation takes place and the stimulus is ignored, but if the stimulus is intense, a strong impulsive reaction takes place, which manifests mechanically without showing evidence of an underlying learning process. With regard to the stimulation accuracy, [45] found that their learning protocol was not effective if the stimulation was not delivered immediately after the leg reached the target position (controllable stimulation). It was also shown that the ability of the SC to learn the new behaviour can be temporarily disabled for 24–48 hours, and impaired for 6 weeks, after 6 min of stimulation to the leg, when the stimuli were provided regardless of limb position (uncontrollable stimulation) [46]. It has been proposed that the uncontrollable stimulation may have promoted central sensitization, which was responsible for the spinal learning deficit, inhibiting the adaptive spinal plasticity promoted during the delivery of timely accurate (controllable) stimulations [46].

It has been suggested that adaptive plasticity mechanisms similar to the ones generated by operant learning may explain the improvements in functional walking, muscle strength and the coordination observed in commercially available foot drop devices [66]. These devices usually rely on external sensors (heel switch or built-in sensors) to trigger the onset of electrical stimulation to the ankle's flexors to elicit flexion during the swing phase of the gait cycle. In this paradigm, the stimulation is controllable and predictable for the SC, and it may promote the adaptive flexion behaviour in order to avoid the electrical stimulus [57, 66]. As for foot drop devices, the learning clues on adaptive and maladaptive plasticity provided by operant conditioning paradigms may be applied to a broader set of available rehabilitation therapies, to improve adaptive plasticity and reduce the chances of impaired learning from central sensitization [46, 56, 57].

4 Targeted Modulation

The accessibility and relative simplicity of the SC make it a suitable locus for targeting and precisely changing specific neural pathways that improve motor function in people with SC injury. Targeted modulation of SC networks can shift SC structure and function from a malfunctioning established equilibrium to a new more functional one, for example limiting maladaptive plasticity effects.

Since these neural rehabilitation strategies can target particular spinal pathways and can either weaken or strengthen the activity of these pathways, these modulation protocols can be designed to focus on each patients specific deficits and needs [124]. This flexibility and specificity are distinctive and desirable features of this new therapeutic approach, and they distinguish it from less focused interventions such as treatment with botulinum toxin or baclofen, drugs which simply weaken muscles or reflexes and may have undesirable side effects [121, 132].

The following sections of this chapter will present two different approaches to facilitate spinal cord rehabilitation based on targeted modulation of specific and functionally relevant spinal behaviours. First, we will review the main alternatives proposed for the modulation of spinal structures based on the induction of peripheral stimuli. Finally, we will describe a set of studies demonstrating functionally relevant, activity-dependent spinal cord changes that are modulated by descending activity from the brain.

4.1 Peripheral Modulation

The finding that animals with complete SCI can relearn to walk after intense treadmill training demonstrates the intrinsic capacity of the SC to integrate incoming proprioceptive and/or cutaneous information, interpret it, and respond with a functional motor output [9]. Successful afferent inputs can be proprioception, lengthening of muscle, cutaneous feedback, or load. Peripheral modulation protocols are designed to modulate SC neural circuits without directly stimulating the brain cortex. In this section, we present examples of the most promising approaches.

4.1.1 Stimulation of Cutaneous Afferent Pathways

Afferent input plays an important role in rehabilitation after SCI. For people with SCI, locomotor training is based on providing sensory cues consistent with normal walking, especially from lower limb stretch- and load-sensitive mechanoreceptors [62], although a plethora of other inputs are also activated during the exercise [107]. In this context, of particular interest are cutaneous mechanoreceptors from plantar foot afferents because of their accessibility and simple integration with the functional task.

Plantar cutaneous feedback contributes to maintaining balance and ensuring a stable walking pattern throughout the step cycle [90, 102]. This has been shown in animal models, of cats [26] and rats [118]. In cats, the loss of cutaneous input does not produce a strong effect on stable walking. [114] observed that, after complete cutaneous denervation of the hindlimbs, cats were still able to walk in a pattern similar to that in intact cats. Using gait analyses instrumentation, subsequent studies detected small changes in limb kinematics and muscle activity [41]. However, in challenging walking conditions, such as ladder or incline walking, or when lateral stability was compromised by unexpected perturbations, the kinematics and locomotor muscle activity were significantly modified, with compromised stability [11, 14]. Walking disruption was even more evident in spinalized cats, suggesting that the remaining intact input of muscles, joints and other receptors was not sufficient in these animals to compensate for the loss of cutaneous information [13]. In rats, which are plantigrade animals as are humans, the elimination of cutaneous input by hypothermic anaesthesia modified hindlimb kinematics to produce less efficient locomotion, with a larger ankle and hip excursion and decreased distance between the hip and the ground, leading to a significant functional deficit [130].

As in the animal models, in humans information from plantar cutaneous afferents plays an important role in postural and walking stabilization. These have been shown to determine postural responses in ankle muscles, to stabilize stance and gait [4, 102, 127, 147]. For example, after a temporary plantar desensitization, motor activity and ground reaction forces during a balance recovery task were reduced [120, 126] and postural adjustments prior to step initiation were compromised in a way that could not be compensated by other inputs [79].

Furthermore, [146] found that in humans, electrical stimulation of plantar cutaneous afferents during walking generates withdrawal responses during swing and stabilizing responses during stance; this phase-dependent behaviour indicates an integration of cutaneous afferent feedback into spinal locomotor networks. In fact, the contribution of plantar afferent feedback to locomotion is not limited to reactive responses: it extends from the modulation of spinal reflex excitability [52] to the selection of motor patterns and the alterations of central pattern generator (CPG) frequency [107].

After SCI, the loss of descending input from supraspinal structures increases the importance of sensory feedback from the periphery [88]. The processing of sensory input within the SC is altered [51] and considerable changes in reflex pathways develop over time as a consequence of the injury [25, 26]. Locomotor training after SCI is based on the fact that appropriate peripheral sensory input can reactivate and reorganize the spinal locomotor circuitry [109].

Critical input comes from proprioceptive signals from the muscles. For example, in incomplete SCI rats, locomotion rehabilitation based on swimming training improves locomotion [118]. However, the therapy is more effective when swimming is potentiated by cutaneous feedback provided by a matrix of buoyant tubes suspended from the bottom of the pool [118]. A similar result was previously observed by [98], using the same protocol to rehabilitate locomotion of hemisected chicks.

In this case, the phasic feedback from cutaneous plantar receptors was sufficient to permanently increase limb extension during swimming.

Cutaneous input is also critical for the recovery of stepping during walking training on a treadmill. For example, in cats, the chemical deactivation of the nerves from the low-threshold mechanoreceptors of the hind paws consistently decreased coordination between forelimbs and hind limbs, and between left and right legs, reducing walking stability and efficiency [117].

In humans, some neuromodulation protocols already take advantage of the strong interaction between feedback from plantar cutaneous afferents and spinal locomotor circuits, to restore a pathological or absent phase-dependent H-reflex modulation pattern or stimulate plastic changes to CNS microcircuits following injury [102]. For example, [52] applied electrical impulses to the sole of the foot to decrease the soleus H-reflex, showing that it is possible to modulate this reflex in both neurologically intact subjects and in subjects with SCI during walking and standing. These results were extended by [71], who used electrical stimuli to enhance sensory feedback during walking in subjects with SCI, producing phase-dependent normalization of H-reflex and tibialis anterior flexion reflexes.

4.1.2 Electrical Spinal Cord Stimulation

Electrical Spinal Cord Stimulation (SCS) is an invasive neuromodulation technique that entails the application of minute electrical impulses to the spinal cord to modulate segmental spinal and/or brain stem/spinal pathways. These techniques have been used to treat motor dysfunction associated with several degenerative diseases of the CNS and has been shown to improve a wide range of functions including motor function, posture, walking, and bladder control [24, 131]. SCS may be applied by epidural electrical stimulation (EES) or intraspinal microstimulation (ISMS).

EES is applied to the dorsal surface of the spinal cord by surgically implanted electrodes, to activate the dorsal root entry zones or dorsal columns. Its principal use has been for the treatment of neurologic pain [2, 23, 73, 74, 128]. However, when applied in association with partial body-weight support training, it has the potential to initiate and sustain locomotion in people with chronic incomplete SCI, even in cases where partial body weight support alone was not able to achieve functional over-ground ambulation [16, 63].

EES, in combination with physical therapy, has also been used in individuals with chronic complete SCI. For example, [3] showed that four subjects with complete SCI (AIS A or B) were able to recover voluntary movement soon after the implantation of the stimulation device, and their condition improved progressively in the following months with the combination of EES and body weight supported standing exercises or manual therapist-assisted locomotor training on a treadmill [3, 60]. The same therapies performed before the implantation of the EES device were not able to produce functional recovery in these patients.

Together, these results suggest that EESs effect on the spinal pathways may enhance the central excitatory drive to the motor neurons; at the same time,

task-specific training may promote force generation and accuracy [3]. In addition, the fact that stimulating specific SC regions (L2 in humans, L5 in cats and between L2 and S1 in rats [53]) can induce or facilitate stepping, has been attributed to the activation of central pattern generators circuits (CPG) in the SC, i.e., neural circuits that generate coordinated alternating flexor-extensor neuromotor patterns in the absence of supraspinal or sensory modulation [50]. Nevertheless, it has not yet been shown whether muscle activity generated with EES will be sufficient in individuals with SCI to support the body during stepping, and what the long-term effects of such a treatment will be [32].

A similar and more invasive technique is ISMS [94]. In this method, arrays of microwire electrodes are implanted in the spinal cord to target the intermediate and ventral gray matter for activation of local circuits. ISMS potential for rehabilitation comes from its capacity to evoke, in the isolated SC, specific functional movements in the hindlimbs and forelimbs. This effect depends on the level and characteristics of the stimulation. For example, standing and stepping movements can be evoked by the application of ISMS to the lumbar SC in spinal cats [7, 59, 99], while forelimb movements can be evoked when ISMS is delivered to the cervical spinal cord in non-human primates [95, 148].

Since these SCS techniques require the use of implanted electrodes near to (EES) or within (ISMS) the CNS, complications may arise during and after the surgical implantation [24]. Principal intra-operatory complications include direct damage to the neuraxial structures and risks associated with the anaesthesia and surgery; in the post-operatory interval, principal risks include pain, seroma, lead migration and hardware failure, and infections [24, 70, 128].

A recent review of documented cases of EES stimulation provided an estimation of the risk of complication associated with EES [91]. Of the 787 patients considered in the review, those who were initially submitted to the EES initial trial lead placement, 11 % reported emergence of pain at the stimulation site and 4.5 % developed documented infections. After the test phase, 200 patients were excluded from the pulse generator implant, with an average implant-to-trial ratio of 75 %. For 38.1 % of the remaining 512 patients who were implanted with the stimulator, hardware related complications (lead migration, lead connection failure and lead breakage) occurred.

ISMS has not yet been tested in humans. The principal challenges of ISMS relate to the safety and durability of the implanted electrodes, since adverse tissue responses are still common following implantation of currently available electrodes within the CNS [92].

4.1.3 Electrochemical Spinal Cord Stimulation

Pharmacological treatments have also shown potential for activating locomotor circuits in rats and mice [5, 76]. [27] proposed an alternative approach to neuromodulation by combining specific pharmacological and electrical stimulation interventions, together with locomotor training [27, 129]. Combining injection of serotonin antagonists ($5HT_{1A/2/7}$), stimulation with EES and locomotor gait training induced full

weight bearing bipedal treadmill locomotion in complete SC-transected rats. In other studies, [12, 133], it was shown that by automatically modulating electrochemical stimulation parameters, it is possible with a closed-loop controller to precisely control leg kinematics in rats during movement. This method allows the animals to voluntarily initiate bipedal locomotion from a resting position, to walk for extended periods of time, to pass obstacles, and to climb a staircase. These results inspire hope for future neuroprosthetic devices as well as for promoting recovery and motor function after severe lesions.

Electrical and pharmacological stimulation of spinal neural networks is still in an experimental stage. Despite promising results in animal models, further research is required before widespread application of these techniques in humans will be possible. Principal concerns are the selection of the appropriate neuromodulators to be used in humans [37] and the timed control of pharmacological and electrical stimulation. Moreover, in animals the techniques have been applied only targeting the hindlimbs. In the future, refinement of animal studies may contribute to greater translational success [32]. Thus, the combination of pharmacological and epidural stimulation to enhance motor function remains a promising research direction yet to be fully explored.

4.2 Descending Modulation

As noted previously, supraspinal inputs to the spinal cord provide a continual flow of activity in a variety of pathways [143]. This descending activity modulates the spinal cord behaviour contributing to motor development in childhood and to learning new motor skills later in life [85, 136]. Understanding the mechanisms of brain-modulated spinal cord plasticity and its interactions with activity-dependent plasticity elsewhere in the CNS is important for explaining normal behaviours as well as the complex disabilities produced by neurological disorders and for proposing new ways to induce spinal changes that will correct pathological motor behaviours. Over the past several decades, a number of studies have been proposed (using sensitization, classical conditioning and operant conditioning protocols among others) to induce plastic SC changes with supraspinal structures having a relevant modulatory role. In some cases, as in the paired associative stimulation paradigm initially proposed by [119] to facilitate cortico-muscular pathways (synchronously stimulating the motor cortex and the peripheral nerves), it was first assumed that the effects were circumscribed to cortical and subcortical regions. However, later studies demonstrated additional changes in spinal structures [93]. Other experimental protocols have been designed specifically to modify certain behaviours of the SC or alter the strength of corticospinal connections (while also acknowledging plastic changes in other spinal and supraspinal areas). This section summarizes two specifically relevant lines of research in which supraspinal modulatory activity is used to induce spinal cord plasticity to improve motor function in individuals with neurological damage such as that in SCI.

4.2.1 Operant Conditioning of Spinal Reflexes

Starting in the 1980s [139–141] and continuing to the present [122–124], Wolpaw and colleagues have shown that descending supraspinal activity may be used to modulate specific spinal behaviours. These studies involved the operant conditioning of spinal reflexes. In the first studies, in monkeys, an operant conditioning protocol was used to train the animals to up-or down-regulate their spinal stretch reflex or its electrical analogue, the H-reflex [139, 140]. The animals were rewarded if they changed the reflex amplitude in the correct direction over 50 days. Approximately 80–90 % of the test animals were able to successfully modulate the reflex in the desired direction [140]. Changes were observable immediately after onset of training and persisted even during inactive periods after cessation of the reward protocol. The protocol had three key features. First, it required maintenance of both a certain elbow angle and a certain level of biceps EMG activity as the animal opposed a constant extension torque in order to generate a stimulus producing the reflex. Second, it based reward on the size of the recorded reflex. Finally, the reward criterion (i.e., requiring successful up- or down-conditioning in the animals) remained constant over days and weeks. In sum, the protocol was designed to induce and maintain a long-term change in descending influence over the spinal arc of the reflex, and to thereby change the spinal cord. Subsequent studies in which the spinal stretch reflex or H-reflex was conditioned in rats [21, 22], mice [20], and humans [43, 112] confirmed the first results with monkeys and served to further elucidate the anatomical, physiological, and biochemical mechanisms of this conditioning (see [124] for review).

Interestingly, in rat studies [22], analysis of the effect of soleus H-reflex conditioning on locomotor kinematics showed that successful conditioning in the intended direction of the reflex produced changes not only in this reflex, but also in the kinematics of locomotion. However, the changes did not alter key aspects of locomotion (such as gait speed, gait symmetry or step length) but rather provoked compensatory changes in other pathways (i.e., the quadriceps reflex) [21]. These compensatory changes demonstrated the ubiquity of plastic changes in the SC and how newly acquired behaviours can cohabitate with existing ones, leaving the latter unaffected despite the change in the soleus reflex [21, 137]. In addition, [22] found that rats with partial SCI undergoing soleus H-reflex up-conditioning could improve locomotion parameters such as soleus burst and locomotion symmetry, providing the first evidence of the potential functional impact of this kind of intervention.

The experimental accessibility of the SC, the relative simplicity of the conditioned reflex (largely monosynaptic), the well-defined descending pathways from the brain, and the direct association to a specific observable behaviour, make H-reflex operant conditioning a unique tool for understanding the basic mechanisms of spinal cord plasticity and how it changes behavior. Moreover, by taking advantage of the targeted modulation of specific spinal pathways, it offers the possibility of new approaches to neurorehabilitative intervention.

An adaptation of the stretch-reflex and H-reflex conditioning paradigm was also tested in humans [44, 122]. Whereas the animal studies included several thousand trials per day, 7 days per week, over 50 days of conditioning [141], the humans

performed only 225 trials per one-hour session three times per week [122]. For the human studies, the electrodes used for stimulation and recording were placed on the skin rather than implanted as in the animal studies. In the animal studies, the animals were rewarded with food for correct performance; in the human studies, the subjects received visual feedback showing performance on a computer display. In these human studies, a small number of trials at the beginning of each session were acquired as control trials: in these trials the subject was not asked to change the reflex and received no feedback [122]. These control trials served to check for intra- vs. inter-session H-reflex changes. These studies showed that 70–90 % of normal human subjects were able to modify the conditioned reflex in the correct direction. Over 24 conditioning sessions H-reflex size increased to an average of 140 % of initial value in up-conditioned subjects and decreased to an average of 69 % in down-conditioned subjects. Reflex changes occurred in two phases: they began (Phase 1) with a rapid small change, in the correct direction, that was attributable to rapid task-dependent adaptations, and then (Phase 2), over days and weeks, changed gradually further in the correct direction (long-term change) [122]. Phase 1 appears to reflect rapid mode-appropriate change in descending influence over the spinal arc of the reflex, while Phase 2 appears to reflect gradual spinal cord plasticity produced by the chronic continuation of the descending input responsible for Phase 1 [122]. These bi-phasic results were consistent with the animal studies previously performed by [142].

A more recent study was carried out in people with incomplete SCI [123]. The experimental procedure was similar to the one with healthy subjects. Success rate and magnitude of reflex change were comparable to those in people with intact SC. As in the previously cited studies of locomotion in rats, the comparison of functional capacities before and after the conditioning showed that appropriate H-reflex conditioning (i.e., down-conditioning in this human study) was associated with faster and more symmetrical locomotion. The improvement was evident both in quantitative testing and, most important, in subjective observations by the subjects themselves: they spontaneously reported improvements in walking speed and endurance, and in other aspects of motor function (e.g., balance). Interestingly, the subjects with SCI showed long-term H-reflex changes that were greater than the changes observed in healthy subjects (24 % vs. 16 %). In contrast, task-adaptation changes (i.e., reflex changes observed within sessions but not maintained between consecutive sessions) were smaller in subjects with SCI (7 % vs. 15 %). Another recent study [82] also found that appropriate H-reflex conditioning had beneficial effects on locomotion in people with incomplete SCI.

The smaller long-term changes in healthy subjects as compared to people with SCI suggests that, in healthy subjects, H-reflex changes are mainly occurring during the experimental sessions. That is, for healthy subjects, the H-reflex changes are unlikely to provide any beneficial effects in terms of functional outcomes outside the experimental sessions (in locomotion for example), and they may even interfere with the already well-functioning circuits for locomotion and other behaviours in the intact SC. Therefore, in these healthy subjects, over the conditioning sessions, additional plasticity may occur to maintain SC equilibrium that ensures that locomotion and other important behaviours are normal . On the other hand, as was the case with

the SC injured rats [22], appropriate H-reflex conditioning in people with SCI led to improvements in lower-limb functions (such as locomotion). Since the H-reflex change was beneficial, the SC retained the neurophysiological change resulting from the experimental protocol. In other words, the injured SC was guided towards a new and more optimal equilibrium [124, 137].

Taken together, these animal and human experiments indicate that reflex conditioning protocols can improve recovery after chronic incomplete SCI, and possibly in other neurological and physical disorders. Mrachacz-Kersting and colleagues are currently exploring ways to up-condition the soleus stretch reflex in healthy people. The main goal in this work is to enhance ankle stiffness in athletes who are prone to suffer ankle sprain. Preliminary data indicate that up-regulating the reflex is possible that this reflex change is associated with enhancement of the intrinsic and total stiffness of the ankle joint and an improved stability after drop landings [96].

4.2.2 Electrical Stimulation of the Motor Cortex

As previously described, plasticity in corticospinal pathways occurs during development of mature motor function [85]. Corticospinal descending axons (mostly from the motor and somatosensory cortical areas) descend through the brainstem down to the spinal grey matter. Corticospinal axon outgrowth and organization during development or after an injury are guided by activity-dependent competition between descending axons [86, 87]. Based on this concept, J. H. Martin and colleagues proposed harnessing the activity-dependent plasticity induced by electrical stimulation of the brain to promote a competitive advantage of ipsilateral-spared corticospinal axons in the spinal cord after a neurological injury [15, 17]. This idea originates from the observations of neural reorganization occurring after injury, where spared corticospinal axons increase their synaptic connections with neighbouring cells but often to a degree insufficient to restore motor function [85].

In these studies animal models of a lesion affecting the pyramidal tract were used to analyse the effects of electrically stimulating spared corticospinal axons in the uninjured pyramidal tract [15, 17]. The analyses focused on: (1) the influence of activity and injury on the corticospinal plasticity, (2) whether continuous stimulation (6 hours/day over 10 days) can promote the outgrowth of descending projections into the spinal cord; and (3) whether activity-dependent plasticity combines with injury-driven sprouting of corticospinal axons to reinforce their connections in the SC.

In one of the first of these studies [15], the experimental rats were divided into four groups: (1) uninjured controls, (2) animals with transected pyramidal tract, (3) animals undergoing electrical stimulation and (4) animals with both pyramidal transection and electrical stimulation of the contralateral pyramidal tract. Results showed that an outgrowth of ipsilateral CS axons and stronger ipsilateral motor responses were observed in group-2 (reducing the competitive activity from the transected descending projection) and in group-3 (increasing the activity of ipsilateral corticospinal terminals). Moreover, it was shown that the combination of injury and

stimulation (group-4) produced the strongest spinal connections and a shift of corticospinal terminations towards the ventral motor areas of the spinal cord. Importantly, connections in the animals with injury and stimulation were stronger than after injury alone. These results highlight the relevant interplay between injury and activity in the spinal cord, and suggests that electrical stimulation provides a competitive advantage of the ipsilateral spared axons, which increased their activity ultimately leading to the development of stronger connections [15]. Interestingly, ipsilateral motor responses generated by stimulating the pyramidal tract were comparable to those generated by contralateral stimulation, although the density of the contralateral axon terminations was much higher. These results therefore suggest that the increased ipsilateral response is mainly caused by an increase in the synaptic strength.

Subsequent studies along these lines further confirmed the robust outgrowth and strengthening of ipsilateral CST axon terminations to the impaired side of the spinal cord and demonstrated functional improvements in injured rats that were stimulated [18, 19]. Stimulated rats showed full recovery of the affected motor function, and the recovery was maintained beyond the intervention period [17]. Martin and colleagues also demonstrated that: (1) electrical stimulation can promote recovery of motor function even when applied long after injury; and (2) this recovery of motor control can be exerted from the ipsilateral motor cortex when the contralateral cortex becomes nonfunctional. Comparable studies in humans are still required in order to determine whether the uninjured motor cortex can be targeted for brain stimulation in people with large unilateral CST lesions and whether this stimulation can improve motor recovery.

5 Conclusion

Despite the historical reluctance to consider the SC a dynamic and learning entity in the nervous system, the last decades have witnessed a marked increase in interest in studying it as a key element in motor restoration of people with neurological damage. The SC has the ability to reorganize itself based on afferent and supraspinal input, and to learn new functions. Experiments with animal SCI models confirmed this by showing that the isolated SC is capable of adaptive motor plasticity and that it can support simple forms of motor learning, including stimulus learning (habituation/sensitization), stimulus association (classical conditioning), and response-outcome (instrumental/operant conditioning) learning. It has also been shown that localized changes in the SC can in turn result in a cascade of further distributed neurophysiological and functional changes that can improve the basic motor functions (such as locomotion) in subjects with SCI.

The active role of the SC in the processes of learning and memory is still not fully harnessed by currently available rehabilitation therapies. Novel targeted neuromodulation therapies aim to take advantage of this rehabilitation potential, in order to increase the functional output of rehabilitation. This is achieved by shaping the neural response of the SC to specific inputs in the direction of more functional behaviours.

An interesting model for the application of these therapies is rehabilitation after SCI. In fact, the effects of the lesion are twofold. On the one hand, the injury stimulates numerous neural changes within the spinal cord; on the other hand, the partial or complete interruption of ascending and descending pathways that occurs with the injury disrupts the close interaction between the supraspinal centres and the rest of the body, often leaving the plasticity of the SC uncontrolled and giving rise to a wide array of maladaptive plasticity-associated changes as for example neurological pain or spasticity.

This chapter presented a review of the evidence for SC plasticity, and of the rehabilitation potential of using it. Novel neuromodulation-based therapies taking advantage of this undisclosed potential for the recovery of locomotor function after SCI have also been described. These techniques have been divided in two main groups, to differentiate between two fundamental approaches to neuromodulation: (i) driving plasticity through the activation of peripheral pathways, either from afferent feedback or directly stimulating SC neural circuitries, and (ii) using supraspinal descending inputs to modulate the neural structures in the SC.

However, the impact and dissemination of these targeted neuromodulation interventions in the SC is still limited and further studies in this research field are therefore needed. In particular, many neural mechanisms in the SC are still unknown or not completely explained. The complex interactions between different spinal mechanisms at distributed SC levels should be modelled, as well as their function in daily activities. Deeper knowledge regarding the precise temporal and spatial properties of the changes occurring in the SC during acquisition of new behaviours will make it possible to improve and optimize current targeted modulation interventions. In the route towards this goal, an increasing number of novel protocols and therapies are expected to emerge, targeting a wider number of functions, that will likely support and increase the effects of more traditional rehabilitation strategies.

Acknowledgments The authors would like to thank Dr. Jonathan R. Wolpaw, Dr. Elizabeth Winter Wolpaw and Dr. Natalie Mrachacz-Kersting for their invaluable help and important contribute in the writing of the chapter.

References

1. Abel, R., Schablowski, M., Rupp, R., Gerner, H.J.: Gait analysis on the treadmill-monitoring exercise in the treatment of paraplegia. Spinal Cord **40**(1), 17–22 (2002)
2. Aló, K.M., Holsheimer, J.: New trends in neuromodulation for the management of neuropathic pain. Neurosurgery **50**(4), 690–703 (discussion 703–4) (2002)
3. Angeli, C.A., Edgerton, V.R., Gerasimenko, Y.P., Harkema, S.J.: Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans. Brain: J. Neurol. **137**(Pt 5), 1394–1409 (2014)
4. Aniss, A.M., Gandevia, S.C., Burke, D.: Reflex responses in active muscles elicited by stimulation of low-threshold afferents from the human foot. J. Neurophysiol. **67**(5), 1375–1384 (1992)

5. Antri, M., Barthe, J.Y., Mouffle, C., Orsal, D.: Long-lasting recovery of locomotor function in chronic spinal rat following chronic combined pharmacological stimulation of serotonergic receptors with 8-OHDPAT and quipazine. Neurosci. Lett. **384**, 162–167 (2005)
6. Baranauskas, G., Nistri, A.: Sensitization of pain pathways in the spinal cord: cellular mechanisms. Prog. Neurobiol. **54**(3), 349–365 (1998)
7. Barthélemy, D., Leblond, H., Rossignol, S.: Characteristics and mechanisms of locomotion induced by intraspinal microstimulation and dorsal root stimulation in spinal cats. J. Neurophysiol. **97**, 1986–2000 (2007)
8. Beggs, A.L., Steinmetz, J.E., Romano, A.G., Patterson, M.M.: Extinction and retention of a classically conditioned flexor nerve response in acute spinal cat. Behav. Neurosci. **97**(4), 530–540 (1983)
9. Behrman, A.L., Bowden, M.G., Nair, P.M.: Neuroplasticity after spinal cord injury and training: an emerging paradigm shift in rehabilitation and walking recovery. Phys. Ther. **86**(10), 1406–1425 (2006)
10. Bélanger, M., Drew, T., Provencher, J., Rossignol, S., Belanger, M., Drew, T.: A comparison of treadmill locomotion in adult cats before and after spinal transection. J. Neurophysiol. **76**(1), 471–491 (1996). http://jn.physiology.org/content/76/1/471.short
11. Bolton, D.A.E., Misiaszek, J.E.: Contribution of hindpaw cutaneous inputs to the control of lateral stability during walking in the cat. J. Neurophysiol. **102**(3), 1711–1724 (2009)
12. Borton, D., Bonizzato, M., Beauparlant, J., DiGiovanna, J., Moraud, E.M., Wenger, N., Musienko, P., Minev, I.R., Lacour, S.P., Millán, J.D.R., Micera, S., Courtine, G.: Corticospinal neuroprostheses to restore locomotion after spinal cord injury. Neurosci. Res. **78**(1), 21–29 (2014)
13. Bouyer, L.: Contribution of cutaneous inputs from the hindpaw to the control of locomotion. II. Spinal cats. J. Neurophys. **90**(6), 3640–3653 (2003)
14. Bouyer, L.J.G., Rossignol, S.: Contribution of cutaneous inputs from the hindpaw to the control of locomotion. I. Intact cats. J. Neurophysiol. **90**(6), 3625–3639 (2003)
15. Brus-Ramer, M., Carmel, J.B., Chakrabarty, S., Martin, J.H.: Electrical stimulation of spared corticospinal axons augments connections with ipsilateral spinal motor circuits after injury. J. Neurosci: official J. Soc. Neurosci. **27**(50), 13793–13801 (2007)
16. Carhart, M.R., He, J., Herman, R., D'Luzansky, S., Willis, W.T.: Epidural spinal-cord stimulation facilitates recovery of functional walking following incomplete spinal-cord injury. In: IEEE Transactions on Neural Systems and Rehabilitation Engineering: A Publication of the IEEE Engineering in Medicine and Biology Society, vol. 12, issue 1, pp. 32–42 (2004)
17. Carmel, J.B., Berrol, L.J., Brus-Ramer, M., Martin, J.H.: Chronic electrical stimulation of the intact corticospinal system after unilateral injury restores skilled locomotor control and promotes spinal axon outgrowth. J. Neurosci. **30**(32), 10918–10926 (2010)
18. Carmel, J.B., Kimura, H., Berrol, L.J., Martin, J.H.: Motor cortex electrical stimulation promotes axon outgrowth to brain stem and spinal targets that control the forelimb impaired by unilateral corticospinal injury. Eur. J. Neurosci. **37**(7), 1090–1102 (2013)
19. Carmel, J.B., Kimura, H., Martin, J.H.: Electrical stimulation of motor cortex in the uninjured hemisphere after chronic unilateral injury promotes recovery of skilled locomotion through ipsilateral control. J. Neurosci. **34**(2), 462–466 (2014)
20. Carp, J.S., Tennissen, A.M., Chen, X.Y., Wolpaw, J.R.: H-reflex operant conditioning in mice. J. Neurophysiol. **96**(4), 1718–1727 (2006)
21. Chen, Y., Chen, L., Wang, Y., Wolpaw, J.R., Chen, X.Y.: Operant conditioning of rat soleus H-reflex oppositely affects another H-reflex and changes locomotor kinematics. J. Neurosci. **31**(31), 11370–11375 (2011)
22. Chen, Y., Chen, X.Y., Jakeman, L.B., Chen, L., Stokes, B.T., Wolpaw, J.R.: Operant conditioning of H-reflex can correct a locomotor abnormality after spinal cord injury in rats. J. Neurosci. **26**(48), 12537–12543 (2006)
23. Colombo, E.V., Mandelli, C., Mortini, P., Messina, G., De Marco, N., Donati, R., Irace, C., Landi, A., Lavano, A., Mearini, M., Podetta, S., Servello, D., Zekaj, E., Valtulina, C., Dones, I.: Epidural spinal cord stimulation for neuropathic pain: a neurosurgical multicentric Italian data collection and analysis. Acta neurochirurgica **157**(4), 711–720 (2015)

24. Compton, A.K., Shah, B., Hayek, S.M.: Spinal cord stimulation: a review. Curr. Pain Headache Rep. **16**(1), 35–42 (2012)
25. Côté, M., Ménard, A., Gossard, J.: Spinal cats on the treadmill: changes in load pathways. J. Neurosci. **23**(7), 2789–2796 (2003)
26. Côté, M.P., Gossard, J.P.: Step training-dependent plasticity in spinal cutaneous pathways. J. Neurosci. **24**(50), 11317–11327 (2004)
27. Courtine, G., Gerasimenko, Y., van den Brand, R., Yew, A., Musienko, P., Zhong, H., Song, B., Ao, Y., Ichiyama, R.M., Lavrov, I., Roy, R.R., Sofroniew, M.V., Edgerton, V.R.: Transformation of nonfunctional spinal circuits into functional states after the loss of brain input. Nat. Neurosci. **12**(10), 1333–1342 (2009)
28. Crown, E.D., Ferguson, A.R., Joynes, R.L., Grau, J.W.: Instrumental learning within the spinal cord. II. Evidence for central mediation. Physiol. Behav. **77**(2–3), 259–267 (2002)
29. Culler, E., Mettler, F.A.: Conditioned behavior in a decorticate dog. J. Comp. Psychol. **18**(3), 291–303 (1934)
30. De Leon, R.D., Hodgson, J.A., Roy, R.R., Edgerton, V.: Full weight-bearing hindlimb standing following stand training in the adult spinal cat. J. Neurophysiol. **80**(1), 83–91 (1998)
31. Dietz, V.: Locomotor capacity of spinal cord in paraplegic patients. Electroencephalogr. Clin. Neurophysiol. **109**, 140–153 (1997)
32. Dietz, V., Fouad, K.: Restoration of sensorimotor functions after spinal cord injury. Brain **137**(3), 654–667 (2014)
33. Dietz, V., Harkema, S.J.: Locomotor activity in spinal cord-injured persons. J. Appl. Physiol. **96**(5), 1954–1960 (2004)
34. Dimitrijevic, M., Kakulas, B., McKay, W., Vrbova, G.: Restorative Neurol. Spinal Cord Inj. (2011)
35. Dimitrijević, M.R., Faganel, J., Gregorić, M., Nathan, P.W., Trontelj, J.K.: Habituation: effects of regular and stochastic stimulation. J. Neurol. Neurosurg. Psychiatry **35**(2), 234–242 (1972)
36. Ding, Y., Kastin, A.J., Pan, W.: Neural plasticity after spinal cord injury. Curr. Pharm. Des. **11**(11), 1441–1450 (2005)
37. Domingo, A., Al-Yahya, A.A., Asiri, Y., Eng, J.J., Lam, T.: A systematic review of the effects of pharmacological agents on walking function in people with spinal cord injury (2012)
38. Dunlop, S.A.: Activity-dependent plasticity: implications for recovery after spinal cord injury. Trends Neurosci. **31**(8), 410–418 (2008)
39. Durkovic, R.G.: Classical conditioning, sensitization and habituation in the spinal cat. Physiol. Behav. **14**(3), 297–304 (1975)
40. Durkovic, R.G.: Retention of a classically conditioned reflex response in spinal cat. Behav. Neural Biol. **43**(1), 12–20 (1985)
41. Duysens, J., Stein, R.B.: Reflexes induced by nerve stimulation in walking cats with implanted cuff electrodes. Exp. Brain Res. **32**(2), 213–224 (1978)
42. Edgerton, V.R., Tillakaratne, N.J.K., Bigbee, A.J., de Leon, R.D., Roy, R.R.: Plasticity of the spinal neural circuitry after injury. Ann. Rev. Neurosci. **27**, 145–167 (2004)
43. Evatt, M.L., Wolf, S.L., Segal, R.L.: Modification of human spinal stretch reflexes: preliminary studies. Neurosci. Lett. **105**(3), 350–355 (1989a)
44. Evatt, M., Wolf, S., Segal, R.: Modification of human spinal stretch reflexes: preliminary studies. Neurosci. Lett. **105**(3), 350–355 (1989b)
45. Ferguson, A.R., Crown, E.D., Grau, J.W.: Nociceptive plasticity inhibits adaptive learning in the spinal cord. Neuroscience **141**(1), 421–431 (2006)
46. Ferguson, A.R., Russel Huie, J., Crown, E.D., Baumbauer, K.M., Hook, M.A., Garraway, S.M., Lee, K.H., Hoy, K.C., Grau, J.W.: Maladaptive spinal plasticity opposes spinal learning and recovery in spinal cord injury. Front. Physiol. **3**(October), 399 (2012)
47. Field-Fote, E.C.: Spinal cord control of movement: implications for locomotor rehabilitation following spinal cord injury. Phys. Ther. **80**(5), 477–484 (2000)
48. Field-Fote, E.C., Roach, K.E.: Influence of a locomotor training approach on walking speed and distance in people with chronic spinal cord injury: a randomized clinical trial. Phys. Ther. **91**(1), 48–60 (2011)

49. Fitzgerald, L.A., Thompson, R.F.: Classical conditioning of the hindlimb flexion reflex in the acute spinal cat. Psychon. Sci. **8**(5), 213–214 (1967)
50. Fong, A.J., Roy, R.R., Ichiyama, R.M., Lavrov, I., Courtine, G., Gerasimenko, Y.P., Tai, Y.C., Burdick, J., Edgerton, V.: Recovery of control of posture and locomotion after a spinal cord injury: solutions staring us in the face. Prog. Brain Res. **175**(09), 393–418 (2009)
51. Frigon, A., Rossignol, S.: Functional plasticity following spinal cord lesions. Prog. Brain Res. **157**, 231–260 (2006)
52. Fung, J., Barbeau, H.: Effects of conditioning cutaneomuscular stimulation on the soleus H-reflex in normal and spastic paretic subjects during walking and standing. J. Neurophysiol. **72**(5), 2090–2104 (1994)
53. Gerasimenko, Y., Roy, R., Edgerton, V.: Epidural stimulation: comparison of the spinal circuits that generate and control locomotion in rats, cats and humans. Exp. Neurol. **209**(2), 417 (2008)
54. Goldshmit, Y., Lythgo, N.: Treadmill training after spinal cord hemisection in mice promotes axonal sprouting and synapse formation and improves motor recovery. J. Neurotrauma **25**(5), 449 (2008)
55. Grau, J., Barstow, D., Joynes, R.: Instrumental learning within the spinal cord: I. Behavioral properties. Behav. Neurosci. http://psycnet.apa.org/psycinfo/1998-03082-007 (1998)
56. Grau, J.W.: Learning from the spinal cord: how the study of spinal cord plasticity informs our view of learning. Neurobiol. Learn. Mem. **108**, 155–171 (2014)
57. Grau, J.W., Russell Huie, J., Garraway, S.M., Hook, M.A., Crown, E.D., Baumbauer, K.M., Lee, K.H., Hoy, K.C., Ferguson, A.R.: Impact of behavioral control on the processing of nociceptive stimulation (2012)
58. Groves, P.M., Lee, D., Thompson, R.F.: Effects of stimulus frequency and intensity on habituation and sensitization in acute spinal cat. Physiol. Behav. **4**(3), 383–388 (1969)
59. Guevremont, L., Renzi, C.G., Norton, J.A., Kowalczewski, J., Saigal, R., Mushahwar, V.K.: Locomotor-related networks in the lumbosacral enlargement of the adult spinal cat: activation through intraspinal microstimulation. IEEE Trans. Neural Syst. Rehabil. Eng. **14**, 266–272 (2006)
60. Harkema, S., Gerasimenko, Y., Hodes, J., Burdick, J., Angeli, C., Chen, Y., Ferreira, C., Willhite, A., Rejc, E., Grossman, R.G., Edgerton, V.R.: 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**(9781), 1938–1947 (2011)
61. Harkema, S., Hurley, S.: Human lumbosacral spinal cord interprets loading during stepping. J. Neurophysiol. **77**(10), 797–811 (1997)
62. Harkema, S.J.: Neural plasticity after human spinal cord injury: application of locomotor training to the rehabilitation of walking. Neuroscientist **7**(5), 455–468 (2001)
63. Herman, R., He, J., Luzansky, S.D., Willis, W., Dilli, S.: Spinal cord stimulation facilitates functional walking in a chronic, incomplete spinal cord injured, pp. 65–68 (2002)
64. Hiersemenzel, L.P., Curt, A., Dietz, V.: From spinal shock to spasticity: neuronal adaptations to a spinal cord injury. Neurology **54**(8), 1574–1582 (2000)
65. Hodgson, J.A., Roy, R.R., de Leon, R.D., Dobkin, B.H., Edgerton, V.: Can the mammalian lumbar spinal cord learn a motor task? Med. Sci. Sports Exerc. **26**, 1491–1497 (1994)
66. Hook, M.A., Grau, J.W.: An animal model of functional electrical stimulation: evidence that the central nervous system modulates the consequences of training. Spinal Cord: Official J. Int. Med. Soc. Paraplegia **45**(11), 702–712 (2007)
67. Hoover, J.E., Durkovic, R.G.: Retention of a backward classically conditioned reflex response in spinal cat. Exp. Brain Res. **77**(3), 621–627 (1989)
68. Hubli, M., Dietz, V.: The physiological basis of neurorehabilitation–locomotor training after spinal cord injury. J. Neuroeng. Rehabil. **10**, 5 (2013)
69. Jindrich, D.L., Joseph, M.S., Otoshi, C.K., Wei, R.Y., Zhong, H., Roy, R.R., Tillakaratne, N.J.K., Edgerton, V.R.: Spinal learning in the adult mouse using the Horridge paradigm. J. Neurosci. Methods **182**(2), 250–254 (2009)
70. Kemler, M., Vet, H.D.: The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy: Two years' follow up of the randomized controlled trial. Ann. Neurol. **55**(1), 13–18 (2004)

71. Knikou, M.: Plantar cutaneous afferents normalize the reflex modulation patterns during stepping in chronic human spinal cord injury. J. Neurophysiol. **103**(3), 1304–1314 (2010)
72. Knikou, M.: Plasticity of corticospinal neural control after locomotor training in human spinal cord injury. Neural Plast. **2012** (2012)
73. Kumar, K., Nath, R., Wyant, G.: Treatment of chronic pain by epidural spinal cord stimulation: a 10-year experience. J. Neurosurg. **75**, 402–407 (1991)
74. Kumar, K., Toth, C., Nath, R., Laing, P.: Epidural spinal cord stimulation for treatment of chronic painsome predictors of success. A 15-year experience. Surg. Neurol. **50**, 110 (1998)
75. Lam, T., Eng, J.J., Wolfe, D.L., Hsieh, J.T., Whittaker, M.: A systematic review of the efficacy of gait rehabilitation strategies for spinal cord injury. Top. Spinal Cord Inj. Rehabil. **13**(1), 32–57 (2007)
76. Landry, E.S., Lapointe, N.P., Rouillard, C., Levesque, D., Hedlund, P.B., Guertin, P.A.: Contribution of spinal 5-HT1A and 5-HT7 receptors to locomotor-like movement induced by 8-OH-DPAT in spinal cord-transected mice. Eur. J. Neurosci. **24**, 535–546 (2006)
77. Latremoliere, A., Woolf, C.J.: Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J. Pain: Official J. Am. Pain Soc. **10**(9), 895–926 (2009)
78. Leonard, C.T., Matsumoto, T., Diedrich, P.: Human myotatic reflex development of the lower extremities. Early Human Dev. **43**(1), 75–93 (1995)
79. Lin, S.I., Yang, W.C.: Effect of plantar desensitization on postural adjustments prior to step initiation. Gait Posture **34**(4), 451–456 (2011)
80. Lloyd, D.P.: Post-tetanic potentiation of response in monosynaptic reflex pathways of the spinal cord. J. Gen. Physiol. **33**(2), 147–170 (1949)
81. Lovely, R.G., Gregor, R.J., Roy, R.R., Edgerton, V.R.: Effects of training on the recovery of full-weight-bearing stepping in the adult spinal cat. Exp. Neurol. **92**(2), 421–435 (1986)
82. Manella, K.J., Roach, K.E., Field-Fote, E.C.: Operant conditioning to increase ankle control or decrease reflex excitability improves reflex modulation and walking function in chronic spinal cord injury. J. Neurophysiol. **109**(11), 2666–2679 (2013)
83. Marsh, B.C., Astill, S.L., Utley, A., Ichiyama, R.M.: Movement rehabilitation after spinal cord injuries: emerging concepts and future directions. Brain Res. Bull. **84**(4–5), 327–336 (2011)
84. Martin, G.F., Cabana, T., Culberson, J.L., Curry, J.J., Tschismadia, I.: The early development of corticobulbar and corticospinal systems. Anat. Embryol. **161**(2), 197–213 (1980)
85. Martin, J.H.: The corticospinal system: from development to motor control. Neuroscientist **11**(2), 161–173 (2005)
86. Martin, J.H., Friel, K.M., Salimi, I., Chakrabarty, S.: Activity- and use-dependent plasticity of the developing corticospinal system. Neurosci. Biobehav. Rev. **31**(8), 1125–1135 (2007)
87. Martin, J.H., Lee, S.J.: Activity-dependent competition between developing corticospinal terminations. Neuroreport **10**(11), 2277–2282 (1999)
88. Martinez, M., Brezun, J.-M., Zennou-Azogui, Y., Baril, N., Xerri, C.: Sensorimotor training promotes functional recovery and somatosensory cortical map reactivation following cervical spinal cord injury. Eur. J. Neurosci. **30**(12), 2356–2367 (2009)
89. Mazzocchio, R., Kitago, T., Liuzzi, G., Wolpaw, J.R., Cohen, L.: Plastic changes in the human H-reflex pathway at rest following skillful cycling training. Clin. Neurophysiol. **117**(8), 1682–1691 (2006)
90. McCrea, D.A.: Spinal circuitry of sensorimotor control of locomotion. J. Physiol. **533**(1), 41–50 (2001)
91. Mekhail, N.A., Mathews, M., Nageeb, F., Guirguis, M., Mekhail, M.N., Cheng, J.: Retrospective review of 707 cases of spinal cord stimulation: indications and complications. Pain Pract. **11**(2), 148–153 (2011)
92. Merrill, D.R.: Materials considerations of implantable neuroengineering devices for clinical use. Curr. Opin. Solid State Mater. Sci. **18**(6), 329–336 (2014)
93. Meunier, S., Russmann, H., Simonetta-Moreau, M., Hallett, M.: Changes in spinal excitability after PAS. J. Neurophysiol. **97**(4), 3131–3135 (2007)

94. Mondello, S.E., Kasten, M.R., Horner, P.J., Moritz, C.T.: Therapeutic intraspinal stimulation to generate activity and promote long-term recovery. Front. Neurosci. **8**(February), 21 (2014)
95. Moritz, C.T., Lucas, T.: Forelimb movements and muscle responses evoked by microstimulation of cervical spinal cord in sedated monkeys. J. Neurophysiol. **97**, 110 (2007)
96. Mrachacz-Kersting, N., de Brito Silva, P., Makihara, Y., Arendt-Nielsen, L., Sinkjaer, T., Kerstin, U.G.: Stretch reflex conditioning in humans implications for function. In: Replace, Repair, Restore, Relieve Bridging Clinical and Engineering Solutions in Neurorehabilitation, pp. 103–111 (2014)
97. Muir, G.D.: Early ontogeny of locomotor behaviour: a comparison between altricial and precocial animals. Brain Res. Bull. **53**(5), 719–726 (2000)
98. Muir, G.D., Steeves, J.D.: Phasic cutaneous input facilitates locomotor recovery after incomplete spinal injury in the chick. J. Neurophysiol. **74**(1), 358–368 (1995)
99. Mushahwar, V., Aoyagi, Y.: Movements generated by intraspinal microstimulation in the intermediate gray matter of the anesthetized, decerebrate, and spinal cat. Can. J. Physiol. Pharmacol. **82**, 702 (2004)
100. Myklebust, B.M., Gottlieb, G.L., Penn, R.D., Agarwal, G.C.: Reciprocal excitation of antagonistic muscles as a differentiating feature in spasticity. Ann. Neurol. **12**(4), 367–374 (1982)
101. Nielsen, J., Crone, C., Hultborn, H.: H-reflexes are smaller in dancers from The Royal Danish Ballet than in well-trained athletes. Eur. J. Appl. Physiol. Occup. Physiol. **66**(2), 116–121 (1993)
102. Panek, I., Bui, T., Wright, A.T., Brownstone, R.M.: Cutaneous afferent regulation of motor function. Acta Neurobiol. Exp. **74**(2), 158–171 (2014)
103. Prosser, C., Hunter, W.: The extinction of startle responses and spinal reflexes in the white rat. Am. J. Physiol. **17**, 609 (1936)
104. Rankin, C.H., Abrams, T., Barry, R.J.: Habituation revisited: an updated and revised description of the behavioral characteristics of habituation. Neurobiol. Learn. **92**(2), 135–138 (2009)
105. Riddoch, G.: The reflex functions of the completely divided spinal cord in man, compared with those associated with less severe lesions. Brain **40**(2–3), 264–402 (1917)
106. Rossignol, S.: Plasticity of connections underlying locomotor recovery after central and/or peripheral lesions in the adult mammals. Philos. Trans. R. Soc. Lond. B Biol. Sci. **361**(1473), 1647–1671 (2006)
107. Rossignol, S., Dubuc, R., Gossard, J.P.: Dynamic sensorimotor interactions in locomotion. Physiol. Rev. **86**(1), 89–154 (2006)
108. Rossignol, S., Frigon, A.: Recovery of locomotion after spinal cord injury: some facts and mechanisms. Ann. Rev. Neurosci. **34**, 413–440 (2011a)
109. Rossignol, S., Frigon, A.: Recovery of locomotion after spinal cord injury: some facts and mechanisms. Ann. Rev. Neurosci. **34**, 413–440 (2011b)
110. Sadowsky, C., Volshteyn, O., Schultz, L., McDonald, J.W.: Spinal cord injury. Disabil. Rehabil. **24**(13), 680–687 (2002)
111. Schneider, C., Capaday, C.: Progressive adaptation of the soleus H-reflex with daily training at walking backward. J. Neurophysiol. **89**(2), 648–656 (2003)
112. Segal, R.L., Wolf, S.L.: Operant conditioning of spinal stretch reflexes in patients with spinal cord injuries. Exp. Neurol. **130**(2), 202–213 (1994)
113. Sherrington, C.S.: Observations on the scratch-reflex in the spinal dog. J. Physiol. **34**(1–2), 1–50 (1906)
114. Sherrington, C.S.: Flexion-reflex of the limb, crossed extension-reflex, and reflex stepping and standing. J. Physiol. **40**(1–2), 28 (1910)
115. Shurrager, P.S., Culler, E.: Conditioning in the spinal dog. J. Exp. Psychol. **26**(2), 133–159 (1940)
116. Shurrager, P.S., Dykman, R.A.: Walking spinal carnivores. J. Comp. Physiol. Psychol. **44**(3), 252–262 (1951)
117. Slawinska, U., Majczynski, H., Dai, Y., Jordan, L.M., Sawiska, U., Majczyski, H., Dai, Y., Jordan, L.M.: The upright posture improves plantar stepping and alters responses to serotonergic drugs in spinal rats. J. Physiol. **590**(Pt 7), 1721–1736 (2012)

118. Smith, R.R., Shum-Siu, A., Baltzley, R., Bunger, M., Baldini, A., Burke, D.A., Magnuson, D.S.K.: Effects of swimming on functional recovery after incomplete spinal cord injury in rats. J. Neurotrauma **23**(6), 908–919 (2006)
119. Stefan, K., Kunesch, E., Cohen, L.G., Benecke, R., Classen, J.: Induction of plasticity in the human motor cortex by paired associative stimulation. Brain **123 Pt 3**, 572–84. http://www.ncbi.nlm.nih.gov/pubmed/10686179 (2000)
120. Taylor, A.J., Menz, H.B., Keenan, A.-M.: Effects of experimentally induced plantar insensitivity on forces and pressures under the foot during normal walking. Gait Posture **20**(3), 232–237 (2004)
121. Thomas, A.M., Simpson, D.M.: Contralateral weakness following botulinum toxin for post-stroke spasticity. Muscle Nerve **46**(3), 443–448 (2012)
122. Thompson, A.K., Chen, X.Y., Wolpaw, J.R.: Acquisition of a simple motor skill: task-dependent adaptation plus long-term change in the human soleus H-reflex. J. Neurosci. **29**(18), 5784–5792 (2009)
123. Thompson, A.K., Pomerantz, F.R., Wolpaw, J.R.: Operant conditioning of a spinal reflex can improve locomotion after spinal cord injury in humans. J. Neurosci. **33**(6), 2365–2375 (2013)
124. Thompson, A.K., Wolpaw, J.R.: Restoring walking after spinal cord injury: operant conditioning of spinal reflexes can help. Neuroscientist (March) (2014)
125. Thompson, R.F., Spencer, W.: Habituation: a model phenomenon for the study of neuronal substrates of behavior. Psychol. Rev. (1966)
126. Thoumie, P., Do, M.C.: Changes in motor activity and biomechanics during balance recovery following cutaneous and muscular deafferentation. Exp. Brain Res. Experimentelle Hirnforschung. Experimentation cerebrale **110**(2), 289–297 (1996)
127. Ting, L.H., Macpherson, J.M.: Ratio of shear to load ground-reaction force may underlie the directional tuning of the automatic postural response to rotation and translation. J. Neurophysiol. **92**(2), 808–823 (2004)
128. Turner, J.A., Loeser, J.D., Deyo, R.A., Sanders, S.B.: Spinal cord stimulation for patients with failed back surgery syndrome or complex regional pain syndrome: a systematic review of effectiveness and complications. Pain **108**(1–2), 137–147 (2004)
129. van den Brand, R., Heutschi, J., Barraud, Q.: Restoring voluntary control of locomotion after paralyzing spinal cord injury. Science (2012)
130. Varejão, A.S.P., Filipe, V.V.M., Varejao, A., Filipe, V.V.M.: Contribution of cutaneous inputs from the hindpaw to the control of locomotion in rats. Behav. Brain Res. **176**(2), 193–201 (2007)
131. Waltz, J.M., Andreesen, W.H., Hunt, D.P.: Spinal cord stimulation and motor disorders. Pacing Clin. Electrophysiol. **10**, 180–204 (1987)
132. Ward, A.B.: Spasticity treatment with botulinum toxins. J. Neural Transm. (Vienna, Austria, 1996) **115**(4), 607–616 (2008)
133. Wenger, N., Moraud, E.M., Raspopovic, S., Bonizzato, M., DiGiovanna, J., Musienko, P., Morari, M., Micera, S., Courtine, G.: Closed-loop neuromodulation of spinal sensorimotor circuits controls refined locomotion after complete spinal cord injury. Sci. Transl. Med. **6**(255), 255ra133–255ra133 (2014)
134. Wernig, A.: Long-term body-weight supported treadmill training and subsequent follow-up in persons with chronic SCI: effects on functional walking ability and measures of subjective well-being. Spinal Cord **44**(4), 265–266; author reply 267–268 (2006)
135. Wernig, A., Nanassy, A., Müller, S.: Maintenance of locomotor abilities following Laufband(treadmill) therapy in para- and tetraplegic persons: follow-up studies. Spinal Cord (1998)
136. Wolpaw, J.R.: Spinal cord plasticity in acquisition and maintenance of motor skills. Acta Physiol. **189**(2), 155–169 (2007)
137. Wolpaw, J.R.: What can the spinal cord teach us about learning and memory? Neuroscientist **16**(5), 532–549 (2010)
138. Wolpaw, J.R.: Harnessing neuroplasticity for clinical applications. Brain **135**(Pt 4), e215; author reply e216 (2012)

139. Wolpaw, J.R., Herchenroder, P.A.: Operant conditioning of H-reflex in freely moving monkeys. J. Neurosci. Methods **31**(2), 145–152 (1990)
140. Wolpaw, J.R., Kieffer, V.A., Seegal, R.F., Braitman, D.J., Sanders, M.G.: Adaptive plasticity in the spinal stretch reflex. Brain Res. **267**(1), 196–200 (1983)
141. Wolpaw, J.R., Lee, C.L., Calaitges, J.G.: Operant conditioning of primate triceps surae H-reflex produces reflex asymmetry. Exp. Brain Res. **75**, 35–39 (1989)
142. Wolpaw, J.R., O'Keefe, J.A.: Adaptive plasticity in the primate spinal stretch reflex: evidence for a two-phase process. J. Neurosci: Official J. Soc. Neurosci. **4**(11), 2718–2724 (1984)
143. Wolpaw, J.R., Tennissen, A.M.: Activity-dependent spinal cord plasticity in health and disease. Ann. Rev. Neurosci. **24**, 807–843 (2001a)
144. Wolpaw, J.R., Tennissen, A.M.: Activity-dependent spinal cord plasticity in health and disease. Ann. Rev. Neurosci. **24**, 807–843 (2001b)
145. Woolf, C.J.: Central sensitization: implications for the diagnosis and treatment of pain (2011)
146. Zehr, E.P., Komiyama, T., Stein, R.B.: Cutaneous reflexes during human gait: electromyographic and kinematic responses to electrical stimulation. J. Neurophysiol. **77**(6), 3311–3325 (1997)
147. Zehr, E.P., Stein, R.B., Komiyama, T.: Function of sural nerve reflexes during human walking. J. Physiol. **507**(Pt 1), 305–314
148. Zimmermann, J.B., Seki, K., Jackson, A.: Reanimating the arm and hand with intraspinal microstimulation. J. Neural Eng. **8**(5), 054001 (2011)