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Review

Neurorehabilitation Based on Spinal Cord Stimulation and Motor Training

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This review presents recent data on the restoration of motor functions after spinal injuries, on spontaneous neuroplasticity, on plasticity dependent on physical activity, on results from the use of epidural and transcutaneous electrical stimulation of the spinal cord to restore motor control, and on the neurophysiological changes and mechanisms initiated by spinal electrical stimulation which may contribute to functional recovery after spinal cord injury.

Keywords: central nervous system, spinal cord, injury, motor activity, plasticity, movement restoration, spinal electrical stimulation.

Abbreviations: SCI – spinal cord injury; CNS – central nervous system; SCS – spinal cord stimulation; BDNF – brain-derived neurotrophic factor; TrkB – tyrosine kinase receptor B; CREB – cellular transcription factor.

Spinal cord injury (SCI) is an event which leaves most people with lifelong disability because of the restricted capacity of the central nervous system (CNS) for recovery and the limited therapeutic options available to date [66]. The clinical picture of traumatic spinal cord injury is characterized by a deficit of motor activity, disturbances of sensory and autonomic functions, and neuropathic pain [3]. The World Health Organization reports that 200,000–500,000 new cases of SCI are recorded annually around the world [105]. Unfortunately, modern methods of treating spinal injuries do not provide sufficient restoration of lost CNS functions [7, 66, 87]. The search for therapeutic methods able to produce effective reductions in the sequelae of SCI is therefore a priority area in neurology [4].

Plastic changes in neural networks are regarded as key to functional recovery after trauma [53]. Plasticity underlies processes such as learning and memory, adaptation to morphological changes during development and aging, and the process of functional recovery after injury [81]. The literature contains many definitions of the phenomenon of neuroplasticity. Common to all is the definition of neuroplasticity as the ability of nervous tissue to change its structure and function in response to the influences of exogenous and endogenous factors [5].

The damaged CNS retains its ability for neuroplasticity [21], and application of various types of physical (motor) activity constitute the most widely recognized method of treating most of the sequelae of SCI [20, 34]. Physical activity causes anatomical and functional changes in the CNS and affects dendritic sprouting, synaptic connections, the production and regulation of neurotransmitters, and ion homeostasis [20]. Other methods of initiating plastic changes after SCI are also known, though their use is, nonetheless, more effective when combined with treatment based on motor activity [23].

With the aim of overcoming post-traumatic movement disorders, rehabilitation therapy seeks to improve motor control and maximize functional recovery by activating neural pathways remaining intact after SCI [32]. Therapy for walking focuses on locomotor training [49, 103, 105]. This training allowed people with subtotal motor and sensory SCI to regain motor function in their paralyzed limbs [91]. However, although improvements in walking were observed in these cases, these were modest, while training alone was insufficient in terms of improving voluntary motor control and walking in individuals with chronic complete motor

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SCI and severe incomplete SCI; at the same time, supplementation of locomotor training with epidural spinal electrical stimulation in these same people led to improvement in voluntary muscle activation and walking [11, 102]. It should be noted that SCI is classified clinically as "complete" when there is complete loss of sensation and voluntary motor control below the level of injury; SCI is clinically "incomplete" when there is some degree of sensation and/or preserved but limited voluntary movement [31].

Neuromodulation using electrical spinal cord stimulation (SCS) [30] is an approach to promoting neuroplasticity [58] in the injured CNS, the resulting plasticity leading to functional recovery [87]. Neuromodulation can enhance the effects of therapies such as locomotor training. As both motor training and SCS have the potential to improve gait, it seems reasonable to suppose that simultaneous use of these approaches might be associated with more significant results [82].

There is as yet no generally accepted mechanism by which SCS promotes motor recovery in people with SCI [32]. Motor recovery is based on the plasticity of multiple networks occurring over long periods of time, making it difficult to identify precisely which factor(s) initiate the recovery process and/or maintain the recovered state [98], so this review presents a range of neurophysiological changes and mechanisms initiated by SCS which may underlie functional recovery after spinal injuries. In addition, the review briefly addresses results from recent years on overcoming motor dysfunctions through the internal capabilities of the CNS and the use of physical exercises/training and spinal electrical stimulation alone and combined.

Spontaneous Neuroplasticity. Neural reorganization of the CNS after SCI occurs spontaneously for some period of time but produces only minor recovery; this process includes compensatory sprouting into adjacent areas of the spinal cord and limited axonal regeneration [22]. Spontaneous neurorestoration is typical of the acute and subacute phases (12–18 months after injury) of the post-traumatic period and ends (reaches a plateau) at the beginning of the chronic phase [22]. In particular, spontaneous recovery of motor function usually reaches a plateau within 1.5 years of SCI [87].

Animal studies have shown that the formation of bypass pathways reconnecting cortical, brainstem, and intraspinal projection neurons to denervated networks below the injury site promotes spontaneous recovery [14].

Spinal injury not only affects the spinal cord, but also immediately initiates changes in the state of the brain and triggers cortical reorganization [21]. However, despite spontaneous reorganization of networks in the brain and spinal cord, CNS recovery remains limited and reaches a plateau by the chronic phase of the post-traumatic period [22].

Neuroplasticity can also lead to undesirable outcomes. For example, maladaptive plasticity after SCI can lead to the formation of abnormal sympathetic reflexes and worsening dysautonomic syndrome [77]. Furthermore, the activity of thoracic spinal VGluT2$^+$-type interneurons was found to influence structural and functional plasticity in damaged spinal cord, while inhibition of these neurons suppressed maladaptive plasticity after SCI [77].

Motor rehabilitation plays an important role in ensuring that the potential of plasticity is directed towards restoring lost functions [76]. Moreover, task-specific proprioceptive and other sensory information during motor activity can influence the nature of the reorganization of neural networks [98].

Physical Activity-Dependent Plasticity. Different types of physical activity (such as climbing stairs, static cycling, and locomotor training on a treadmill) reduce inflammation, increase neurotrophin levels, can improve preserved function after SCI, and guide spinal reorganization [23]. Movement-based therapy is a neurotherapeutic intervention which activates the neuromuscular system below and above the level of the lesion, promoting nervous system plasticity [17]. In individuals with SCI, this therapy can promote functional recovery [9] via activity-dependent plasticity [23]. Apart from influencing motor functions, it can help maintain general health and improve autonomic responses [11, 33, 56].

Brain-derived neurotrophic factor (BDNF) plays a critical role in the adaptive plasticity of the CNS and promotes functional recovery after SCI [23]. Even short periods of exercise increased serum BDNF levels both in healthy people and people with SCI [44, 62].

A number of studies have confirmed the critical role of BDNF and its tyrosine kinase receptor B (TrkB) in repair processes. Blockade of BDNF in animals abolished exercise-induced reductions in locomotor impairment [64] and spasticity [19]. Blockade of TrkB after SCI prevented activity-dependent functional recovery [63, 104]. Taken together, these studies clearly identify BDNF and TrkB as critical elements in the transformation of motor activity into functional recovery.

Current concepts of rehabilitation suggest that repetition of movements leads to the strengthening of any projections surviving injury and to stabilization and strengthening of connections newly formed as a result of axon sprouting [52]. Surviving and newly formed fibers and connections are integrated into functional networks through intensive rehabilitation training, restoring a degree of both structural connectivity and motor function [53].

Motor training in mice with spinal contusions at the thoracic level increased motor neuron activity and led to restoration of locomotion [89]. Motor training in rats with SCI at the cervical level promoted axonal sprouting and synaptic plasticity, also improving forelimb motor function [37].

Exercise increased the synthesis of cellular transcription factor CREB and its phosphorylated form (pCREB) in the spinal cord caudal to injury, and this was associated with improved functional recovery [63]. In addition, exercise reversed SCI-induced suppression of perineuronal net-

works around lumbar motoneurons below the level of the lesion [89], while restoration of perineuronal networks correlated with decreased hyperreflexia and better recovery of locomotor activity [89].

Synaptic influences and spinal interneuron connections also undergo plastic changes as a result of motor training [106, 108]. Both activation of excitatory and modulation of inhibitory interneurons can be critical for functional recovery [106]. Motor activity-dependent plasticity also occurred in spinal reflex pathways [23], as well as in proprioceptive feedback pathways [98]. In particular, Beverungen et al. [19] found that activity-dependent increases in potassium chloride ion cotransporter (KCC2) levels in rats with spinal cord transection led to restoration of the properties of H-reflexes, this being critically dependent on BDNF activity.

Formation of bypass pathways by propriospinal neurons, i.e., pathways redirecting supraspinal signals to pools of interneurons and/or motoneurons located below the level of the lesion, promotes spontaneous recovery after SCI, and strengthening of these mechanisms using motor training may lead to improved functional recovery [105].

Axon sprouting induced by spinal injury was enhanced by physical activity in mice [67], while motor training in genetically modified mice lacking a corticospinal tract induced collateral sprouting of descending monoaminergic and rubrospinal axons and promoted the formation of their connections with motoneurons [107].

The sizes, densities, and total numbers of different synapses on lumbar motor neurons in trained animals with SCI were significantly different from those in intact animals [60], despite significant recovery of locomotor ability, suggesting that recovery from CNS injury does not necessarily entail recovery of pre-injury characteristics, but is a functional adaptation to the "new norm" [20].

After SCI, the spinal cord undergoes physical activity-dependent plastic changes, though exercise/training in people with SCI can – as with spontaneous recovery – reach a plateau phase of functional recovery [56, 99], i.e., an upper limit beyond which there is no further increase in therapeutic effect. This plateau can, however, be overcome by combining exercise/training withSCS.

Electrical Spinal Cord Stimulation. Neuromodulatory strategies such as SCS activate spinal networks, promoting activity-dependent plasticity [23, 48]. This helps to improve the processes of recovery of motor functions after SCI [94]. Two spinal neuromodulation strategies are currently known: one uses tonic SCS, which optimizes spinal network excitability, and the other is designed to impose rhythmic stimulation on afferent fibers in the dorsal roots projecting to specific pools of motor neurons, with the aim of controlling the swing and stance phases of walking [47, 102].

SCS can be either invasive (e.g., epidural), where it uses electrodes surgically implanted on the dura mater of the spinal cord, or non-invasive (e.g., percutaneous), where electrodes are placed on the surface of the skin over the vertebrae [38, 94]. Published data indicate that transcutaneous stimulation affects the same spinal networks as epidural SCS[32, 50, 54].

The authors of a recent study reported that SCS combined with activity-based training produced improvements in motor function which were previously thought to be impossible in the chronic stage of spinal cord injury [91]. Thus, contrary to medical prognoses, the ability to perform movements was restored in chronically paralyzed individuals diagnosed with complete SCI [11, 84]. Other studies reported restoration of the ability to stand independently and generate voluntary movements of the trunk and legs in people with total motor lesions of the spinal cord after courses of rehabilitation including motor training combined with SCS [11, 43, 72].

SCS has not only demonstrated effectiveness in improving locomotion and voluntary muscle control even in people with injuries classified as clinically total [11, 42, 102], but it has produced positive results in restoring autonomic functions after SCI [26, 29, 80, 86].

Results of combined use of epidural stimulation and motor training. The ability of epidural SCS to improve motor function after paralysis was not immediately appreciated during its early clinical application, possibly because the positioning of epidural electrodes in early work was adequate for analgesia but not for motor responses, while clinical use involved low-intensity ESSC without a training component [91].

The idea that epidural spinal stimulation combined with exercise training could improve functional outcomes in individuals with SCI was first tested in a person with a incomplete motor and sensory spinal cord lesion, whose motor performance improved with treadmill and training walking on a flat surface combined with epidural stimulation to a greater extent than achieved with physical training alone [51].

Subsequent work in three people with complete spinal cord motor lesions showed that voluntary movement arose on the background of epidural stimulation immediately after its first application [12]. Intensive treadmill training and epidural stimulation in two patients with total motor spinal cord lesions was followed by their being able to walk independently on a level surface with minimal assistance in maintaining balance [11]. After similar interventions, a patient with paraplegia was able to walk independently on a treadmill, as well as walk on a level surface using a front-wheeled walker with the help of a trainer to maintain balance [42]. These results were supported by data showing that three patients with incomplete motor [102] and three patients with complete sensorimotor SCI [85] experienced recovery of motor function during spatiotemporal epidural stimulation, starting from the first stimulation session. Moreover, after several months of locomotor training combined with SCS, two out of three patients with subtotal motor SCI demonstrated voluntary control of paralyzed leg

muscles and some functional mobility even without epidural stimulation [102].

Seáñez and Capogrosso [91] note that from the point of view of clinical and scientific data, recent results, although using different techniques, are surprisingly consistent: first, the authors report the ability to initiate movements using SCS in previously paralyzed limbs from the first day after epidural electrode implantation; second, patients *gradually* acquired the ability to perform increasingly complex tasks after starting physical training combined with SCS. Perhaps the most important point was partial recovery of motor function by the end of training even without electrical stimulation. Together with earlier work, these studies showed that SCS combined with exercise training promoted neurorestoration and produced lasting changes that led to improved movement performance (with and without SCS) [91].

All of these studies used intensive physical rehabilitation combined with epidural stimulation. However, some researchers have used SCS without intensive training. Darrow et al. [26] treated two patients with total motor and sensory SCI and they displayed improvements in voluntary muscle activity under the influence of epidural stimulation alone. In another clinical study, four of seven participants with chronic complete SCI who received epidural stimulation for 5–9 months without intensive training displayed long-term (stable) recovery of voluntary movement in the absence of electrical stimulation [79]. Furthermore, Lu et al. [68] found that epidural stimulation in patients with total motor SCI increased hand grip strength by a factor of three (from baseline) after 20–22 sessions of epidural stimulation of the cervical spinal cord, despite the absence of intense physical training. Hand clenching force without epidural stimulation was also increased (in pauses between tests with stimulation). These data suggest that intense and repeated training may not be necessary to improve motor recovery with SCS therapy, though further research is needed to answer this important question.

Results obtained by combined use of transcutaneous stimulation and motor training. Gerasimenko et al. used non-invasive electrical stimulation of the spinal cord using electrodes placed on the skin over the spine, a procedure termed transcutaneous spinal cord stimulation [2, 38]. This work provided the first evidence that transcutaneous electrical stimulation is capable of activating neural locomotor networks and initiating stepping movements in healthy subjects in conditions of external leg support [39]. This technology was later translated into clinical studies and demonstrated its effectiveness in restoring voluntary control of movements in spinal patients [41]. Use of combined transcutaneous stimulation of the cervical spine and epidural stimulation of the lumbar spinal cord was found to provide the best effect in regulating stepping movements in paralyzed patients [13].

Tharu et al. [100] reported that the combined use of transcutaneous stimulation and motor training in five patients with complete cervical spinal cord injury improved voluntary control of the trunk, with significant improvements in maintaining static and dynamic balance in the sitting position. In addition, this effect significantly increased the range of motion of the torso and the electromyographic responses of its muscles in patients. The discomfort of accompanying electrical stimulation has been reduced by some researchers by applying SCS with a carrier frequency of up to 10 kHz [10, 56]. Even use of a modulated frequency of 5 kHz was found to make it possible to tolerate almost twice as much current in neurologically healthy people [70].

Lumbosacral transcutaneous stimulation combined with physical therapy improved walking in people with incomplete motor spinal cord injury, either using a 10-kHz carrier [10] or no carrier (stimulation with biphasic pulses at a frequency of 50 Hz) [71]. The combination of transcutaneous stimulation with an exoskeleton and employment of a 10-kHz carrier increased the number of voluntary movements requiring less robotic assistance in a patient with total motor SCI [36]. Tonic transcutaneous stimulation with a 10-kHz carrier enabled people with chronic total motor and sensory paralysis to stand and maintain balance [90]. In addition, improvements in walking after cervical and lumbosacral percutaneous SCS (with a 10-kHz carrier) combined with locomotor training were demonstrated in two patients with chronic subtotal cervical motor SCI [88].

Transcutaneous stimulation of the cervical spinal cord improved upper limb motor function. This stimulation, without the use of intensive training, improved hand grip strength in six patients with complete cervical motor but incomplete sensory SCI [35]. Cervical transcutaneous stimulation with a 10-kHz carrier, combined with intensive hand and arm exercises, was shown to improve both immediate and long-term upper limb function in people with chronic complete and incomplete cervical motor SCI [56, 57].

Although transcutaneous SCS has lower selectivity for activation of motor pools than epidural [27], rehabilitation with transcutaneous SCS combined with activity-based training has ben shown to be effective in promoting voluntary leg movements, posture, and independent standing, as well as in improving upper and lower limb functions in people with chronic SCI [94, 95]. Functional improvements and decreases in dependence on external assistance were quantitatively similar to those observed with epidural stimulation [91]. In addition, although transcutaneous SCS resulted in similar improvements as epidural stimulation, it did not require electrode implantation [57].

Spinal electrical stimulation increases the effectiveness of motor training. The effectiveness of the combined use of exercise/training and SCS ("paired interventions") for improving motor function in people with SCI was assessed in a review by Shackleton et al. [92]. Of the studies published up to June 2022, only 15 were included in the review because they were the only studies in which responses to either physical training/exercise or SCS could be com-

pared with responses to combined intervention. Of these studies, which included a total of 79 people with SCI (60 in 14 studies), 73% were conducted within the last five years.

As compared with physical training alone, training combined with SCS improved walking speed [8, 32, 87], the ability to stand without assistance [11, 51], and the ability to walk without assistance [11, 93]. Increases in motor activity of the upper limbs after paired interventions as compared with motor training alone have been demonstrated [56, 57, 68]. Inanici et al. [56, 57] reported improvements in hand sensitivity and grip strength, as well as the force of pressing the thumb onto the lateral surface of the index finger, in all subjects after adding SCS to physical activity-based exercises. Inanici et al. [56] also reported that two study participants even returned to their previous hobbies after treatment, including playing the guitar and drawing.

The authors of review [92] concluded that although exercise-based methods and SCS are beneficial as two different interventions for restoring function, combined strategies produce better results. However, they emphasize that only two studies were randomized controlled studies, the remaining 13 being case reports. In addition, the authors also noted significant variability in study designs and SCS parameters.

The variability of interventions, together with cohorts with different demographic compositions, small sample sizes, the small number of controlled studies, and poor methodological quality (mostly case studies) of the material reviewed pose challenges in interpreting the effectiveness of paired interventions for functional recovery [92].

Neurophysiological Changes and Mechanisms Initiated by Electrical Spinal Stimulation. Plastic changes dependent on motor training and the use of SCS are ultimately transformed into functional recovery, though the specific mechanisms responsible for this transformation remain largely unknown. These mechanisms, along with factors promoting recovery from spinal cord injuries, have received intense study, primarily in animals.

Experimental studies provided the first demonstration that rats with an anatomically complete spinal cord transection were able to perform locomotion initiated by epidural stimulation, whose kinematic and kinetic characteristics did not differ from those of locomotion of intact animals [24].

Studies using pharmacological interventions in combination with epidural stimulation in spinalized animals have demonstrated the importance of monoaminergic agonists in the regulation of spinal locomotion. Experimental results provided the basis for cocktails of serotonergic agonists and noradrenergic antagonists which effectively control locomotor function in animals with spinal cord injury [75]. The use of such cocktails in combination with epidural stimulation produced locomotion in spinalized rats which was no different from the locomotion of intact animals.

Asboth et al. [14] -performed the studies in rodent models of spinal cord contusion and elucidated the mechanisms providing post-trauma recovery, as well as demonstrating the ability of neuromodulation therapy and physical training to improve motor control. The use of SCS, agonists of serotonergic and dopaminergic receptors, as well as locomotor training in these experiments supported restoration of supraspinal control of locomotion in rats, this being maintained without neuromodulation even during performance of previously untrained tasks natural to the animals. Using optogenetic inactivation of neural networks and microscopy of the brain and spinal cord, the authors showed that reorganization of cortico-reticulospinal connections mediated the recovery of movement in these animals.

Asboth et al. [14] reactivated the lumbar networks both pharmacologically and by epidural electrical stimulation of the lumbosacral segments of the spinal cord. Combined application of these approaches immediately restored automated (involuntary) locomotion on the treadmill. Rats were trained to walk on their hindlegs on a treadmill for nine weeks; continuous tonic epidural stimulation was performed during walking. After training, all rats were able to perform locomotion (with weight support) during electrochemical neuromodulation. Some 88% of the rats were able to walk with electrical stimulation alone (no chemical modulation); without any neuromodulation, 62.5% of rats still moved forward. In contrast, untrained rats had minimal motor improvements and were unable to perform locomotion even with electrochemical neuromodulation.

Asboth et al. [14] found that the motor cortex restored adaptive control of paralyzed limbs during electrochemical neuromodulation of lumbar networks. Glutamatergic reticulospinal neurons with surviving connections with areas lying below the damaged area transmitted cortical commands to them. Intensive locomotor training on the background of neuromodulation therapy supported reorganization of neuronal connections, with the result that cortical information was redirected through reticulospinal connections. This reorganization, according to the study authors, mediated the restoration of natural walking.

Thus, evidence from animals with SCI suggests that corticoreticulospinal connections can provide voluntary control of previously paralyzed limbs, with restoration by SCS, and the activity-dependent reorganization of these connections facilitated bySCS may be a major contributor to the restoration of motor function observed in spinal patients [11, 42, 102].

Clinical studies have shown that the reorganization of neuronal connections providing voluntary control after SCI may be realized as a result of intensive motor training and epidural stimulation of the spinal cord. The first studies showed that paralyzed patients with complete motor lesions of the spinal cord were able to experience restoration of voluntary control of movement after such rehabilitation treatment [12, 48].

Rejc et al. [84] used magnetic resonance imaging to evaluate the spinal cord and voluntary motor control in 13 individuals with chronic complete motor SCI. None of the

study participants was able to modulate lower limb muscle activity by attempting leg flexion or ankle dorsiflexion in the absence of epidural stimulation. Conversely, all were able to generate movement and/or activation of the major muscles involved in the intended movement when epidural stimulation was applied. The authors of this study observed that the amount of surviving tissue differed significantly between individuals and that the quantities and locations of tissue within lesions were not linked with the ability to generate voluntary movements of the lower limbs. The authors discussed axon sprouting from individually specific surviving tissue as a possible cause of the restoration of voluntary control of lower limb movements when using epidural stimulation. As magnetic resonance imaging and voluntary motor function were assessed before any physical training with epidural stimulation, the authors were able to take the view that these potential neural adaptations may result from spontaneous anatomical plasticity after SCI. In addition, these results may be evidence that supraspinal signals, passing through preserved areas of the spinal cord, which vary from person to person such that the signals pass through nonidentical supraspinal-spinal connections, can lead to the generation of voluntary movements of the lower limbs on the background of epidural stimulation, even without prior intense motor training.

The possibility of restoring voluntary movements without intensive motor training is also evidenced by data reported by Peña Pino et al.[79], who observed them using long-term epidural stimulation (mean daily use of stimulation was 13.7 ± 5.8 h and the total duration of use was 255.3 ± 115.3 days) in seven patients with chronic complete motor SCI. The study included 13 consecutive assessments of motor function at intervals of 30–45 days. Each assessment was carried out in two situations – with and without ESSC. During courses of chronic epidural spinal cord stimulation, sustained voluntary movement was observed in four patients even without stimulation. These movements, performed without stimulation, showed progressive, statistically significant improvement over the study period. This resulted in statistically significant improvements in the ability to pedal a stationary bicycle without the aid of the motor fitted to the apparatus. These data suggest that long-term SCS can induce plastic changes in the chronic phase of a severely injured spinal cord without significant intensive motor rehabilitation.

The actions of SCS are not restricted to promoting the reorganization of neuronal pathways occurring as a result of motor training. For example, SCS was recently shown to reduce apoptosis in spinal cord white matter and to enhance the preservation of myelin and oligodendrocyte differentiation, which are processes promoting motor recovery after experimental SCI in rats [65]. Oligodendrocytes cover axons with myelin sheaths, provide them with trophic support, and protect axons and neurons. Loss of oligodendrocytes and axon demyelination are pathological phenomena which impede functional recovery after SCI, so increasing the number of mature oligodendrocytes can significantly improve motor recovery [55].

The influence of SCS on anatomical plasticity is also evidenced by data reported by Urban et al. [101], who demonstrated the previously unknown phenomenon of the reorganization of neuronal connections in the CNS in response to many hours of epidural SCS in rats with hindlimb paralysis resulting from SCI at the thoracic level. Before injury, the rats had developed a conditioned reflex consisting of a sharp movement of the right hindlimb in response to a sound signal of a particular frequency. Neural reorganization after injury was stimulated by subjecting the rats to prolonged application of subthreshold electrical stimulation three times per week combined with training to walk on the hindlimbs on a treadmill. During subthreshold SCS, the animals moved freely around their cage, and sessions were generally of duration 3 h. The duration of each step training session was 15 minutes. Treadmill training was stopped at one month postinjury and prolonged stimulation sessions at two months. The ability to stand and walk independently was restored at one month post-SCI, as evidenced by tests using SCS, though the animals did not display the conditioned reflex during this time period; SCS began to provide the ability to mount the conditioned motor reflex only after two months postinjury. The authors of this study noted that their results indicated that long-lasting electrical neuromodulation of the lumbosacral enlargement could promote the formation of new functional connections between highly specific supraspinal and spinal networks to restore motor behavior learned before spinal injury. These new connections were formed two months after injury but remained inactive in the absence of additional SCS.

Connection of residual (surviving after injury) supraspinal control is critical for restoring voluntary movement control. A diagnosis of complete motor and sensory impairment below the area of injury usually implies severe limitations to functional recovery [87]. However, despite such a clinical diagnosis, most patients still have some capacity for residual, but reduced, descending supraspinal control. The fact is that most SCI, including those classified as *clinically complete*, are *anatomically incomplete* [31] i.e., they do not completely separate the spinal cord below the injury from the brain. However, the fibers surviving after SCI for some reason do not support communication between the brain and this part of the spinal cord, i.e., they are non-functional. This profile is called “discomplete,” where the sensorimotor function is functionally silent but remains anatomically preserved [31]. A clinical diagnosis of complete damage to the spinal cord below the level of injury does not mean that the surviving but inactive connections between the brain and spinal cord after SCI cannot be returned to a functional state. This is evidenced in particular by data reported by Angeli et al. [12], who found that voluntary movements were restored on the background of epidural stimulation

immediately after its first application in patients diagnosed with complete motor and complete sensory damage to the spinal cord.

Locomotor networks below the level of injury remain intact and are able to process sensory information [28]. In addition, some propriospinal networks connecting various spinal segments may remain intact after injury. Descending nerve fibers, propriospinal fibers, and local networks of interneurons and motoneurons surviving after SCI provide the basis for use-dependent recovery of motor functions after incomplete spinal cord injury [25]. Although in and of themselves they are not sufficient for functionally relevant recovery, they can be returned to a functional state by repeated performance of specific motor tasks [42, 105] or electrical stimulation of the spinal cord [47].

However, it should be borne in mind that the effectiveness of SCS also depends on a person's volitional efforts to perform movements: at rest, the effectiveness of SCS can be low without accompanying volitional effort, though it increases with effort, which is important for developing physical activity-dependent plasticity of spinal neural networks [97, 102].

Descending pathways are critical for voluntary control of areas below the site of injury, especially if they can be "switched on" using SCS [87]. Even if the corticospinal tracts are completely damaged, surviving reticulospinal and propriospinal tracts can help restore voluntary control [14].

A possible mechanism for the effect of SCS on the state of the CNS may consist of an increase in the sensitivity of motor neurons to supraspinal signals, as cervical-lumbar transcutaneous SCS increased the amplitudes of motor evoked potentials in the flexor carpi radialis muscle initiated by transcranial magnetic stimulation in intact subjects [78]. Furthermore, both epidural and transcutaneous SCS increased forelimb muscle responses induced by intracortical microstimulation in monkeys [46].

SCS can evidently be regarded as a method which enhances residual (surviving after injury) descending signals relating to voluntary movement, while simultaneously providing excitatory effects on motor neurons, thereby improving motor function and muscle strength [46, 73]. This unique combination allows voluntary movement signals to be mapped to the movements performed, which can lead to activity-dependent plasticity – this has been observed in animals and humans with SCI [74, 105].

Another possible mechanism for SCS-induced functional recovery consists of changes in the excitability of the cortical and subcortical areas of the brain under the influence of signals initiated by this stimulation. For example, a single session of cervical SCS in individuals with incomplete chronic SCI at the cervical level influenced the excitability of cortical and spinal networks, exerting an excitatory effect at the spinal level and an inhibitory effect at the cortical level. These parallel physiological effects influenced the magnitude of improvements in voluntary motor activity [18]. Recent studies have shown that SCS can induce cerebral neuroplasticity both in patients with SCI [18] and in neurologically intact participants [69].

Research following the first reports of motor improvements in response to spinal electrical stimulation sought to elucidate the mechanisms of action of SCS and, in particular, to identify the specific neural elements primarily affected by SCS and how they lead to the recruitment of motoneurons [91]. Two decades of preclinical and clinical studies have demonstrated that spinal electrical stimulation of the lumbosacral spinal cord can reactivate spinal sensorimotor networks after spinal cord injury [47]. Theoretical and experimental work has suggested that SCS applied to the lumbosacral spinal cord primarily activates large-diameter myelinated afferent fibers, which have the lowest activation threshold (group Ia afferents) and run in the dorsal roots and dorsal columns of the spinal cord, i.e., fibers forming synaptic connections with spinal interneurons and motor neurons in the lumbosacral region and also providing synaptic connections with multiple spinal segments [45].

The prevailing view in the literature is that SCS promotes the restoration of motor function after SCI via recruitment of large myelinated *dorsal root* fibers associated with somatosensory and especially proprioceptive information [83]. However, note should be made of the recently expressed view [59] that the thesis whereby most of the effects of transcutaneous and epidural spinal cord stimulation are attributed to stimulation of the dorsal roots should be replaced by the notion that the effects of SCS arise as a result of stimulation of afferent fibers in the dorsal columns or afferent fibers with unspecified stimulation site (possibly excepting the effects of stimulation of the coccygeal segments of the spinal cord or cauda equina), as the areas with the lowest activation threshold of such fibers should be in areas in which they branch, this branching occurring fractions of a millimeter below the surface of the dorsal column, where most afferent fibers branch after entering the spinal cord.

One hypothesis holds that SCS induces mono- and polysynaptic spinal reflexes through primary afferent fibers. It is proposed that the sequence of afferent activation as the intensity of spinal cord stimulation undergoes graded increases is: Ia afferents, group Ib afferents, group II afferents, groups III and IV flexor reflex afferents (FRA), spinal interneurons, and direct activation of motor axons (Fig. 1, *a*). In addition to the dorsal roots and dorsal columns, spinal cord stimulation can also activate the pyramidal and reticulospinal tracts, ventral roots, motor neurons, dorsal horns, and sympathetic pathways. The analysis showed that EMG activity accompanying walking movements is generated in different ways for extensor and flexor muscles. Gerasimenko et al. reported that the formation of burst EMG activity in extensor muscles in spinal patients with SCI is based on amplitude modulation of monosynaptic responses, while the main role in this process in flexor muscles is played by the polysynaptic reflex system (Fig. 1, *c*) [40].

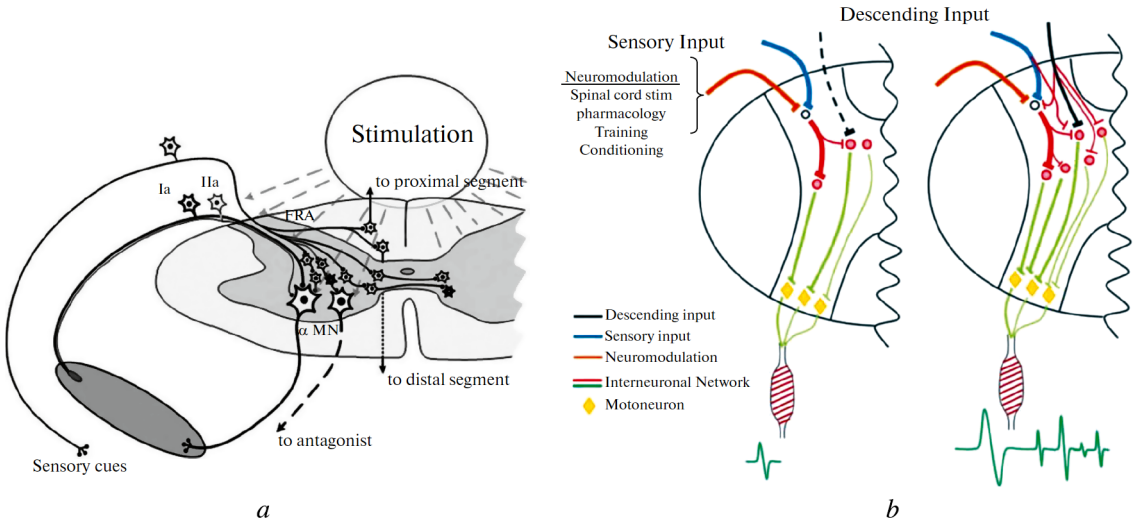

Fig. 1. *a*) Neural structures activated by electrical stimulation of the spinal cord. Depending on location, intensity, pulse configuration, and frequency, transcutaneous spinal cord stimulation can activate different neural structures, including sensory dorsal root afferents, motoneuron axons, interneurons, and neural networks. FRA – flexor reflex afferent neurons; MN – motor neurons. From [38] with modifications. *b*) Electrophysiological testing of corticospinal integration. From [41] with modifications.

Descending supraspinal signals, peripheral sensory signals, and neuromodulatory signals project to the neural networks generating motor patterns and are addressed to the motor pools of the corresponding muscles (Fig. 1, *b*, left side). Repeated training appears to form new synaptic connections, leading to structural and functional reorganization of the spinal cord and restoration of motor functions (Fig. 1, *b*, right side). A logical interpretation of these results is that there are neural networks above, within, and below the level of the lesion in significant numbers of people with complete chronic paralysis which are able to transform into a functional state on reaching some particular critical level of activation.

The influence of SCS on somatic reflexes has been studied by many authors. Knikou et al. [61] addressed the effects of repetitive transcutaneous SCS on soleus muscle H reflex excitability and spinal inhibition in 10 individuals with chronic SCI and 10 healthy subjects who received monophasic transcutaneous pulses of duration 1 msec at a frequency of 0.2 Hz at subthreshold and suprathreshold intensities in terms of eliciting transspinal evoked potentials in the soleus muscle. Patients with SCI received a total of 16.6 ± 1 stimulation sessions with a mean duration of 60 ± 2 min per session. Healthy subjects underwent 10 stimulation sessions (40 ± 0.1 min per session). The soleus muscle H reflex was used to assess changes in motoneuron recruitment and its homosynaptic and post-activation depression. Repetitive stimulation increased homosynaptic depression in all subjects with SCI but produced no change in healthy controls. Post-activation depression remained unaltered in all groups of subjects. Percutaneous SCS reduced the severity of spasms and clonus of the ankle joint. The authors of this study noted that the results indicate a reduction in reflex hyperexcitability and restoration of inhibitory spinal control in the injured human spinal cord as a result of repeated transcutaneous stimulation. The authors took the view that transcutaneous stimulation is a non-invasive neuromodulation method able to restore spinally mediated afferent reflex responses after SCI and that it could be an effective therapeutic strategy for regulating motor neuron excitability after SCI in the injured spinal cord.

Electrical stimulation, acting on the spinal cord via afferent fibers passing in the dorsal roots, provides subthreshold excitation of interneurons and motor neurons located distal to the lesion [18]. This modulation of spinal cord networks increases their sensitivity to residual (partially surviving after the spinal lesion) supraspinal control [56] and sensory signals arising from movements of the trunk and limbs [74]. Through a combination of these effects, spinal electrical stimulation improves voluntary control of movements, including locomotion and upper limb function [92].

Polysynaptic activation involving spinal interneurons and propriospinal neurons leads to modulation of spinal cord excitability [15, 74]. Recent studies reported by Skinnider et al. [96] confirmed that signals induced by spinal electrical stimulation activate interneurons through a series of polysynaptic connections in experiments on mice with SCI. These authors took the view that epidural SCS, *inducing locomotion*, led to the activation of excitatory (V2a) and inhibitory (V1/V2b) interneurons located in the lumbar segments with synapses from proprioceptive afferents. These data confirm that SCS-induced afferents activate both excitatory and inhibitory spinal cord interneurons, pointing to the complex nature of the functional recovery seen during and after application of SCS [87].

Spinal electrical stimulation can influence a variety of spinal networks through propriospinal interneurons. Cervical transcutaneous SCS has been shown to suppress

the amplitude of the soleus muscle H reflex in neurologically intact subjects [15]. As propriospinal neurons connecting the cervical and lumbar locomotor networks are involved in the transmission of locomotor commands from supraspinal locomotor areas, these data also indicate that commands from the brain propagating along propriospinal circuits may possibly be modulated by SCS [78]. It can be suggested that SCS targeted at one function can indirectly influence other functions by activating long propriospinal neurons. For example, one recent study demonstrated improvements in lower urinary tract function following transcutaneous SCS designed to improve upper limb motor function [56].

Recent studies have shown that functional improvements obtained as a result of courses of spinal electrical stimulation with or without intense physical training can be maintained in the absence of SCS [56, 57, 79, 102]. Some improvements in movement could be maintained for many months after the cessation of SCS therapy, pointing to structural and functional neuroplasticity in the injured CNS [56, 79]. As evidenced by improvements due to neuroplasticity, epidural stimulation either with intensive training [82] or without it [79] could produce improvements in motor function beyond the period of electrical stimulation in patients with chronic total motor SCI.

SCS allows patients with SCI to exercise more intensely because it promotes activation of weakened or paralyzed muscles [16, 56]. Gad et al. [36] showed that SCS increased the level of physical effort that the study patient was able to generate. Improvements in sensorimotor function may also result from a greater range of exercises which patients with SCI can perform as a result of using SCS[36]. This increase in the range of physical activity raises the question of whether improvements resulting from paired interventions come from the broader range of exercises able to be performed by people with SCI or whether electrical stimulation of spinal networks promotes plasticity by creating an environment favorable for plasticity [92]. In our view, the fact that SCS appears to increase the plastic capabilities of the CNS is evidenced by the fact that the plateau in sensorimotor recovery (i.e., the upper limit of improvement beyond which the therapeutic effect does not increase) achieved after use of physical training alone can be overcome by adding SCS without increasing exercise.

We have already noted above that SCS also affects autonomic functions. It is important to note that SCS can increase the likelihood of motor recovery by influencing autonomic functions. Indeed, by improving hemodynamic stability via SCS, episodes of hypotension and hypertension can be avoided during physical rehabilitation such that training frequency and intensity can be increased to promote greater activity-dependent neuroplastic recovery [92]. In addition, SCS can reduce the energy expenditure of walking and enhance physical performance [51]. In turn, reductions in effort may allow the range of possible exercises to be enlarged and exercise tolerance to be improved, thereby promoting long-term activity-dependent neuroplasticity.

Conclusions. Spinal cord injury (SCI) is associated with high levels of disability, with enormous socioeconomic impact on the victim, family, community, and healthcare system [1, 6, 31, 92, 105]. Despite advances in the field of neurorehabilitation, the treatment of disorders due to SCI remains a challenge for both scientists and clinicians [53]. Electrical spinal cord stimulation is a new emerging neuromodulation strategy for restoring motor function and recent studies using this approach have demonstrated impressive improvements in the voluntary control of these functions.

Employment of rehabilitation measures based on motor activity indicate that SCS helps restore motor functions in people with SCI when used in conjunction with SCS. Clarification of the mechanisms by which this method increases the effectiveness of functional recovery is required in order to improve the results of rehabilitation methods using it. This will lead to optimization of stimulation parameters and personalization of rehabilitation protocols.

The results of epidural and transcutaneous spinal cord stimulation for paralyzing chronic spinal cord injuries are currently limited to observational and neurophysiological studies in relatively small numbers of subjects, such that well-designed studies are needed to consolidate theoretical findings in humans [31].

Research in recent years suggests that integrating sensory information about trunk and limb movements, training specific motor tasks, and optimizing the excitability of human spinal neural networks are critical spinal mechanisms of functional recovery [47].

The CNS response to SCS consists of a number of events at different levels, each of which has its own temporal variations and, evidently, its own strength of influence on functional recovery. The use of SCS is associated with various forms of plasticity, including the formation of new neuronal connections, prevention of apoptosis, axon sprouting, and many other changes likely to contribute to functional recovery. Such diversity of influences on the state of the CNS shows the value of using SCS in SCI, as "spinal cord injury creates a complex set of multilayered complications and disruptions that create the need for rehabilitation programs that involve many targets and processes" [23].

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