Chapter

Noninvasive Modalities Used in Spinal Cord Injury Rehabilitation

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Abstract

In the past three decades, research on plasticity after spinal cord injury (SCI) has led to a gradual shift in SCI rehabilitation: the former focus on learning compensatory strategies changed to functional neurorecovery, that is, promoting restoration of function through the use of affected limbs. This paradigm shift contributed to the development of technology-based interventions aiming to promote neurorecovery through repetitive training. This chapter presents an overview of a range of noninvasive modalities that have been used in rehabilitation after SCI. Among others, we present repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), surface electrical stimulation tools such as transcutaneous electrical spinal cord stimulation (tcSCS), transcutaneous electrical nerve stimulation (TENS), and functional electrical stimulation (FES), as well as its integration with cycling training and assistive robotic devices. The most recent results attained and the potential relevance of these new techniques to strengthen the efficacy of the residual neuronal pathways and improve spasticity are also presented. Future efforts toward the widespread clinical application of these modalities include more advances in the technology, together with the knowledge obtained from basic research and clinical trials. This can ultimately lead to novel customized interventions that meet specific needs of SCI patients.

Keywords: spinal cord injury, rehabilitation, noninvasive modalities, functional electrical stimulation, transcranial magnetic stimulation, exoskeletons

1. Introduction

Spinal cord injury (SCI) is an event that affects the quality of life of patients as a consequence of affected sexual function, impaired sensory and motor function, including bowel and bladder control, walking, eating, grasping, pain, and spasticity [1–3]. For many years, SCI has been considered irreversible [4]. However, research on plasticity after SCI has opened new paths and generated a shift in rehabilitation of SCI patients in the past three decades: its former focus on learning compensatory movements to regain function gradually changed to restoration of function through repetitive movement training combined with the stimulation of the nervous system [5].

The term neural plasticity describes the ability of the nervous system to adapt a new functional or structural state in response to intrinsic or extrinsic factors [6]. Thus, plasticity encompasses the underlying mechanisms that lead to a spontaneous return or recover of motor, sensory and autonomic functions to different degrees. The concept of plasticity at the cellular level can be tracked back to Ramon y Cajal's work, who suggested that modification of synaptic connections could play a very important role in memory [7]. After that, the work of Donald Hebb was very important to the concept of long-term potentiation (LTP), namely by suggesting that two neurons that fire together and are close enough may grow some connections or undergo metabolic changes that increase their ability to communicate [8]. This happens because chemical synapses have the ability to change their strength [9].

Sensory information from Ia afferent fibers (transmitting information about muscle activity and movement) play an essential role in inducing functional and morphological changes that lead to the maturation of the brain and the spinal cord [9], independently of the SCI level and whether it is complete or incomplete [10]. Thus, activity-dependent plasticity refers to the changes in the central nervous system (CNS) associated with movement [9] and reflects one of the basic forms of learning in humans [11]. These neural changes happen throughout the life span at both the brain and spinal cord level. However, not all plasticity is beneficial: adverse changes may also appear [12]. This is known as maladaptive plasticity and encompasses events such as excessive plasticity associated with some disease symptoms like focal dystonia, spasticity, and chronic pain. Current SCI rehabilitation is based on task-specific programs aiming at promoting neurorecovery through beneficial activity-dependent plasticity and avoiding maladaptive plasticity [6].

This chapter summarizes the main effects on motor and functional recovery, as well as spasticity and pain, when using noninvasive modalities in the rehabilitation of SCI patients, either in the research or the clinical setting. Some of these techniques aim at stimulating different levels of the central (brain or spinal cord) and peripheral nervous system, while others combine some sort of stimulation with devices that may assist and allow for repetitive motor training (e.g., hybrid exoskeletons and FES driven cycling).

2. Brain stimulation

Recent research has shown that even complete SCI patients may preserve some residual pathways connecting supraspinal and spinal circuits [13]. Given that these patients may preserve muscle activity below the level of injury, target rehabilitation for SCI also includes modalities that stimulate the brain. This might strengthen the efficacy of the residual neural pathways and, therefore, improve volitional control after SCI [14]. This section describes two different types of noninvasive brain stimulation (NIBS): repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). Both techniques have been used in the research and clinical setting aiming at improving motor and functional recovery, as well as spasticity and pain after SCI [4].

2.1 Repetitive transcranial magnetic stimulation (rTMS)

Transcranial magnetic stimulation (TMS) is a form of noninvasive brain stimulation in which short magnetic fields are generated by a coil in order to induce electric current pulses in the brain, which can then elicit depolarization and action potentials in cortical neurons (see **Figure 1**). Since its first application in humans in 1985, TMS has become a standard electrophysiological technique to

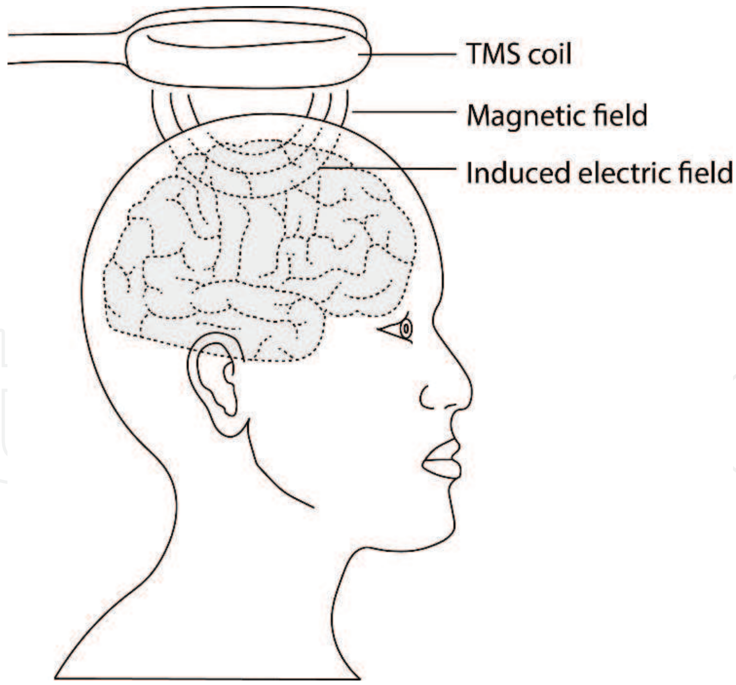

Figure 1.
The magnetic field generated by the TMS coil will induce electric current pulses in the brain, which can elicit depolarization and action potentials in cortical neurons.

assess the excitability of the corticospinal circuitry, due to its usability and ability to directly activate brain structures without causing harm to the subject. The most extended protocol applies single TMS pulses to activate motor cortex at a specific area where topographic projections of a group of muscles are represented. This cortical activation elicits action potentials that propagate until reaching the muscles, inducing a motor evoked potential (MEP), which can be measured by electromyography (EMG) [2].

Repetitive transcranial magnetic stimulation (rTMS) is a form of TMS where several TMS pulses are applied sequentially in order to induce long-term changes in the targeted neural pathways. The underlying physiological mechanism of rTMS lies in the repeated activation of a network of synapses that may lead to long-term potentiation (LTP) or long-term depression (LTD) of those synapses [4]. The induction of long-term changes in neural circuits using rTMS can be applied to revert the effects of neurological disorders. For instance, rTMS received FDA approval and has become a promising treatment for major depression.

Due to its ability to induce long-term changes in neural systems, rTMS has been also applied in patients with motor disorders as a modality to modulate the activity of residual (cortical, subcortical, and corticospinal) pathways and thus promote functional recovery [2]. Moreover, rTMS has been applied in a wide range of protocols, with varying frequencies and intensities of stimulation, or even the number of pulses and sessions, among others. The main stimulation protocols explored so far may be encompassed in the following:

- Theta burst stimulation (TBS) consists of three 50 Hz pulses delivered in blocks at 200-ms interval (5 Hz). Intermittent TBS (iTBS) involves the delivery of TBS for 2 s, followed by a resting period of 8 seconds, for a total of 3 min; this is hypothesized to facilitate LTP [15]. On the other hand, continuous TBS (cTBS) applied in 40 s blocks promote LTD.

- QuadroPulse (qQPS) applies four high-frequency pulses repeated every 5 s. The facilitator or inhibitory excitability effects depend on the inter-pulse intervals.

- I-wave protocol involves the repetitive stimulation of the motor cortex at 1.5 ms rate, seeking to mimic the indirect waves (I-waves) of corticospinal neurons and to increase their excitability [4].

- Paired associative stimulation (PAS) relies on the Hebb's theory, which states that a synaptic connection is enhanced when two stimuli converge in time repeatedly. PAS protocol combines a peripheral nerve stimulus with a TMS pulse over the motor cortex, aiming to pair both stimuli in time at the cortex, which will promote corticospinal excitability. PAS can present different variants, in which the TMS pulse can be replaced by physiological activation of the motor cortex (e.g., imaginary movement), or the pairing site targets of TMS and peripheral stimulus are the motoneurons at the spinal cord.

Regardless of its incipient stage and current limitations, rTMS has become a promising approach for SCI rehabilitation, not only to improve motor function but also to decrease spasticity and neuropathic pain. This technique enables targeting and promoting long-term changes in neural pathways, by exploiting the plastic properties that may facilitate function recovery. Improvements seem to be present when higher rTMS stimulus intensities are used [2]. On the other hand, the few studies that investigated the effects of rTMS on spasticity in iSCI patients reported some reduction in the clinical symptoms of spasticity [2]. Moreover, the few studies that tested the effect of rTMS on neuropathic pain reported some reductions in the clinical symptoms of pain [2].

Notwithstanding, these results hold a great variability, are not reproducible in all patients, and are limited to certain clinical assessment scales or neurophysiological measurements. Several constraints can explain current limitations of the rTMS application in SCI patients. First, there is a shortage of studies providing evidences of sustained benefits of rTMS therapy beyond conventional treatments. Besides the different stimulation protocols and parameters applied, type of lesion and nonuniform assessment methodologies hamper the development of consistent evidences. Although evidences so far do not suggest any harm to the subjects, safety issues should be also considered when using rTMS in SCI patients, especially because of the high threshold needed to evoke motor responses in the impaired pathways [16].

More research is needed to provide robust evidence that can support the use of rTMS as an alternative to standard therapies. In addition to bigger sample sizes used in each study, researchers should also test the same (or very similar) stimulation parameters and protocols to provide reproducible results. Finally, it is critical to better understand the pathophysiology of neural structures affected by rTMS to design optimal and customized protocols that might boost beneficial neural changes coupled with functional recovery after SCI [2].

2.2 Transcranial direct current stimulation (tDCS)

Transcranial direct current stimulation (tDCS) is a technology that delivers continuous low current stimulation (1–2 mA) via paired anode and cathode electrodes over the scalp [4, 14, 17] (see **Figure 2**). This modality is usually combined with motor training to promote activity-dependent plasticity [14]. tDCS may change brain function by causing neurons resting potential to depolarize or hyperpolarize. Depolarization happens when positive stimulation (anodal tDCS) is delivered, which increases neural excitability and, therefore, neural firing. Cathodal tDCS (negative stimulation) causes hyperpolarization and, thus, decreases neural firing [4].

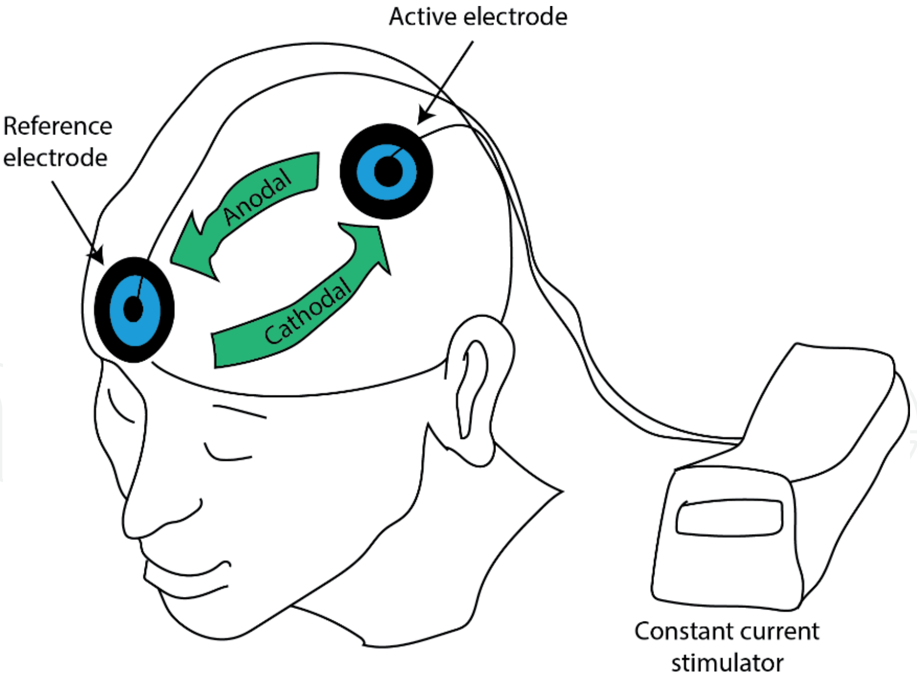

Figure 2.
Transcranial direct current stimulation delivers continuous low current stimulation by applying a positive (anodal) or negative (cathodal) current via paired electrodes over the scalp.

This technique is still in the early stage. To our knowledge, just seven studies have examined improvements in motor function after SCI related to the use of tDCS: four studies evaluated its effect on upper limb function [18–21] and three studies evaluated the tDCS effect on lower limb function and gait [22–24]. All these studies used anodal stimulation and showed improvements in upper and lower limb motor function.

The use of tDCS has led to improvements in pinch force, manual dexterity, and force modulation when combined with repetitive practice [18]. Other study reported that stimulation intensity affects functional outcomes when tDCS was delivered at rest: increased corticospinal excitability to affected muscles was obtained when using 2 mA stimulation, but not 1 mA, in nine chronic SCI patients [19]. Another study also reported gains in hand motor function after a single session of 2mA tDCS, though no improvements were described in clinical scales [20]. When combining tDCS with robot-assisted arm training, SCI patients improved arm and hand function post-treatment and at the 2-month follow-up [21].

The three studies that evaluated the tDCS effect on lower limb function and gait showed improved motor function [22–24]. However, one of these studies combined tDCS with robotic gait training and also showed no significant differences between these improvements and those verified in the group who received sham stimulation combined with robotic gait training [22].

tDCS is an attractive noninvasive modality option for the treatment after SCI: it is affordable and does not present substantial adverse events (when present, they included redness of the skin, sleepiness, headache, and neck pain [4]). However, further research is still needed to provide robust evidence that support the use of tDCS to improve motor function and to be used in the clinical setting as a long-term strategy after SCI.

3. Transcutaneous spinal cord stimulation (tcSCS)

In the recent years, spinal cord electrical stimulation (SCS) has arisen as a promising tool to modulate corticospinal excitability and modify the motor output in

SCI individuals. The most extended form of SCS is epidural SCS, which consists on delivering electrical currents through arrays of electrodes implanted in the epidural space of the spinal cord, in order to modify the excitatory output of the spinal cord. It has been widely studied as an application for chronic pain relief [14]. Promising results from a recent research showed its potential to improve neurological recovery and support the activities of daily living (including walking) after SCI [25].

Transcutaneous spinal cord stimulation (tcSCS) is a novel form of SCS that delivers superficial stimulation, usually over the skin that overlies the lower thoracic and/or lumbosacral vertebrae [26]. The principles underlying tcSCS rely on the physiology of the corticospinal pathways in the spinal cord that can produce excitability changes in the different neural populations of the spinal circuitry [27, 28]. Central pattern generators (CPGs) are pools of neurons able to elicit rhythmic and coordinated movements without the contribution of supraspinal centers. CPGs use proprioceptive information to provide real-time and coordinated control of motor output. The propriospinal system serves as an integratory interface between supraspinal and spinal centers, modulating motor activity. tcSCS is able to modulate the excitability properties of these systems by means of different stimulation protocols, in which the surface array placement along the spinal cord, direction of the current, intensity, frequency, and timing of stimulation result in different modulation outcomes. tcSCS was able to activate GPGs in healthy volunteers, eliciting coordinated and synchronized nonvoluntary movements of the lower limb [28]. These findings have been reproduced in SCI individuals, namely by reactivating damaged spinal circuitries that were previously considered as nonfunctional. When tcSCS was applied over several training sessions in SCI patients, there was improved voluntary modulation of movement of the lower limbs [29]. Moreover, combining tcSCS training with pharmacology therapy and exoskeletons increased motor control enhancement [26].

tcSCS overcomes the invasiveness and costs of epidural SCS with the trade-off of poor spatial stimulation resolution. Although the number of studies using this technique is considerably low, and the exact physiological mechanisms behind the improvements shown are still yet to be fully understood, tcSCS is already a promising tool to be considered in future SCI rehabilitation. Multi-approach therapies including tcSCS, pharmacological, active movement, and robotic-assisted training should be considered to exploit the combination of different physiological effects produced by each modality and maximize motor recovery [26].

4. Peripheral stimulation and assistive devices

Motor control and the execution of voluntary movements require the interaction between afferent feedback and supraspinal input to accurately plan and execute movements. This interplay induces activity-dependent plasticity at both the brain and spinal cord level [30, 31]. After SCI, afferent feedback is impaired and becomes essential to reorganize spinal circuits below the lesion area [30]. Therefore, non-invasive modalities that apply surface electrical stimulation at the peripheral level (either alone or combined with assisted training) to augment or modify neural function are very appealing and have been applied in SCI rehabilitation.

This section overviews two forms of surface stimulation that are user friendly and can be easily administered by a therapist during SCI rehabilitation: transcutaneous electrical nerve stimulation (TENS) and functional electrical stimulation (FES). The second part of this section reports the main results attained when using cycling driven by electrical stimulation and the combination of electrical stimulation with external robotic devices.

4.1 Transcutaneous electrical nerve stimulation (TENS)

TENS is the most common noninvasive modality used in physical therapy [32]. This type of stimulation delivers high-frequency (50–150 Hz) and low-intensity (below motor threshold) surface electrical current [33].

Though TENS has been commonly used in pain control and to reduce muscle stiffness/tone, there are also some reports on decreased spasticity due to the use of this modality. For instance, TENS has recently reduced spasticity in SCI patients and the effects outlasted up to several hours after treatment [34]. This is because TENS activates sensory nerves that in turn may activate inhibitory interneurons that will inhibit the spastic muscle activity [34]. More specifically, these anti-spastic effects are due to the release of gamma-aminobutyric acid (GABA) that acts as inhibitory neurotransmitters, achieving similar anti-spastic effects to those of baclofen [32], which is a first-line treatment for spasticity, especially in adults who suffered a SCI [35]. Results of spasticity treatment using TENS seem to improve when combined with physical therapy [36].

Given its low cost, lack of adverse event effects, and ease to use, TENS seems to be a very good solution to treat spasticity after SCI. Moreover, since TENS alleviates pain and fatigue and can be used for periods of several hours, it seems to be appropriate for the beginning of the rehabilitation after SCI, when training is not very intensive.

4.2 Functional electrical stimulation (FES) and brain-machine interfaces (BMIs)

FES is another modality of electrical stimulation that has become very popular in the clinical setting. FES is similar to TENS in the sense that the two modalities use electrodes on the skin to provide electrical stimulation to a desired location of the body; but they differ in the settings and especially in the purpose of their use. Unlike TENS, FES delivers trains of electrical stimulation above motor threshold to stimulate a muscle or the efferent nerve supplying a muscle in order to attain a muscle contraction [14]. The higher the amplitude of this stimulation, the bigger is the number of recruited efferent fibers and, therefore, the higher the muscle contraction.

FES has been used to restore bladder and bowel control, as well as sexual function, which are ranked among the most important functions to regain among SCI patients [37]. FES has also been widely used for the treatment of muscle weakness, gait training, and muscle reeducation [34]. In the case of SCI, it is well known that artificially induced contraction of weak or paralyzed muscles brings several therapeutic benefits, such as prevention of lower limb muscle atrophy, increased muscle strength, endurance, and cardiovascular fitness [38, 39]. In addition to these benefits, the coordinated stimulation of efferent nerves (usually to stimulate agonist-antagonist muscles of a joint) can be paired with a functional activity to produce a given biomechanical task and, thus, restore motor function [34].

On the other hand, there is evidence that peripheral stimulation, if synchronized with patients' voluntary effort, can further promote recovery [14]. In fact, improved modulation together with volitional control seems to be key factors to reinforce connectivity during rehabilitation of SCI patients, presumably through synaptic enhancement [14]. In this sense, brain-machine interfaces (BMIs) are currently the most sophisticated neuromodulation tools to restore voluntary limb movements after SCI. In the context of the noninvasive modalities described in this chapter, BMIs can be used to stimulate the peripheral nervous system by use of decoded brain signals recorded with electroencephalography (EEG) [14].

Finally, FES has also been used to reduce spasticity in SCI patients, usually by stimulating the spastic muscle. This is hypothesized to modulate recurrent inhibition via Renshaw cells [34]. These inhibitory interneurons are excited by collaterals of the axons of motoneurons and make inhibitory synaptic connections with several populations of motoneurons, including those that excite them [40]. This reciprocal inhibition is important to prevent overshooting muscle contraction induced by FES.

Despite all the benefits here described, FES presents several challenges for tasks that are executed for long periods of time. Limited muscle force generation, rapid onset of muscle fatigue, and nonlinear, time-dependent mechanical responses, as well as the redundancy of the musculoskeletal system are the main challenges of this technology that traditionally hamper generalized use for rehabilitation and/or motor compensation of walking. However, multi-electrode techniques are showing promising results [41] and should be explored.

4.3 FES driven cycling

Physical activity of SCI people whose limbs are paralyzed is very important to maintain their physiological well-being. A promising approach is the application of FES during cycling movements. This technique, called FES cycling, is a noninvasive training protocol used in medical rehabilitation, mostly addressed to individual affected by SCI. This method can be applied continuously for tens of minutes, with direct benefits on muscle strength. Besides muscle strengthening, FES cycling is beneficial for cardiovascular and respiratory functions [42].

FES training for lower limb muscles can be performed on stationary cycle ergometers or mobile tricycles. As shown in **Figure 3**, FES is managed by a controller, which receives signals from a crank angle sensor and, depending on the actual crank position, transfers sequences of electrical impulses to surface electrodes to stimulate muscles and generate active muscle force. The power output produced by the application of FES depends on three main aspects. The first is the number of muscle groups stimulated. The second is the parameters of the stimulating current, that is, amplitude, pulse width, and frequency. The third is the timing of the stimulating signal sent to the individual muscles.

FES cycling is usually applied on several lower limb muscles simultaneously [43]. The main muscle groups considered are the hamstrings and quadriceps and, in

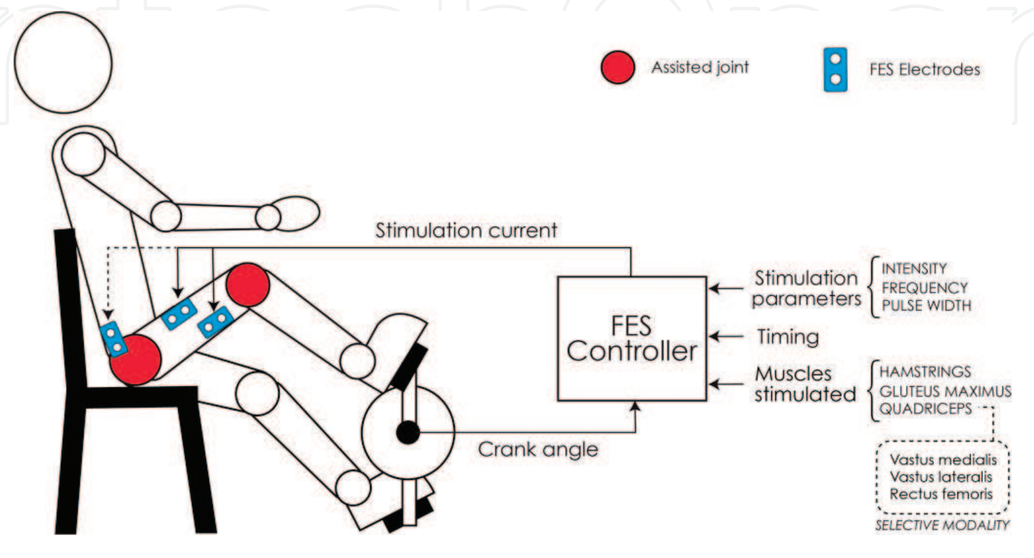

Figure 3.
FES driven cycling: a controller sends electrical signals (stimulation current) to selected muscles. The actual muscle forces depend on the actual crank angle value transferred to the controller and on the parameters and timing of the stimulation signals sent to individual muscles.

some cases, the gluteus maximus. The quadriceps are stimulated either as a whole, that is, using only one pair of electrodes, or more selectively, in which three muscles composing them—that is, the vastus medialis, vastus lateralis, and rectus femoris—are stimulated individually. This more selective stimulation has demonstrated, in a recent pilot study, to improve up to 27% the power output in one patient with spastic muscles [44]. In this case, while the total stimulation current (the sum of the amplitude of currents applied in all of the channels) was higher, lower stimulation current amplitudes per muscle groups were sufficient to generate the required movement. The average current amplitude applied in FES cycling in SCI individuals is around 50–70 mA per muscles and it varies in a wide range. In some protocols, the current amplitude is increased until 120–140 mA to achieve power output around 10 W [45] and in extreme cases 20 W [46]. Others stimulated muscles with a frequency of 30 Hz, current amplitude of 70–90 mA, and pulse width of 500 μs, reaching a power output around 30 W [47]. The timing of stimulation is usually set according to recorded and processed muscle activities of able-bodied persons and/or on physiological, biomechanical parameters of the muscles and limbs of the participants. Nevertheless, these approaches are either not adaptive to the patient-specific musculoskeletal conditions, or very difficult to calibrate. For instance, when applying selective stimulation of the three quadriceps muscles separately [44], we found that the participant, even reaching higher power output, preferred to cycle for a shorter time, possibly due to a nonphysiological stimulation strategy. In our opinion, more studies are needed to explore these control combinations, in particular considering the case of selective stimulation. This will likely lead to new more efficient, natural, and adaptable stimulation protocols.

Cadence is another important variable in FES-cycling rehabilitation. In the case of ergometer-based training, cadence is on average set to 45–50 rpm, in most of the stimulating conditions. To adapt the treatment to patient residual motor ability, cadence can be changed in combination with various crank resistances during the rehabilitation process. Tricycles have been proposed as an alternative to stationary cycle ergometers [48]. A recent study reported that the series of FES trainings on a tricycle resulted in increased speed of cycling of paraplegics with denervated muscles [49], which is normally not observed in similar ergometer-based protocols. FES-driven tricycling is gaining relevance, as testified by several competitions organized during the last couple of years [50–53]. However, these competitions are only targeting people with SCI. We expect that wider range of participants, for example, stroke, will also be addressed in the near future, as supported by recent promising research works in this direction [54, 55].

4.4 Exoskeletons and hybrid exoskeletons

Repetitive and intensive task-specific training drives beneficial neuroplasticity, thus enhancing functional recovery [56]. Therefore, exoskeletons for motor rehabilitation purposes have emerged in the last decade as a convenient technology that allow multiple, intensive, and more effective sessions of gait training, allowing SCI patients to ameliorate their performance in daily life [56]. Moreover, a study reported that spasticity and pain intensity of SCI patients decreased after one single session of walking assisted by a powered robotic exoskeleton [56].

A paradigmatic development of a stationary rehabilitation robot for gait training is the Lokomat system, which combines body-weight supported treadmill-training (BWSTT) with the assistance of a robotic gait orthosis. These robotic systems are able to provide guidance forces to the lower limb segments to induce a consisting stepping pattern with adjustable guidance. It has been shown that although the mechanical coupling and added guidance may change the task constraints and in turn alter voluntary leg movements, the basic neuromuscular pattern is preserved when intact humans walk assisted by this robot [57]. Robot-assisted gait training with the Lokomat after SCI has been shown in some studies to improve outcomes related to mobility when compared to conventional overground training [58, 59]. For example, it was shown improved gait distance, strength, and functional level of mobility and independence of acute SCI patients receiving robotic-assisted gait training than the group of patients receiving conventional overground training [60]. Also, it has been demonstrated that robot-assisted gait training combined with conventional physiotherapy could yield more improvement in ambulatory function of SCI patients than conventional therapy alone. However, the impact of such complementary tools to provide neuromuscular education is still not well established for a convincing penetration of these systems in the clinical rehabilitation environments. Some limitations of such stationary robotic tools are that robotic-assisted training can be limited in the range of gait speed at which the exoskeleton robot can provide a comfortable gait pattern. Also, the stationary machine imposes restrictions to the user movements to the sagittal plane, significantly preventing motion in the frontal and transversal plane that are required for overground walking.

Wearable robots (WR) for overground untethered assisted walking are emerging devices that have the potential to overcome some of the above-mentioned constraints and opening a range of clinical application scenarios. Through wearable mechanical actuation and sensing, WRs are proliferating for their use as assistive and rehabilitation technologies due to their ability to replicate the complex motions involved in human movement. As a result, the past few decades have seen an increasing amount of research focused on developing robotic systems intended to interact with the neurologically impaired human body. This interaction (of the human body) with WRs has been established in foundational literature [61] as dual, bidirectional physical (pHRi), and cognitive (cHRi) interactions. While these systems have been proven to be useful for specific applications, such as in-clinic rehabilitation, current research in the area of pHRi for WRs is focusing more on developing lightweight and flexible force interactions with hardware solutions that might be more suitable to a broader range of applications (by adding compliance to rigid exoskeletons [62, 63] or developing "soft exosuits" [64]). However, these soft exoskeletons are in early stage and the majority of clinical evidence of their efficacy for treatment of SCI is in studies with motorized powered exoskeletons. A systematic review of the literature on powered WRs for overground gait rehabilitation pointed out that, although current technology is still under development, and hence its ultimate impact remains still unclear, a number of revised studies report positive changes in outcome variables and suggest that training time and improvements in gait speed using powered WRs are correlated in SCI population [65].

On the cHRi side, efforts are focused on developing means for interpretation of mechanical and neural signals to establish adequate control methods that integrate WRs as parts of human functioning. In this regard, a scheme for "symbiotic interaction" between humans and WRs has been recently developed in the FET Project BioMot (FP7-ICT-2013-10-611695), yielding new technologies to interface human neuromechanics with robot-control algorithms to guide assistance; the point of increasing their proficiency is to make them more capable of sophisticated interdependent joint activity with the human wearer. Under this approach, a tacit adaptability is provided to modulate the compliance in the robot torque controller, to automatically modulate in turn the difficulty of the task [66].

There is currently no agreement on the optimal robot-mediated treatment programs to induce plasticity and promote recovery of motor function following SCI, and the understanding of recovery mechanisms is still an open matter [67]. Whatever the robot hardware and patient's functional status, a WR-mediated neurorehabilitation model could pave the way for effective restoration of mobility after major neurological conditions. In the last few years, the development of computational neurorehabilitation models is becoming a relevant topic in the domain of neural repair, as these computational models can be expected to provide the basis for future clinical robot software that suggests timing, dosage, and content of therapy. For example, an analytical modeling approach has been applied to robot-mediated rehabilitation data of a group of SCI subjects, providing insights with regard to patient grouping and gait recovery prognosis and also providing predictive quantitative measures to consider before starting the treatment [68]. This, together with the fact that in the past years we are witnessing an unprecedented number of wearable interactive robotics products that will populate even more the clinic environments, a reasonable long-term vision is to gather multicenter clinical data to equip rehabilitation WRs with computational neurorehabilitation modeling tools that will in turn provide enriched data to establish scientific bases of exoskeleton-guided recovery.

On the other hand, the combination of FES with external orthotic devices that provide joint support and mechanical constraint to undesired movements was early proposed [69], but the challenges associated with the rapid onset of muscle fatigue and movement control still remained. In an attempt to further diminish the energy demand from the muscle while providing better joint control, FES systems were combined with lower limb exoskeletons, also called hybrid exoskeletons [70]. The combination of the lower limb robotic exoskeleton and the FES system can be shaped in different ways, depending on the configuration of the FES system and/or the exoskeleton. Regarding the former, the FES can be implanted [71] or superficial [72] and can be found either under open [71, 73] or closed-loop [72, 74] control of stimulation. With regards to the exoskeleton joints, it can provide means of dissipating energy, via the use of clutches or brakes [75, 76], or can feature active joints, which can also provide energy to the joints.

The hybrid configuration presents some advantages with respect to the FES or exoskeleton applications alone. First, the exoskeleton structure provides passive control to the joints, constraining undesirable movements. The actuators can provide support to the joints, diminishing or eliminating the need for stimulation of certain muscles (e.g., quadriceps muscles during the stance phases of walking). In the case of active actuators, the movement produced by the FES is supported by the actuator, improving the control of the joint trajectory while delaying muscle fatigue [77]. On the other hand, the sensors of the exoskeleton provide information for closing the control loop of the FES system, which may further help on optimizing the performance of the muscle in terms of either force production or muscle fatigue [72].

Despite hybrid exoskeletons show several advantages, the field is not mature. There is a markedly low activity in this field, and most of the groups working on this technology have discontinued their research on this topic. The rationale for this may come from the bottlenecks of each technology. First, hybrid exoskeletons share drawbacks with lower limb robotic exoskeletons, in which the combination with a FES system add complexity on the control and wearing aspects. Besides, although alleviated by the exoskeleton, the nonlinear muscle response of the stimulated muscles and the muscle fatigue is not adequately solved yet, and eventually all hybrid exoskeletons still have to be designed to function as conventional robotic exoskeletons once muscle fatigue appears.

Lastly, there is a need of conducting clinical studies that can demonstrate the benefits of using hybrid exoskeleton with respect to exoskeleton alone that actually justify the extra complexity, cost, and cumbersomeness of the FES system.

5. Conclusions and future directions

This chapter presents an overview of the main effects on motor and functional recovery, as well as spasticity and pain, when using a wide range of noninvasive modalities in the rehabilitation of SCI patients, either in the research or the clinical setting. According to the level of stimulation, these modalities were divided into three different sections: brain, spinal cord, and peripheral stimulation. Regarding the last one, stimulation of the peripheral nervous system can also be combined with external devices that assist and allow repetitive motor training (e.g., hybrid exoskeletons and FES driven cycling).

Noninvasive brain stimulation (NIBS) techniques such as rTMS and tDCS have the potential to improve motor function recovery and spasticity after SCI. Moreover, NIBS techniques are safe and relatively easy to administer, presenting infrequent mild effects. Very few studies have investigated motor function after delivery of rTMS on SCI patients. Improvements seem to be present when higher rTMS frequencies are used. On the other hand, the few studies that investigated the effects of rTMS on spasticity in iSCI reported some reduction in the clinical symptoms of spasticity [2]. There are less studies of the application of tDCS in motor function or spasticity than those of rTMS [4], though they all showed improvements in upper or lower limb motor function. Thus, more research is needed to address the full potential and incorporate NIBS techniques into SCI rehabilitation [4].

At the spinal level stimulation, tcSCS has irrupted in the last years as a neurorehabilitation tool in SCI. It overcomes the limitation of invasiveness and costs of epidural stimulation at the expense of poor spatial stimulation resolution. The few evidences suggest that tsSCS alone improves voluntary modulation of lower limb movement [29] and increases motor control enhancement when combined with pharmacology therapy and exoskeletons [26].

Noninvasive modalities that deliver different types of surface stimulation at the peripheral level (either alone or combined with cycling or robotic-assisted training, for example) are very appealing and have been applied in SCI rehabilitation. Surface electrical stimulation can modulate afferent and efferent pathways in order to induce corticospinal plasticity. For instance, TENS and FES have reduced spasticity in SCI patients and the effects outlasted up to several hours after treatment, though the two techniques target different nerve groups in order to reduce spasticity: TENS activates afferents that in turn activate inhibitory interneurons that will inhibit the spastic muscle activity; FES induces muscle contraction and is oriented to the spastic muscle [34]. The development of fatigue and discomfort produced by the intensity of stimulation of FES is a drawback for long sessions. Thus, TENS may be appropriate for the beginning of the rehabilitation, while FES may have better effects on those SCI patients presenting spasmodic behavior [34]. On the other hand, BMIs may enhance brain and spinal cord neurorecovery through activity dependent plasticity. Future advances in wireless devices may potentiate the widespread use of BMIs in the clinical setting.

FES cycling is another modality that presents direct benefits on muscle strength, as well as cardiovascular and respiratory functions of SCI patients. However, more research on this technique is needed in order to design more efficient, natural, and adaptable stimulation protocols, which will likely improve motor function outcomes during SCI rehabilitation.

Robotic devices, such as exoskeletons, are other solutions that have been used for rehabilitation purposed after SCI. These devices can provide intensive, long lasting repetitive task specific training to SCI patients, which is the principle behind motor rehabilitation and beneficial neuroplasticity [78]. These devices have allowed SCI patients to ameliorate their performance in daily life [56]. The hybrid configuration (exoskeleton combined with FES) presents some advantages with respect to the FES or exoskeleton applications alone: actuators can provide support to the joints, diminishing or eliminating the need for stimulation of certain muscles; the sensors of the exoskeleton provide information for closing the control loop of the FES system, which may further help on optimizing the performance of the muscle in terms of either force production or muscle fatigue. However, the field is not mature and there is a need of conducting clinical studies that can demonstrate the benefits of using hybrid exoskeleton with respect to exoskeleton alone that actually justify the extra complexity, cost, and cumbersomeness of the FES system.

Part of the current SCI rehabilitation research uses the modalities described in this chapter and has presented promising results including neurorecovery.

Some of these modalities are already being widely introduced into the clinical rehabilitation of SCI, such as TENS and FES. However, the actual uptake of technology in the clinical setting, especially for SCI rehabilitation, has been very low [5]. There are still some barriers to the clinical implementation of these techniques. Three of those barriers are the feasibility, appropriateness, and the cost. While the research here described is practical for SCI rehabilitation, some of these techniques are less practicable: they require specialized equipment and knowledge, which make them less feasible [5]. Despite the scientific evidence in favor of these technologies, the expertise required to operate and repair emerging technology is usually not found in the clinical setting, which makes it less appropriate. A third barrier that deserves attention is the economic cost, given the fact that most of the clinical centers cannot afford the maintenance of these technologies. To overcome these barriers, it is essential to develop a proactive dialog between researchers and clinicians in order to properly examine each of the emerging modalities that can maximize the outcomes for each individual that suffered a SCI.

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Conflict of interest

The authors declare that this work was conducted in the absence of any commercial or financial relationships that could be considered as a potential conflict of interest.

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