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Chapter

The Role of Supraspinal Structures for Recovery after SCI: From Motor Dysfunction to Mental Health

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Abstract

Neural circuitry controlling limbed locomotion is located in the spinal cord, known as Central Pattern Generators (CPGs). After a traumatic Spinal Cord Injury (SCI), ascending and descending tracts are damaged, interrupting the communication between CPGs and supraspinal structures that are fundamental to initiate, control and adapt movement to the environment. Although low vertebrates and some mammals regain some physiological functions after a spinal insult, the capacity to recover in hominids is rather limited. The consequences after SCI include physiological (sensory, autonomic and motor) and mental dysfunctions, which causes a profound impact in social and economic aspects of patients and their relatives Despite the recent progress in the development of therapeutic strategies for SCI, there is no satisfactory agreement for choosing the best treatment that restores the affected functions of people suffering the devastating consequences after SCI. Studies have described that patients with chronic SCI can achieve some degree of neurorestoration with strategies that include physical rehabilitation, neuroprosthesis, electrical stimulation or cell therapies. Particularly in the human, the contribution of supraspinal structures to the clinical manifestations of gait deficits in people with SCI and its potential role as therapeutic targets is not well known. Additionally, mental health is considered fundamental as it represents the first step to overcome daily adversities and to face progression of this unfortunate condition. This chapter focuses on the consequences of spinal cord disconnection from supraspinal structures, from motor dysfunction to mental health. Recent advancements on the study of supraspinal structures and combination of different approaches to promote recovery after SCI are discussed. Promising strategies are used alone or in combination and include drugs, physical exercise, robotic devices, and electrical stimulation.

Keywords: spinal cord injury, supraspinal, therapy, motor dysfunction, mental health

1. Introduction

Supraspinal circuits related to motor function have a complex neuronal organization which physiological function is highly conserved in most of the vertebrate species. Those have an important role in the neural control of locomotion and other complex motor tasks [1]. Enormous effort has been made to discover a therapeutic strategy aiming descending pathways to recover movement after SCI, but there are still no effective results promoting recovery [2]. The loss of specific descending tracts is related to the levels of motor dysfunction after SCI. For example, the corticospinal tract is an important pathway for achieving fine adjustments during locomotion, thus, restoring its connectivity may partially contribute to recover some locomotor functions after injury [3]. Additionally, several studies have described the role of the red nucleus and rubrospinal tracts in the activation of the flexor phase within the gait locomotion [4, 5]. The reticulospinal neurons of the pons and the medulla activating the flexor phase during stepping provide position information related to the motor response. The reticular formation provides control of the posture during locomotors tasks [6].

Seminal studies made by Russian researchers in the last century described a region in the cat within the mesencephalon (midbrain) which was named as mesencephalic locomotor region (MLR) [7]. They concluded that electrical stimulation to the MLR elicits coordinated locomotion. This circuit accesses descending spinal neurons from the reticular formation to transmit locomotion signals [8]. Today, this region is considered a target for electrical stimulation following a SCI because there is proof that homologous areas in the brainstem of humans can be identified as a MLR with some differences due to the possible adaptation to bipedalism [9].

It has been well documented that the above mentioned supraspinal circuits can contribute to remodel the spinal cord and promote in some extent, recovery after incomplete SCI [10]. The neural circuits within the spinal cord can exhibit a degree of plasticity at cellular level [11], therefore, these newly connections would allow the formation of new pathways that may contribute to functional sensorimotor recovery.

Although the neurologic classification of the AIS-ASIA (The American Spinal Injury Association Impairment Scale) as A represents total motor and sensory loss below the injury level, a complete section of the spinal cord is not frequently observed in the clinic. In a postmortem study, it was found that around 75% of subjects diagnosed with complete SCI, some portions of the spinal cord in the site of injury were preserved, representing "continuity" across tissue [12]. In 1998, Dimitrijevic and colleagues [13] described that some subjects AIS-ASIA A were able to produce voluntary motor activation in some muscles during epidural stimulation. It was evident that some spared fibers across injury were still functional, suggesting the term "discomplete" to describe this observation. This concept opened new questions regarding potential rehabilitation strategies developed in animal models. Unfortunately, translation into the clinic has not succeeded so far. Anatomical and physiological aspects are among the differences between animal models and humans [14]. However, in the last decade, new approaches have shown promising results in subjects with complete and incomplete SCI.

1.1 Neuroplasticity

Afferent inputs integrate sensory information that modulates the process of movement and theproprioception phenomena, cutaneous stimulation promotes the increase of spinal cord excitability and promotes plastic changes within the locomotor apparatus in humans [15]. Proprioceptive feedback contributes substantially

to the posture maintenance phase of extensor activity as described in cats during treadmill locomotion [16, 17] and in humans [18], as well as improving motor functions with physical exercises designed to stimulate cortical and subcortical neural circuits [19] When SCI occurs, the supraspinal elements such as the corticospinal tracts often decreases its connectivity to its direct or indirect targets (i.e. lumbar CPGs); interestingly, the terminal territory of the motor cortex do not change significantly as compared to the somatosensory cortex, while the afferents fibers exhibit aberrant connections into deafferented regions of the spinal cord as described in monkeys [20]. In addition, proprioceptive neurons are relevant in the process of recovery within SCI, for example, it has been suggested that the neurons receiving feedback signals can help to reorganize motor circuits [21, 22].

The process for mediating remodeling of supraspinal circuits requires the specific selection for synaptic reconnection between supraspinal circuits and the deafferented spinal cord regions. Bradley et al. [23] proved that cyclic AMP response element-binding protein and NMDA receptors have a significant role in the process of reconnection since those promote the and reinforce the connections of relay neurons to the spinal cord in the mouse.

As mentioned above, many supraspinal circuits contribute to activate locomotor tasks. Strategies involving a combination of clinical treatments have been developed with the aim to predict restoration based on early clinical symptoms. Most of these methods correlated variables that indirectly influence supraspinal centers in the production of walking in humans [24].

After an SCI, the reaction of the glial tissue ends in the formation of a scar. There is great therapeutic potential in the ability to modulate the healing of glial cells in response to damage in the CNS. *In vivo* and *in vitro* studies, although relatively limited, have shown improvement in axonal regeneration and functional recovery after specific constituent's inhibition of the glial scar. Enzymatic digestion of GAG's (Glycosaminoglycans) chains of CSPGs (chondroitin sulfate and keratane proteoglycans), for example, stimulates axonal regeneration at the site of damage or injury [25, 26]. Axons chronically damaged in the SC can regenerate through implants of peripheral nerve grafts after 4 weeks of injury [27]. Even in lesions of one year of progression, regeneration of the rubrospinal tracts in adult animals has been described. This can be achieved with cells that are treated with the application of BDNF, allowing the normal conditions of the soma to be restored [28]. In the last decade, combined treatments with Chondroitinase ABC, or with novel forms to release and integrate this enzyme in the tissue has also been developing to improve plasticity and reconnection of the cells found at the injury site [29–32]. Therefore, biochemical and pharmacological management is important to reduce the glial scar and facilitate axonal regeneration and neuronal reconnection.

2. Motor pathways reorganization after SCI

To develop key strategies for functional improvement of injured spinal cord, the knowledge of the central nervous system organization under physiologic and pathophysiologic conditions is essential.

Premotor spinal oscillators (alternating flexor and extensor activity in neuronal spinal cord circuits) exhibit neuronal network organization based on their firing patterns and driving afferents. This oscillatory activity is also observed by firing patterns recorded in muscles, thus making possible to follow up therapeutic interventions in patients with SCI based on the activity of the muscles during flexor and extensor phases of locomotion. At the same time, it is possible to assess the abnormal firing patterns and dysfunction in spinal reflexes.

The concept of re-organization and pattern formation in imbalanced systems is associated to the firing patterns of groups of identified neurons in the spinal motor networks was extensively developed by Schalow and Zach [33]. Human CNS has integrative functions for learning, re-learning, storing and recalling, being all these necessary elements contributing to plasticity following injuries. Thus, understanding the Central Nervous System (CNS) reorganization in the short and the long-term memory process during a therapeutic intervention as an approach for re-learning adequate motor behavior is fundamental to achieve functional motor improvements. This intervention consists in the training of innate automatisms like creeping, crawling, up-righting, walking, and running. Moreover, the training of rhythmic, dynamic, stereotyped and movements could substantially be improved by applying different protocols of coordinate on dynamic therapy [33, 34]. Among therapeutic goals during coordination dynamic therapy are to induce cell proliferation and neurogenesis, so this could contribute to promote structural changes during the reconnection process in the injured tissue. New training paradigms are being created as a tool for retraining the spinal cord looking to engage the innate locomotor circuitry with appropriate afferent input to avoid lasting maladaptive sensory and motor effects, such as central pain and spasticity [35]. For accurate motor control, proprioceptive information from the body and environment has to be integrated and transformed into an appropriate motor command under physiological conditions [36, 37]. The inherent neural transmission and integration for motor output and the perception of limb position activated in the cortical areas during kinesthetic sensations are based on proprioceptive information [38]. This lead the notion that the activation of the propriospinal pathways in its different configurations may help activating supraspinal areas such as cortical regions where senses involved in modulating motor control are processed, and these can be used to take advantage of strategies for motor recovery from a SCI.

Interestingly, depending on the severity of the SCI, humans and animal models in most cases presentsome degree of spontaneous functional recovery during the first months after injury [39–43]. This outcome has been attributed to spared descendent axons bypassing the site of injury, although precise mechanisms underlying this phenomenon are not known. Courtine and collaborators investigated the spontaneous recovery in a spatially and temporally separated lateral hemisections in a mouse model, using kinematic, physiological and anatomical approaches. Their findings suggest that functional recovery can occur after severe SCI facilitated by the reorganization of descending and propriospinal connections [44]. Interventions headed for enhancing the remodeling of spread connections are important to explore in the various novel therapeutic strategies to reconnect spared tissue and restore function after SCI.

Neurorehabilitation must be in accordance with the re-organization of neuronal networks. Movement patterns re-learned by pattern formation and coordination dynamic therapy progress by cooperative and competitive interaction between intrinsic and extrinsic therapeutic inputs (afferent input) [45].

3. Combination of exercise and therapeutic strategies

Physical exercise provides important benefits after SCI both in clinical studies and in animal models [1, 46]. Specifically, studies in animal models have emphasized the importance of exercise and combined strategies to boost motor recovery. However, the functional recovery of locomotion has so far been limited, preventing its translation into the clinic.

Exercise and physical training demand adaptation in a wide range of movements and locomotion in upper, lower limbs and trunk, promoting interaction between CPG's, propriospinal neurons and supraspinal structures. Plastic changes induced by activity and sensory entry can take place both in the spinal cord and other supraspinal regions in the brain.

Studies have given evidence supporting the notion that exercise produces "motor learning" in the spinal motor circuits. One hypothesis is that the complex network of components of the extracellular matrix, inhibits the remodeling or reconnection [47]. Therefore, exercise induces the plasticity in the SCI circuitry, which could produce an interneuronal network reorganization [48]. For example, training intervention in a treadmill (20-minute protocol, 5 days a week for 3 weeks, after the complete injury) improved locomotion performance with a reversal in the asymmetric alternating movements that had occurred after a hemisection in a cat SCI model. The untrained group maintained the hemisection-induced asymmetry after the recovery period [49]. Increased excitability and the recruitment of motoneuronal populations drive limb coordination during gait and restores symmetry in a hemisection model of adult rats [50].

In other study in rats, a combination of Tamoxifen and treadmill exercise had a notorious improvement in the angular displacement kinematics after a hemisection SCI model. The untreated subjects remained considerable discrepancy in the hip and ankle joints. The drug tamoxifen presented neuroprotective effects as well as increased tissue integrity and inflammation reduction [51, 52] and the exercise exerted beneficial effects ameliorating the damage [48].

Complex network of the extracellular matrix components, which includes CSPGs, inhibits the axonal reconnection that exercise can induce, limiting plasticity in the damaged spinal circuitry. A Chondroitinase ABC treatment study was performed to see if it could enable plasticity in adult mice, combined with voluntary physical training on a rotating wheel. The results have not been positively conclusive [47]. It is necessary identifying an adequate protocol for pharmacological interventions as well as the type and amount of exercise. In 2016, another study with Chondroitinase ABC combined with intensive treadmill rehabilitation had a slight recovery, suggesting a beneficial role for chronic SCI in adult rats [32].

Physical training and elements such as the density of functional synapses, and the neurotrophic factors (NF) provide important clues to optimize recovery after injury [53]. Motoneurons and other ventral horn cells in sectioned rats synthesize BDNF in response to treadmill training, suggesting a support mechanism by which postsynaptic release of BDNF from motoneurons contribute to synaptic plasticity [54]. Moreover, BDNF levels had a significantly increase in the lumbar SC region in injured rats with training compared to the non-trained injured rats [55].

Exercise raise the levels of NT-3 and BDNF in the spinal cord, causing modulation of the NMDA receptor, which generates greater activation of the hindlimb muscles [53]. Neurotrophic factors, which include NT-3, NGF, and IGF, modulate neuronal growth, differentiation, and survival [56]. Endogenous NF higher levels can be better than exogenous administration. Exercise is also involved in the nervous system gene regulation, associated to apoptosis and cellular growth signaling pathways (PTEN, PDCD4, RAS mRNA and Bcl-2/Bax). This can produce axonal growth and reconnection improving injured SC morphology [57, 58].

Neurotrophic factors are fundamental for the normalization of spinal reflexes [59]. Limb spasms are phenomena of hyperreflexia that occur after SCI. AAV-NT3 gene therapy, exercise, and combination therapy all attenuated the frequency of spasms in the swimming test conducted at 6 weeks after SCI and increased

rate-dependent depression of H-reflex in rats. Combination therapy was significantly superior to AAV-NT3 alone in protecting motoneurons and remodeling spinal cord circuits. Gene therapy and exercise can alleviate muscle spasm after spinal cord injury by altering the excitability of spinal interneurons and motoneurons, but adjusting the combined strategy is needed to get better results [60].

Exercise produces benefits such as improving strength and conduction to adaptations in skeletal muscle and nervous system [61]. In humans, with almost total loss of voluntary muscle activity in one or both lower extremities, free field gait rehabilitation can be performed [62]. Based on this, the improvement can be achieved by appropriate treadmill training due to the activity of the voluntary muscle [63].

The effectiveness of physiotherapy in people with SCI studied in randomized controlled trials give evidence that a small number of this interventions increase voluntary strength in muscles directly affected by SCI, comparing sham or no intervention, and different physiotherapy interventions [64]. Other randomized control trials studies provide outcomes of specific features of training interventions to improve both sitting and standing balance function in SCI indicate negligible effect sizes [65–70]. Given the importance of balance control underpinning all aspects of daily activities, there is a need for further research [71].

Passive cycling can be an alternative rehabilitation for patients who are too weak or medically unstable to repeatedly practice active movements. Experimental animal studies [72] revealed that passive cycling modulated spinal reflex, reduced spasticity and autonomic dysreflexia as well as elicited cardio-protective effects [73–76]. Also, increased BDNF mRNA levels, GDNF and NT-4 [77]. In contrast, human studies did not show an effect on spasticity reduction nor prevention of cardiovascular disease-related secondary complications [78, 79]. However, it is possible that passive cycling could provoke sensory inputs to induce cortical plasticity to improve lower limb motor performance, further wide perspectives are necessary in this direction [72].

In patients with chronic incomplete SCI, targeted physical exercises are designed to simultaneously stimulate cortical, and spared subcortical neural circuits. Participants of a study underwent 48 sessions each of weight-supported robotic-assisted treadmill training and a combination of balance and fine hand exercises. Multimodal training tended to increase short-interval H-reflex facilitation, whereas treadmill training tended to improve dynamic seated balance. The low number of participants who completed both phases was a limitation. However, it is important to address engagement of lower extremity motor cortex using skilled upper extremity exercises; and skill transfer from upright postural stability during multimodal training to seated dynamic balance. These multimodal approaches incorporating balance with skilled upper extremity exercises showed no benefit compared to an active control program of body weight-supported treadmill training. Thus, it is necessary to improve participant retention in long-term rehabilitation studies [19].

Criteria for exercise guidelines represent an important step for developing exercise policies and programs for people with SCI around the world. According to current guidelines, for cardiorespiratory fitness and muscle strength benefits, SCI patients should engage in at least 20 min of moderate to vigorous intensity aerobic exercise and strength exercises for each main functioning muscle group are a strong recommendation. For cardiometabolic health benefits, at least 30 min of moderate to vigorous intensity aerobic exercise 3 times per week are a conditional recommendation [80].

The study and analysis of exercise is a major issue for the developing of synergistic strategies in the SCI treatment with pharmacological treatments and stimulation of the damaged tissue (electrical or magnetic). Different combined treatments produce positive interaction that improve or optimize the results in functional motor recovery, and revealing the knowledge of which parameters work is fundamental, so it can be adjusted to the individual needs of people suffering from SCI.

3.1 Robotic exoskeletons

Mobility possibilities of SCI people in a wheelchair, are very limited. They usually adopt a sedentary lifestyle, with progressive physical deterioration and risk of musculoskeletal, cardiovascular and endocrine/metabolic morbidity and mortality increase [81]. Robotic exoskeletons can allow individuals with SCI with varying levels of injury to functionally walk or exercise and mitigate these potential negative health consequences. The aim of these powered exoskeletons devices is to improve the mobility for people with movement deficits by providing mechanical support and facilitate the gait training [82]. All long-term manual wheelchair users who participated in a robotic rehabilitation session, predominantly perceived improvements in their overall health status and felt motivated to engage in a regular physical activity program adapted to their condition [83].

Use of exoskeletons take advantage of spared fibers in incomplete injuries and involve the use of voluntary motor control as well as proprioception to promote recovery. Therapies with exoskeleton comprises 16 to 30 sessions [84, 85], during three 60-minute sessions a week [86]. Results indicate potential benefits on gait function and balance [87]. For example, a study measured walking progression, sitting balance, skin sensation, spasticity, and strength of the corticospinal tracts. Results indicate that about 45 sessions are needed to reach 80% of optimal performance. Functional improvements were reported, especially in people with incomplete injuries. Spasticity had mixed changes, suggesting differences between high versus low spasticity prior to training [88].

The sensory information in SCI subjects is missing below the level of lesion, which made difficult to control body posture and balancing with an exoskeleton making its use difficult according to another research group [89]. It is hypothesized that part of the missing sensory information can be provided to improve the control of an exoskeleton by delivering discrete vibrotactile stimulation [89]. Following a training robotic-based proprioception training protocol in people with chronic incomplete SCI, significant improvements in endpoint and knee joint position sense and in a precision stepping task performance were shown. These results suggest altering proprioceptive sense is possible in people with incomplete SCI using a passive proprioception training [90].

An autonomous wearable robot able to assist ankle during walking, utilizes a Neuromuscular Controller with assistance based on specific residual functional abilities of subjects. According to the study, 5 training sessions were necessary to significantly improve robot-aided gait speed on short paths and consequently to optimize the human-robot interaction [91].

Exoskeletons technology have different settings depending on the needs and requirements of protocols. Existent information and evidence must be integrated to optimize rehabilitation SCI therapies. Also, is important to fulfill main goals of exoskeletons as to define basic elements for restoring movement and sensitive functions in the people living with a SCI. Finally, the refinement of the robotic devices is highly desirable to assess the adjustment to individual cases and the application in conjunction with treatments focused on the spared tissue reconnection, as well as electrostimulation therapies.

3.2 Limitations

Exoskeleton control can be challenging for users and requires a long period of training [89]. Then, functional interaction subject-exoskeleton is a main factor to produce or increase walking abilities with interlimb coordinated movements [86]. The exoskeleton rehabilitation strategies transferring from laboratories to clinical

settings and their effects remain uncertain due to the absence of large-scale clinical trials. Some researchers and clinicians call for developing pre-training rehabilitation programs to increase passive lower extremity range of motion and standing tolerance [84]. Future studies with larger sample size are needed to investigate the effectiveness and efficacy of exoskeleton-assisted gait training as single gait training and combined with other gait training strategies [92].

4. Electrical and magnetic stimulation strategies for evaluation of spinal and supraspinal circuits after SCI

Electrical and magnetic stimulation can be used to evaluate supraspinal and spinal structures and promote restoration of the motor function. These approaches consist of electrical or magnetic stimulation delivery into neural structures as therapy in motor, sensory and behavioral disorders such as chronic pain, Parkinson's disease, essential tremor, among others. Electrical stimulation can be invasive or noninvasive and complemented with imaging and electrophysiology to assess therapeutic strategies in subjects. At the same time, studying the mechanisms underlying electrical stimulation is essential to understand short- and long-term effects on neural tissue, explore novel approaches, and guarantee biosafety on implementation.

Electrical epidural stimulation (ES) was originally implemented for chronic pain in 1967 [93]. Later, it was evidenced that ES produced passive rhythmic activity in lower limbs in paraplegic subjects [13], initiating this seminal study a series of clinical investigations with the exploration of specific ES parameters in combination with physical therapy and locomotor training [94–97].

ES consist of the delivery of electrical current (typically square pulses) at different frequencies depending on the designed protocol (see below). An electrode composed of several contact leads (commonly 16) is placed on the dorsal midline of dura spanning the lumbar enlargement (T11-L1 vertebrae). Adequate positioning is monitored through electromyographic responses evoked by electrical pulses delivered at low frequencies (0.2 Hz). Implantation surgery and electrophysiology testing during surgery are described by Calvert et al. [98]. Once the subjects recovered from surgery, initial testing consists of monitoring motor activities (electromyography, EMG) produced by simple tasks during ES, including voluntary contractions on selected muscles and passive movements with suspended limbs [94, 95]. First sessions are essential to optimize parameters individually, for instance, intensities and frequencies to enable motor function in the upper [99, 100] and lower extremities [94–97]. After a couple of weeks, depending on the level and severity of SCI, subjects can be suspended on a treadmill using body weight support devices, allowing them to walk at low speeds (< 2 km/h). Even some subjects AIS-ASIA A can regain some steeping capabilities without using body weight support [94, 95]. The fact that ES enables voluntary motor activation even in subjects classified as AIS-ASIA A, suggests that some spare descending fibers can still be activated even at chronic SCI stages after several years [95, 96, 101, 102]. It is noteworthy to mention that in the absence of ES, the capacity to perform voluntary motor activities is somewhat limited, concluding that facilitation provided by ES should be continually administered in otherwise "dormant" spinal circuits. ES has shown improvements in motor function, and unexpectedly also in sensory and autonomic function [103–105]; however, a small number of highly selected subjects have been enrolled to date, making difficult to extrapolate results to general SCI population.

From animal [106–109] and human [110–113] studies, it is assumed that ES excites low threshold afferent fibers (posterior roots). Depending on the intensity of stimulation, anterior roots can also be activated, hence producing potentials (Motor Evoked Potentials, MEP) identified by their latencies. By producing MEP with known latencies, combination of other approaches such as Transcranial Magnetic Stimulation (TMS) and peripheral functional stimulation (FENS) allows the study of spinal and cortical plasticity as discussed below.

Transcranial magnetic stimulation (TMS) has also been used to stimulate muscles below the injury level in SCI subjects. Differences in latencies and thresholds of activation between controls and are widely described as well as emerging protocols to study plasticity in the spinal cord and cortex using TMS [65]. Changes in the motor cortex excitability have also been described [114–116].

Similarly, changes in cortical representations and events involving neural reorganization in rostral and caudal structures to lesion have been described after SCI [117–119]. Although precise mechanisms involving plasticity in cortices after trauma or SCI remains unanswered, animal models have provided valuable information [120].

In humans, targeting upper and lower limb muscles along with FENS has shown to promote spinal and cortical plasticity as partially explained by long-term potentiation mechanisms (LTP) [121]. Together, TMS and FENS are termed Paired Corticospinal-Motor Neuronal Stimulation (PCMS). For example, Jo and Perez [67] hypothesized that exercise promotes cortical plasticity in incomplete lesions. In the same study, the authors found that PCMS produced higher voltage amplitudes recorded in selected muscles. Performance during motor tests in upper and lower limbs also improved, although subjects not included in the "exercise plus PCMS group" also showed advancements. A conclusion is that TMS combined with other methods such as FENS and exercise, produces plasticity in spinal and supraspinal circuits (i.e., motor cortex), which benefits people suffering from SCI. Moreover, the effects on motor performance can last several months [67].

Yet some caveats remain unsolved. For instance, TMS technical aspects are not homogeneous across studies, for example, coils, motor tasks, and the number of muscles recorded [122]. Additionally, results obtained in small samples will be sustained in the heterogenous SCI spectrum, and potentially undesirable side effects should be discarded, as headaches are commonly reported during TMS [123]. Finally, technology advancements must overcome the high cost of TMS nowadays and to offer devices that can be used by patients and caregivers at home.

Noninvasive electrical stimulation techniques called transcutaneous electrical stimulation (tSCS) and transcranial or trans-spinal direct current stimulation (tDCS) have also been implemented as therapy for SCI. Both procedures include delivery of electrical current by surface electrodes placed on the back (as the cathode) and a pair of electrodes located over the iliac crest (as anodes). Like with ES, tSCS activates low threshold afferents, although higher stimulation intensities must be delivered as current must overcome high-resistance structures (skin, muscle, ligaments, and bones). For this reason, high intensities usually produce discomfort in subjects, perceived as painful abdominal muscle contractions. Recently, a strategy was proposed to mitigate pain and reduce current administered transpinally: a carrier frequency (10 KHz) and a lower frequency (40 Hz, for example) [124].

tSCS has shown that delivered electrical current excites large diameter fibers, thus evoking motor potentials with same characteristics (i.e., latencies) as previously demonstrated during ES [111, 125–128]. For this reason, research has explored this noninvasive technique recently as therapy for SCI subjects.

Spasticity appears after an insult to the central motor system compromises descending monoaminergic modulation of spinal circuitry [129]. Unfortunately, this sensory and motor disorder commonly develops in SCI subjects. In chronic, incomplete SCI subjects, Hofstoetter and colleagues applied tSCS over the T11 and T12 showed improvements in spasticity as measured by the Watenberg pendulum test, electromyography and 10 minutes walking. tSCS consisted of a single session of 30 min of stimulation at 50 Hz with subjects lying in supine position. The intensity of stimulation is an important parameter to consider. For example, tSCS is delivered at levels that produce paresthesia but below motor activation [130]. The involvement of brainstem inhibition seems to play a role in the activation of neural circuits through long-loop mechanisms, although the whole picture is not clear for now, as remaining fibers depending on the severity of the lesion may take part on results [131].

Additionally, spinal inhibitory circuitry could be transiently modified, decreasing exaggerated reflexes, such as during cutaneous stimulation on the foot's surface. Interestingly, motor incomplete SCI subjects increased their walking speed and voluntary control, making it less likely that reduced spasticity occurred as a diminished motor output [130, 132]. tSCS delivered tonically at 30 Hz, showed an immediate change in spinal circuitry, i.e., enabling motor output measured by EMG and kinematics [132] similarly as previously shown during ES (see above). At the same time, supraspinal and propriospinal circuitry could participate during steeping in incomplete injuries. For example, ES and tSCS are supposed to increase the excitatory drive necessary to activate central pattern generators [13]. However, tSCS is not feasible as a home-based therapy and carry-over effects are not easy to study. It was recently found in one subject with chronic SCI (AIS-D) that tSCS self-applied during 6 months improved spasticity as measured by several scales and functional tests and that beneficial effects lasted for seven days after cessation of tSCS [133].

Combining TMS and tSCS is possible to explore changes in cortical excitability before and after low frequency (0.2 Hz), continuous (52 m) tSCS after SCI. After 14 sessions of tSCS, paired TMS pulses on the left motor cortex delivered at different interstimulus intervals (ISI) in a range of 1–30 ms, evoked motor potentials that exhibited intracortical facilitation and inhibition that was related to a decrease in latencies and an increase in amplitudes recorded in right wrist flexor and extensor muscles [134]. Authors interpreted these results as changes in cortical map representations, bilateral connection strengthening, and increase in cortical drive, although plasticity in the spinal cord may also play an important role. Importantly, the subject enrolled in this study also reported improvements in autonomic and sensory functions below the lesion, as reported for ES (see above).

Few studies have used the transcutaneous spinal Direct Current Stimulation (tsDCS) technique to study motor activation in complete and incomplete SCI. Cathodal or anodal stimulation can be applied, and corticospinal excitability evaluated in recorded muscles by TMS [135] or spinal reflexes [136]. Although nonsignificant results have been reported, modifications in MEPs suggest differences in cathodal versus anodal stimulation, meaning lateralization in responses depending on the location of the reference electrode [135]. Cathodal tsDCS stimulation did not show differences in spinal reflexes compared to sham stimulation [136]. Overall, results with tsDCS must be taken cautiously as few SCI subjects have been enrolled, and motor outcomes are not readily comparable with healthy population.

4.1 Limitations

Although these findings may represent a new alternative to invasive methods to restore lost functions, limitations impede translation into the clinic. Research must

be extended into the heterogeneity of injuries (extension, level, time after lesion, age, etc.). To date, a small sample of subjects have been included in trials, and carry-over effects have not been fully explored. It is important to mention that beneficial results during neurostimulation are immediate, observable, quantifiable, and self-perceived; however, after cessation of electrical stimulation, there is a notable reduction in the effects, being voluntary muscle contraction the most evident, although some improvements remain as described consistently, especially in incomplete SCI. In this context, evaluation of daily activities should be included in trials to assess patients' quality of life. Finally, long-term effects, especially adverse effects, must be appropriately assessed, being one of the barriers the difficulty of self-applied home-based therapy.

Spinal cord injury is a severe clinical issue that affects in the acute stage the body of the patient and in a chronic stage the mental health. As above mentioned, a cascade of phenomena occurs after a SCI such as: inflammatory response that lead to neurons and axon degeneration, muscular damage, cardiopathy process, etc. If a group of health practitioners give a proper clinical and or surgical management, its patient preserves his life but not his sensitivity and motor control (depending on the degree and location of the injury).

Therefore, patients tend to develop an important state of mental health problems that includes depression [137], chronic sadness states and mood changes [138], delirium [139], and suicidal thoughts [140]. Therefore, is important to address mental health management after SCI in a proper way to ensure an integral patient recovery.

5. Mental health after SCI

Mental good health is important for transitioning our life with equilibrium; however, a traumatic SCI can disrupt that equilibrium since it causes the loss of our ability to have motor independency. Although the life expectancy of SCI patients has improved in the last decade [141], unfortunately, this condition has no cure to date and therapeutic strategies are limited to physical rehabilitation and support groups.

Psychiatric professionals have studied the relation between depression and anxiety as a SCI sequel and found that one out of two patients share in common continuous anxiety outbreaks and depression with a profound suicidal desire [142]. In addition, there is a significant higher risk of suffering psychiatric disorder in patients with a SCI such as dementia, psychosis, bipolar disorder, sleep disorder and illicit drug use [143]. The previous statement reveals that retrieving a life with normal parameters of mental health represents a challenge for patients and the doctors involved in the recovery of such disease.

Among all the mental illness that patients with SCI can develop, depression prevails over all mental health disorders. A cross sectional survey revealed that over 30% of the patients had depressive disorder diagnosed [144].

Although the initial injury is only the first of many traumata in the life of these patients, there are other factors that are related to increase mental illness; intermittent catheterization, sphincterotomy, continuous bed shift among others insults that endure for the rest of their life [145]. Though these procedures are for the patients benefit, they often chose to protect themselves from being oppressed by these disruptions, some patients retrieve themselves into the conservation-withdrawal response until they become uncooperative, express of wanting to be left in loneliness and passively acquire depressive signs [146].

As previously mentioned, physical exercise has positive results at a systemic level in the rehabilitation therapies, this beneficial effects includes diminishing of depression in individuals with SCI. Mood data (POMS questionnaire) and analysis for inflammatory mediators resulted in a significant reduction in total mood

disturbance pre to post-exercise, and pre to one-hour post-exercise and there was a significant decrease in TNF-α from pre to post-exercise. Thus, acute exercise can positively affect mood in SCI patients and exercise-induced changes in inflammation contribute to such improvements [147].

At last, is important to mention that pharmacological therapies may give the patients some relief but are not always sufficient to promote adaptability to such condition. Emotional assessment may play a role in long-term adjustment [148].

Neurobiological and psychiatric assessments for SCI have been evolving throughout the years and the results are promising, but social issues are important for the reinsertion of these patients to society. It has been documented that social necessities are as important as physical [149]. Lack of job opportunities, transportation, marriage, social relations are a few of a big list of the social outcomes followed by a SCI [150].

Several studies has demonstrated that a proper social assessment such a reintegration to the community, interaction with groups of SCI injured patients, sports and psychosocial treatment can improve the clinical health issues [151].

The family context is very important in order to achieve higher health scores within SCI patients. Family brings support and comprehension of the patient's situation. However, when family integration falls apart due to diver's socioeconomics, demographics and emotional variables the recuperation of the patients may be a challenge [152].

The economic weight of the health care systems and the family financial difficulties to deal with, are a great challenge. As it is, raising awareness for improve prevention to reduce occurrence of these types of injuries, and medical and technological advances management for medical care in the social resources allocation [153]. And socioeconomics impact that damage severely the life quality of the patients. However, since the life expectancy of these patients has improved in the last decade [141] these patients often present functional impairments in several areas of their life such as: psychological/psychiatric, organ dysfunction, sexuality, economics, family and social interactions [154].

6. Conclusions

SCI is a highly complex condition that affects several aspects of the patient's life. Physicians and society focus within this condition has been improving the physiology of the spinal cord *per se* and the indirect repercussions in the body. However, less is been done in terms of psychosocial issues that the patients are suffering. A better assessment to this terrible illness is to approach the patients in a more comprehensive way that includes physical, psychological and socioecomic methods. Mental health is vital for adaptation to dysfunctions and overcome challenging conditions in daily life after SCI.

An understanding of mechanisms following spinal cord injury to prevent extension of the damage and development of below-level pain aimed at a therapeutic approach. To improve outcomes and reduce morbidity in patients with SCI it is essential to work with an objective of supporting the standardization of precise protocols for the immediate care based on updated reports and international classification systems, and encouraging clinicians and patients to make evidence-informed decisions. Afterwards, the subsequent attention of the inflammatory and degenerative effects after the acute stage. For the long term, to establish rehabilitation strategies integrating the most current studies to restore autonomic, sensorimotor functions, pain management and psychological effects, having a clear picture of the sequelae. Finally, the improvement of the health system for priority care in these patients.

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