Brain-Computer Interface, Neuromodulation, and Neurorehabilitation Strategies for Spinal Cord Injury

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KEYWORDS

- Neuromodulation • Neural interfaces • Brain-computer interfaces • Neurorehabilitation
- Neural plasticity

KEY POINTS

- There has been significant progress in the use of brain-computer interface, neuromodulation, and neurorehabilitation strategies to help restore function after spinal cord injury (SCI).
- Many brain-computer (neural bypass) interfaces aim to translate cortical signals into peripheral motor responses, in effect bypassing spinal cord lesions.
- Neuromodulation strategies aim to recruit residual functional spinal/supraspinal circuits and/or potentiate the formation of new functional connections within the nervous system.
- Neurorehabilitation strategies have been shown improve neurologic function in patients with incomplete SCI and lead to improvement in cardiovascular and metabolic functions that are associated with improved quality of life.

INTRODUCTION

Over the past several decades, survival rates following acute spinal cord injury (SCI) have increased substantially, paralleled by a similar increase in life expectancy,[1,2] making restoration of function a central focus of current research in order to maximize community independence. Many different therapeutic modalities have been explored to improve outcomes in people with chronic SCI. This article reviews some of the recent progress in brain-computer interfacing, neuromodulation, and neurorehabilitation for functional restoration in patients with SCI (**Fig. 1**).

BRAIN-COMPUTER INTERFACING

Neural interface research has been strongly motivated by the need to restore communication and control to more than 5.4 million individuals in the United States with various neurologic disorders and diseases of the central and peripheral nervous system such as stroke (33.7%), SCI (27.3%), and multiple sclerosis (18.6%) resulting in paralysis.[3–8] The long-term use of rehabilitative neuroprosthetics could significantly improve the quality of life of paralyzed individuals with technology to reanimate nonfunctional limbs, replace missing limbs, and enable new modes of direct neural communication.[3,6]

Over the last 20 years, there has been a surge in the number of successful applications of brain-computer interfaces (BCIs) for upper extremity control involving reaching and grasping.[9–14] However, current implantable neural bypass systems for tetraplegia require patients to be constantly tethered to an external power source and recording hardware, limiting their application to a laboratory setting.[9,11,15] Further, decoding algorithms generally rely on single-neuron

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Neurosurg Clin N Am 32 (2021) 407–417
https://doi.org/10.1016/j.nec.2021.03.012

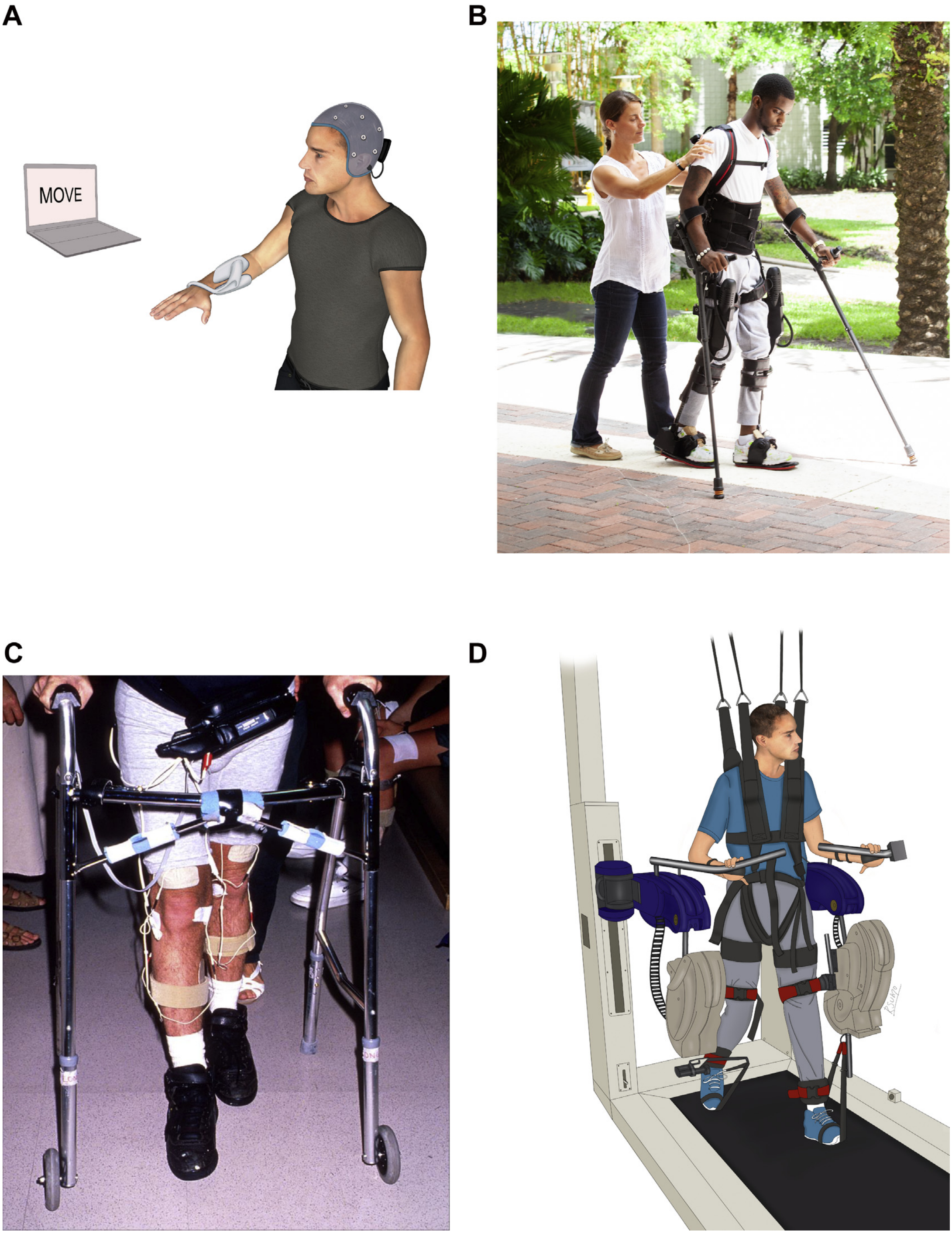

Fig. 1. (*A*) A brain-computer interface driven by event-related desynchronizations detected on scalp electroencephalogram when a patient with spinal cord injury with cervical quadriplegia thinks about moving the dominant upper extremity and is used to trigger functional electrical stimulation of the dominant right upper extremity, as described by Gant and colleagues.[23] (*B*) Patient with thoracic SCI walking with the assistance of an exoskeleton. (*C*) A patient with incomplete SCI ambulates with the assistance of a walker using functional electrical stimulation of the lower extremity muscles. (*D*) Robotic-assisted weight-supported treadmill training being using in a patient with SCI to facilitate high-intensity training. (Photo in B courtesy of Dr. Jennifer Maher, Dr. Mark S. Nash, and Robert Camarena at the Miami Project to Cure Paralysis.)

activity,[10,12,14] the recording quality of which degrades over time in animals and humans.[16] Motivated by this observation, studies have sought to develop algorithms that rely on electroencephalography (EEG) signals recorded noninvasively from the scalp.[17–20] However, these signals suffer from low signal-to-noise ratio and are therefore prone to contamination from artifact.

Further studies have relied on more stable electrocorticography (ECoG) signals recorded from the brain surface.[19] These latter attempts have thus far been limited to temporary implantations because of the clinical indications for ECoG (eg, seizure mapping).[19] Successive continuous movement of the hands was first noticed by Jasper and Penfield[21] in 1949 to block beta rhythm in the precentral and postcentral hand area measured by ECoG.[21] Interestingly, these beta-rhythm reductions, called event-related desynchronizations (ERDs), are also observed during imagined movements of the limb. Recently, a fully implanted ECoG-based BCI triggered by ERDs successfully allowed a locked-in patient with amyotrophic lateral sclerosis (ALS) to communicate through typing.[22] Therefore, it is not surprising that ERDs and other frequency characteristics of the EEG and ECoG are at the forefront of current research for a variety of end-organ uses from controlling a cursor on a computer screen[18] to moving paralyzed muscles.[23]

Surface activity recorded from the sensorimotor cortex of the upper limb with bilateral wireless 64-channel epidural electrodes has been used to promote movement in a patient with C4 American Spinal Injury Association Impairment Scale (AIS) A SCI. An adaptive decoding algorithm was used to send commands to either a virtual avatar or an exoskeleton during a 24-month trial. Over the duration of the trial, the subject was able to control activation of a 4-limb neuroprosthetic exoskeleton (up to 8 degrees of freedom) simultaneously without recalibration for up to 7 weeks.[24] Continued improvements in computational power governing implantable circuits suggest the possibility of even more sophisticated BCIs emerging in the short term.

Neuromodulation After Spinal Cord Injury

Neuromodulation makes use of electrical stimulation to modify neuronal activity in the central and peripheral nervous systems. The goal of neuromodulatory strategies in SCI are to recruit residual functional spinal/supraspinal circuits to improve function, and/or to potentiate formation of new neuronal connections within the nervous system to replace damaged networks. Improved understanding of spinal cord circuits in animals has led to translation of neuromodulation to assist neurologic rehabilitation after human SCI.

Scientific basis

The central nervous system shows both structural and functional changes after injury. Animal studies show spontaneous formation of new neural circuits in spared neural fibers after SCI.[25–27] Preservation of corticospinal connections after incomplete cervical SCI has been shown to be essential to spontaneous motor recovery.[28] Cortical input to brainstem reticulospinal axons also contributes to recovery of hindlimb function after incomplete SCI.[25] Both maladaptive (ie, increased spasticity, gliosis) and positive functional (ie, migrations of neurons across site of injury) changes occur in intraspinal neural circuits and motor neurons after SCI, further highlighting neuroplasticity along the neuroaxis after injury.[26] Together, this information provides evidence for innate adaptations of the central nervous system after SCI.

Deep brain stimulation, spinal cord stimulation, epidural electrical stimulation, functional electrical stimulation, and peripheral nerve stimulation are types of neuromodulation that have been explored in the context of SCI. These modalities stimulate descending neuronal fibers, spared motor neuron, and interneuron circuits.[29] Repeated stimulation of these targets can produce functional reorganization, which can lead to regeneration and new neuronal connections.[30] Activity-based neuroplasticity, which forms the basis of physical rehabilitation, can be paired with electric neuromodulation to enhance gains in motor function.[31,32] The induction of neuroplasticity by combining these 2 complimentary techniques has been the most successful approach in spinal cord neuromodulation. There is mounting evidence that multimodal techniques using BCI, neuromodulation, and neurorehabilitation may have augmented effects compared with their individual application.[33]

Epidural spinal cord stimulation

Epidural spinal cord stimulation (SCS) using surgically implanted electrodes in the posterior epidural space was initially used to treat chronic pain. Early investigators expanded the use of epidural SCS and noted considerable improvements in spasticity, bladder function, and motor function in patients with multiple sclerosis.[34] Studies investigating epidural SCS in subjects with SCI found that stimulation below the level of injury produced improvements in spasticity, and in some cases motor recovery,[35,36] to a greater degree than stimulation above the level of injury.[31,37] Epidural SCS in the conus region (L1-L2) has been shown to control severe spasticity in patients with chronic SCI.[38] Those with incomplete SCI may benefit more than those with complete SCI.[37] Motor unit activity has been seen to increase in some patients undergoing epidural SCS, suggesting that stimulation may improve motor function in addition to reducing spasticity.[39]

Mechanism of action

The primary intrathecal target in lumbar SCS is the posterior sensory roots with large and medium fiber afferents arising from the lower limbs and ascending primarily in the dorsal columns.[40,41] Proprioceptive afferents and muscle spindle feedback are essential for locomotor recovery after SCI.[27,42] Lumbar epidural SCS activates these afferents in addition to firing spinal interneurons and motor neurons via intraspinal monosynaptic and polysynaptic circuits.[43] In incomplete SCI, it is also thought that stimulation of the posterior columns creates orthodromic signals that affect brainstem control (via reticulospinal pathways) of the lumbar intraspinal circuits. These mechanisms are postulated to contribute to increased spontaneous motor activity and improved voluntary control.

The effect of epidural SCS on complex lower limb movement is amplified by increasing the state of excitability of the intraspinal circuit.[35] Intensive motor training increases the excitability of the lumbar motor circuits, and has been shown to improve functional intraspinal connections.[44] In a rat SCI model, lumbar epidural SCS complemented with motor training led to improved hindlimb motor function via activation of previously silent axonal projections across the lesion.[45] Importantly, active initiation of hindlimb movement by the injured animal is critical to neuroplasticity induced by lumbar epidural SCS.[46] Animal SCI models have been used to better understand the configuration of lumbar epidural SCS required to induce gait and locomotor motion.[46] Real-time electromyography recordings from leg muscles during gait and stimulation have been used to further refine lumbar epidural SCS from tonic stimulation to specific spatiotemporal activations, facilitating more rapid improvement in locomotion after injury.[47] Spatiotemporal lumbar epidural SCS can be coupled with intracranial microelectrode arrays to decode motor cortex signals responsible for gait. The culmination of these experiments was the demonstration of a wireless system that decodes intracranial motor cortex signals, bypasses the lesion, and produces specific epidural lumbar SCS to restore locomotion after primate SCI.[48]

A newer, reversible, and painless paraplegia model has recently been developed with the hope of making device development in nonhuman primates more accessible to other laboratories hoping to show efficacy of certain bypass BCI devices in primates without needing to induce permanent SCI.[49]

Clinical Efficacy

Improved voluntary motor activity after lumbar epidural SCS was first reported in a single patient with a chronic motor complete T1 SCI. The patient underwent surgical placement of a 16-electrode array in the conus region. Tonic epidural stimulation, combined with intensive locomotor training, was able to induce voluntary leg movements and help with weight bearing, standing, and stepping.[36] The same team repeated this experiment in 3 other patients with chronic SCI and showed that neuromodulation of lumbosacral networks was able to restore voluntary leg movements. Intensive rehabilitation further improved the gains observed with epidural SCS, allowing patients with SCI to stand independently with full weight bearing for short periods of time.[35] These studies provided a remarkable demonstration of motor reactivation in chronically paralyzed limbs after SCI.

Epidural SCS also produces improvements in other neurologic deficits, such as voluntary control of bladder function,[50] normalization of blood pressure,[51] improved sexual function,[52] and body composition[53] in patients with SCI. Current evidence supports the theory that patients most likely to show improvement from epidural conus stimulation have an incomplete, or discomplete,[54] SCI (ie, clinically complete but with evidence of anatomically intact fibers spanning the lesion) and an intact conus medullaris, because attempts to apply this treatment to patients without these features have been less successful.[55]

In contrast with tonic stimulation, spatiotemporal epidural stimulation can produce specific leg movements associated with gait. This technique involves identifying areas in the spinal cord that are active during a specific gait phase. A closed-loop system of inertial sensors identifies the phase of gait of the participant and then synchronizes the electrical impulses to the corresponding muscle groups. This type of simulation seems to be superior to continuous epidural SCS and enables over-ground ambulation.[56] When combined with a rehabilitation program, SCI participants show substantial improvements in walking and voluntary leg movements with and without epidural SCS.[57] The development of closed-loop systems for spatiotemporal epidural SCS is a step toward expanding the use of neuromodulation in a home environment for patients with SCI.

Transcutaneous spinal cord stimulation

Transcutaneous stimulation of the spinal cord is being explored as a minimally invasive technique to activate local spinal cord circuitry. Electrodes are placed on the skin, and direct current stimulation is used for neuromodulation. Stimulation protocols include both biphasic and monophasic currents with high-frequency pulses. Most studies use high-intensity currents that near the threshold tolerated by participants.[58] Similar to epidural SCS, transcutaneous SCS targets the proprioceptive pathways via the posterior roots.[59] Transcutaneous SCS can modulate both upper and lower limb function. Transcutaneous SCS combined with training can produce sustained gains in bilateral hand function after chronic incomplete cervical SCI[60] and has been shown to produce volitional stepping in the lower limbs.[61] Most case reports and small series using this technique have studied participants with incomplete SCI, and have included a training paradigm in addition to transcutaneous SCS.[58] Transcutaneous SCS produces increased electromyographic activity in the corresponding muscles, and enhances voluntary motor control and trunk stability.[61,62] Commercially available cutaneous electrodes are easier to set up and less inexpensive than epidural SCS. Limitations of transcutaneous SCS include stimulation-induced sensory side effects as well as the lack of fine spatiotemporal stimulation to activate specific muscle groups.

Transcranial magnetic stimulation

Studies in subjects with clinically complete SCI have shown evidence of spared anatomic and functional connections across the lesion.[63,64] In 1 report, more than half the subjects with AIS A and B SCI showed preservation of volitional electromyographic responses in muscles innervated below the neurologic level of injury.[65] A small proportion of patients continued to show neurologic improvement after complete SCI even at 1 to 5 years after the injury.[66] Transcranial stimulation to induce motor movement is predicated on preservation of supraspinal connections across the level of SCI. Transcranial magnetic stimulation (TMS) generates electrical responses in the cortex using magnetic fields, which is less painful than electrical stimulation. Direct activation of corticospinal neurons as well as indirect synaptic stimulation of these neurons produce signals along the corticospinal tract.[67] Repetitive TMS over the motor cortex can produce motor movement via this cortical activation. These effects depend on duration of the magnetic stimulation, direction of the field, and cortical excitability.[68–70] Voluntary task-based motor activity increases cortical excitability and can augment cortical stimulation via TMS.[70] In patients with SCI, TMS impulses can improve grasp strength when combined with task-based hand activity.[71] When paired with peripheral nerve stimulation, timed TMS modulates synaptic transmission between corticospinal fibers and anterior horn cells. This process has been shown to augment hand function in tetraplegic patients undergoing TMS.[72] Other studies have shown that TMS improves ambulation in patients with incomplete SCI when combined with locomotor training,[73] pointing to the positive effect of TMS on corticospinal plasticity. TMS is a promising adjunct to rehabilitation and training protocols.

Challenges and future areas of research

Despite promising results, neuromodulation for SCI faces several challenges.[74] Some of the approaches, such as epidural SCS, include totally implantable components and can be used by participants in their home environments. However, technologies that access supraspinal circuits, such as TMS, require nonportable, specialized, and costly external machines along with user expertise. The clinical translation of wireless cortical implants that communicate with lumbar epidural electrodes[75] will further push the boundaries of accessible neuromodulation for patients with SCI. At this time, the mechanism of action of these technologies has been incompletely elucidated, and a better understanding of spinal neuroplasticity is necessary to optimize stimulation paradigms. As described earlier, most studies are limited to small case series and case reports; large-scale clinical trials are awaited to validate the early positive results. In addition, long-term durability and cost will need to be addressed to maximize access and adoption of this technique for patients with SCI.

NEUROREHABILITATION

The most common neurorehabilitation interventions for SCI include functional electrical stimulation, high-intensity repetitive movement training, use of robotic exoskeletons to assist with physical therapy, and combination therapies that leverage simultaneous neuromodulation and intense physical therapy.[76] Although a detailed description of each of the neurorehabilitation approaches is outside the scope of this article, a few of the most widely used techniques are reviewed.

FUNCTIONAL ELECTRICAL STIMULATION

Functional electrical stimulation (FES) consists of the application of small electrodes to paralyzed muscles through which electrical pulses are delivered to help restore or improve function. In patients with complete or incomplete SCI, there is now proof of FES-induced activation of central pattern generators within the spinal cord responsible for locomotion. Increased stepping responses have been observed in response to FES.[36,77,78] In addition, some patients regularly treated with FES have shown improved AIS motor and sensory scores[79] and decreased spasticity.[80]

In addition to the neurophysiologic changes observed with FES, overall health measures have also shown significant positive improvements. These improvements tend to be more immediate and can significantly improve quality of life.[81] The most well-studied effect of FES is the subsequent improvement in muscle size, strength, and composition with overall improved oxidative capacity[81] and fatigue resistance.[82] Recovery of lost bone mass, particularly in the lower extremities, has also been reported with FES.[83] Moreover, improvements in cardiovascular conditioning and metabolic function (ie, decreased insulin resistance[84] and decreased adipose tissue[85]) have also been shown in patients with SCI.

HIGH-INTENSITY, HIGH-VOLUME TARGETED TRAINING

Recent SCI rehabilitation has concentrated on the delivery of high-intensity, high-volume, repetitive rehabilitative exercises, providing clinical improvements to both patients with complete SCI and patients with incomplete SCI.[86] Approaches such as activity-based restorative therapy were developed from the understanding that motor activation could be achieved with intensive training following motor injury or complete transection.[87–93] This work is based on the theory that locomotion after SCI could be preserved by repetitive training in tandem with the simulation of central pattern generators (CPGs), ambulatory motor reflex pathways operating without brain input below the level of SCI.[86,92,93] Studies by Grillner and others have explored the underlying function of CPGs, showing that spinalized cats can be conditioned to stand, attain full hindlimb weight-bearing strength, and achieve locomotion at varying speeds on a treadmill with intensive physical training.[89,93,94] Weight-bearing activity is an important component of post-SCI rehabilitation, because Harkema and coworkers have shown treadmill activity to increase spontaneous hip extensor activity following injury.[92,94] However, patients with motor complete SCI are a more complex entity and have so far proved refractory to clinical benefit from intensive locomotor training.[92,95,96]

EXOSKELETON USE IN SPINAL CORD INJURY

Exoskeleton use in acute rehabilitation and for long-term activities of daily living (ADL) represents a novel approach to the complex biological processes of central nervous system regeneration and repair that have curbed progress in many areas of SCI treatment. Accompanying the rapid process of muscle atrophy following SCI, especially in the context of complete SCI, are several cellular mechanisms that remain poorly understood.[97,98] As such, increased exertional effort required by patients with SCI for even small tasks, although extremely beneficial in the acute SCI period, ultimately limits rehabilitation efforts, expends significant levels of energy with or without an orthosis or wheelchair, and can significantly limit a patient’s ADLs.[99] Exoskeletons have emerged as a way to address some of the limitations of body weight–supported treadmill training, which is frequently used to restore the ability to walk after SCI but is significantly limited by fatigue of patients and therapists.[100] The use of passive or actively powered robotic exoskeletons increases efficiency of work by supporting weakened stabilizer muscles, increasing sustainable workloads, and decreasing energy use by both patient and therapist. Actively powered robotic exoskeletons use an external battery source, support joints at risk for injury, are ergonomic, and are becoming more efficient in design.[101]

More recently, Grasmücke and coworkers implemented a Hybrid Assistive Limb Exoskeleton (Hal, Cyberdyne Inc, Japan), which uses electromyographic stimuli from a wearer with incomplete SCI to serve as an impulse for gait and limb assistance within the powered exoskeleton. They report through their experiences that motivated patients can be trained effectively using this device to improve ADLs.[102,103] Although neither the Hal or any other exoskeleton is a permanent substitute for daily ambulation yet, these incremental advancements in exoskeleton technology and efficiency are gradually improving the lives of patients with SCI. There are currently numerous treadmill-based and fully mobile exoskeletons being tested in clinical trials that may alter how patients with chronic SCI receive therapy in and out of the hospital in the near future. Although there are nuances to each exoskeleton and study protocol, the results of these trials generally support the idea that exoskeletons help patients improve cardiopulmonary function and muscle physiology, and potentially improve walking performance.[100,104,105]

SUMMARY

The drive to restore motor function and independence in patients with SCI has driven numerous developments within neuromodulation, neurorehabilitation, and brain-computer interfacing. There is mounting evidence that combinations of each of these techniques may yield superior outcomes compared with when each is used separately. Clinical experience on a large scale will be required to determine the optimal combinations of the distinct interventions that yield the best outcome, and this is likely to depend significantly on the level of residual neural function for each patient. However, the continued improvements that have been shown in chronic SCI, previously thought impossible, raise the possibility of significant improvements in the function and quality of life of individuals affected with SCI.

CLINICS CARE POINTS

- BCI, neuromodulation, and neurorehabilitation approaches have been developed to maximize motor function and restore functional independence after SCI.
- Even in the absence of improvements in motor function, modest improvements in cardiovascular and metabolic function achieved via neurorehabilitation can yield a significant improvement in quality of life.
- Current clinical applications of these techniques typically leverage combinations of multiple modalities because these have shown the most promising results.

ACKNOWLEDGEMENT

Iahn Cajigas IC was supported in part by NIH R25NS108937-02.

DISCLOSURE

The authors have nothing to disclose.

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