Historical development and contemporary use of neuromodulation in human spinal cord injury

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Purpose of review

There is a long history of neuromodulation of the spinal cord after injury in humans with recent momentum of studies showing evidence for therapeutic potential. Nonrandomized, mechanistic, hypothesis-driven, small cohort, epidural stimulation proof of principle studies provide insight into the human spinal circuitry functionality and support the pathway toward clinical treatments.

Recent findings

Individuals living with spinal cord injury can recover motor, cardiovascular, and bladder function even years after injury using neuromodulation. Integration of continuous feedback from sensory information, task-specific training, and optimized excitability state of human spinal circuitry are critical spinal mechanisms. Neuromodulation activates previously undetectable residual supraspinal pathways to allow intentional (voluntary) control of motor movements. Further discovery unveiled the human spinal circuitry integrated regulatory control of motor and autonomic systems indicating the realistic potential of neuromodulation to improve the capacity incrementally, but significantly for recovery after severe spinal cord injury.

Summary

The discovery that both motor and autonomic function recovers with lumbosacral spinal cord placement of the electrode reveals exciting avenues for a synergistic overall improvement in function, health, and quality of life for those who have been living with the consequences of spinal cord injury even for decades.

Keywords

autonomic recovery, epidural stimulation, motor recovery, neuromodulation, spinal cord injury

INTRODUCTION

Electrical spinal neuromodulation was introduced for the management of chronic pain [1,2] and involved dorsal roots, dorsal roots entry zone, dorsal horn, and dorsal columns [3]. Dimitrijevic *et al.* [4] demonstrated that nonpatterned electrical stimulation of the posterior structures of the lumbar cord (20–60 Hz) can induce patterned locomotor–like activity in clinically motor complete Spinal Cord Injury (SCI) individuals. This phenomenon was attributed to the activation of a spinal neuronal network having central pattern generation (CPG) properties with externally generated tonic drive applied to the spinal cord supporting loss of tonic activity from the brainstem neurons that initiate locomotor activity in those with SCI. Sensorimotor activity generating peripheral afferent input also modulated the CPG to control the locomotor-like movement through feedback and feedforward mechanisms to improve hindlimb locomotion with step training on a treadmill in spinal cats [5]. Following this evidence, Wernig *et al.* [6] termed these concepts 'rules of spinal locomotion' used for the recovery of walking in incomplete SCI [7–13]. The same principles resulted in independent leg movements during step training (manually facilitated assistance on a treadmill) in individuals with motor complete SCI indicating that peripherally induced afferent input associated with locomotor activity modulated the neuronal spinal locomotor networks in humans [14–17]. Some with incomplete SCI were able to transfer this relearning to overground walking, but not all, and not those with motor

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KEY POINTS

- One neuromodulation approach uses tonic submotor threshold neuromodulation, optimizing spinal networks excitability (spinal cord epidural stimulation).
- Another neuromodulation approach uses targeted and patterned, epidural electrical stimulation directed to stimulate the posterior roots rhythmically, projecting to specific motor neuron pools, intending to control the swing and stance phases of stepping.
- Motor and autonomic function can be improved using epidural stimulation in those with chronic spinal cord injury.

complete injuries. Thus, tonic input generated by electrical spinal cord stimulation targeting the locomotor-related neuronal network was considered for individuals with severe motor incomplete [18–20] and motor complete SCI [21,22].

Minassian *et al.* [23,24▪▪], continued with the study of neuromodulation of the human spinal circuitry and demonstrated burst-generating elements that flexibly combine to obtain varied locomotor-like muscle activity from continuous lumbosacral neuromodulation. Studying evoked responses to 'single stimuli' (low-frequency stimulation at 2–6 Hz) or rhythmic patterns of electromyography (EMG) activity in response to continuous tonic stimulation (25 Hz and higher) identified engaged components of these networks (Fig. 1). They showed crossed reflexes via afferent projections (Fig. 1a) and evidence of flexor-related oligosynaptic reflex pathways (Fig. 1b) with long latency polysynaptic responses in the tibialis anterior indicating late flexion reflex [25]. They concluded that epidural stimulation applied over the human lumbar spinal cord provides access to afferent fibers from lower extremity nerves that connect to spinal networks involved in sensorimotor control and locomotion. Further, a subset of these circuits may underlie the therapeutic effect of spinal cord stimulation for locomotor recovery.

MOTOR RECOVERY WITH EPIDURAL STIMULATION

There are two current spinal neuromodulation strategies, one uses tonic neuromodulation optimizing spinal networks excitability (spinal cord epidural stimulation, scES) enabling locomotor-related networks to alter the functional state facilitating sensory input to generate voluntarily intended trunk and leg movements, standing or stepping [18,19,21,22,26–33,34▪▪,35▪]. Another strategy is targeted and patterned, epidural electrical stimulation (EES) directed to stimulate the posterior roots rhythmically, projecting to specific motor neuron pools, to control the swing and stance phases of stepping [36,37]. Both approaches report the transfer of independent steps to overground walking with balance assistance in some individuals with clinically motor complete [32,33,35▪] and incomplete SCI [18–20,36,37].

Recent breakthrough studies reported chronic paralyzed individuals diagnosed with a clinically motor complete injury recovered motor abilities contrary to their medical prognosis [26–28,30,32]. Independent standing as well as the ability to voluntarily generate intentional trunk and leg movements were recovered in people with motor and sensory complete spinal cord injury using task-specific motor training, intent for the task, and tonic scES [22,31,32,35▪,38]. Three individuals with chronic motor complete spinal cord injury achieved walking over ground with balance assistance through interleaved, continuous lumbosacral (L2-S2, 16 electrode array) scES and task-specific locomotor training [32,33]. In one study, two of the four individuals in the cohort achieved independent overground walking with only balance assist [32]. As training continued, in all four the individual's intent to step one leg or the other (left or right) generated appropriate motor activation and coordination between flexors and extensors resulting in independent step cycles in that leg (Fig. 2). The interleaved, tonic scES stimulation distributed within the lumbosacral spinal cord reestablished a state of excitability so the networks integrated the proprioceptive input related to stepping with the ongoing intentional signals from supraspinal centers driving long-term activity-dependent plasticity and ultimately the recovery of walking over-ground (Fig. 2). Once training occurs within an optimized state by neuromodulation, sensory, and supraspinal signals are integrated to produce independent stepping. This long-term adaption was evident when after training, with epidural stimulation and when the proprioceptive input was provided with manual assistance on the treadmill, *without* the distinct intent of walking, the ability to step was abolished [32]. In a replicative study with the same electrode placement and stimulation approach, the person underwent similar task specific training that included stepping on a treadmill with body weight support, physical assistance, and over-ground practice. The individuals maintained a conscious intent to move to achieve over-ground stepping with minimal physical assistance and a walker for balance [33].

The new knowledge derived from these observations is that a combination of spinal neuromodulation, training, and conscious intent, can form new functional connections between the brain and spinal networks that were dormant since all were

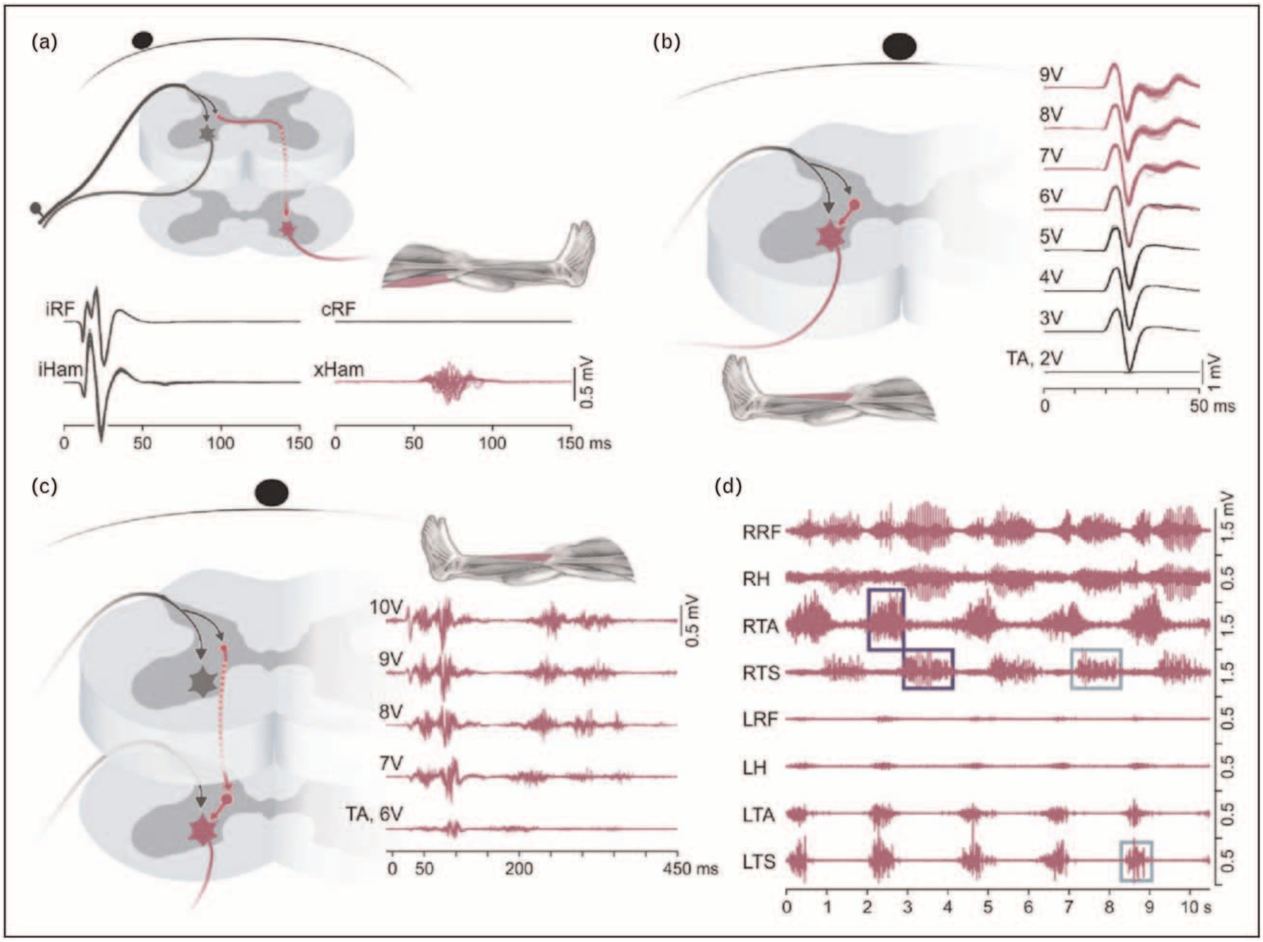

FIGURE 1. Human electrophysiological studies demonstrate the activation of components of the central pattern generator by epidural lumbar spinal cord stimulation. (a) Epidural stimulation with a laterally placed percutaneous linear lead (active electrode in black) at 6 Hz elicited ipsilateral monosynaptic posterior root-muscle reflexes (black EMG traces) and, in addition, responses in the contralateral hamstrings muscle group (Ham, magenta) with distinctly longer onset latencies of 55 ms. These crossed reflexes suggest the transsynaptic activation of commissural neurons by epidural stimulation through afferent projections. i, ipsilateral; RF, rectus femoris; x, crossed. (b) With graded stimulation, epidural stimulation at 2 Hz initially recruits monosynaptic posterior root-muscle reflexes (black EMG traces) in the tibialis anterior and evokes additional, delayed EMG potentials (magenta) at higher stimulation amplitudes, the latter likely reflecting the recruitment of flexor-related oligosynaptic reflex pathways. (c) Long-latency (>200 ms) polysynaptic responses in the tibialis anterior with consistently increasing onset latencies with increasing stimulation amplitude, a behavior reminiscent of the late flexion reflex previously observed in individuals with chronic SCI [25]. (d) Locomotor-like EMG activity in multiple lower limb muscles evoked by tonic stimulation at 25 Hz. The EMG activity demonstrates key features of central pattern generation, that is, rhythmicity, recruitment of multiple muscles involved in walking, the alternation between homologous muscles of the right and left lower limb (green boxes), and alternation between extensors and flexor muscles acting at the same joint (blue boxes). (a)–(c), 20 stimulus-triggered EMG responses shown superimposed; (d), continuous EMG recording. EMG, electromyography; SCI, Spinal Cord Injury. Reproduced by courtesy of Drs Minassian and Hofstoetter.

diagnosed as clinically motor complete. The tonic, nonpatterned delivery of epidural stimulation indicates that the motor activity was not a result of direct suprathreshold activation. Rather, the functional state of neuronal networks was altered, allowing interpretation of afferent input from the ensemble of peripheral nervous system sensors translating this information into the appropriate motor outputs – in real-time. The stimulation was used to create a state of readiness or appropriate level of network excitability to enable movements based on the integration of two communications to the spinal cord: the appropriate proprioceptive information; integrated with 'intentional' signals from supraspinal networks.

In addition, two of three chronic motor incomplete spinal cord injured but severely paralyzed (unable to walk or severely limited in ability to walk

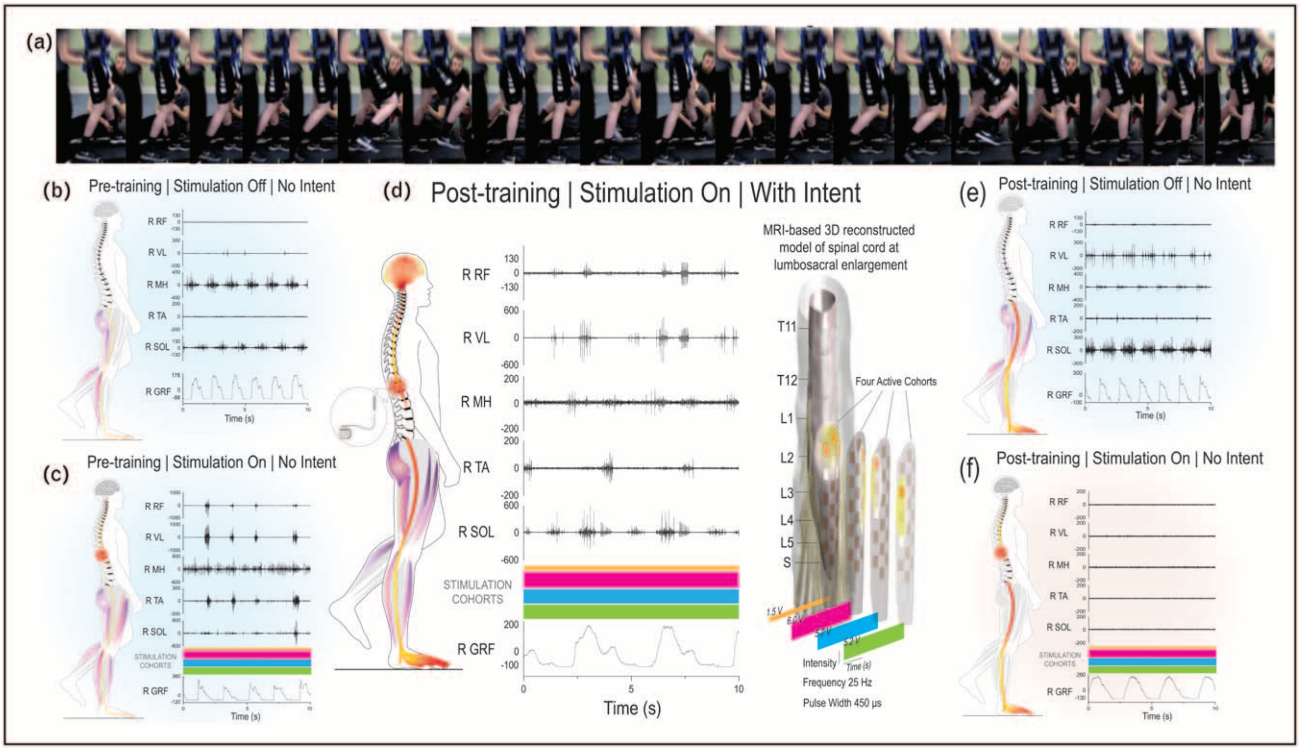

FIGURE 2. Recovery of locomotion in the presence of tonic epidural lumbar spinal cord stimulation. (a) Photographs of an individual with motor complete spinal cord injury stepping his right leg independently. (b) Sensory information is interpreted during assisted step training to generate motor activity during the step. (c) The addition of spinal cord epidural stimulation before training enhances the state of excitability of the spinal networks to increase motor activity. (d) Following training, the intent is a required signal for the integration of sensory information and generation of appropriate motor output during stepping leading to independence. In the absence of stimulation (e) and intent (f), posttraining, the spinal networks are unable to interpret information from the periphery to generate locomotor output.

over-ground) individuals improved over-ground walking with balance assist using EES [36]. The electrode and lumbosacral placement of the epidural stimulation device were the same as in the other two studies, however, epidural stimulation was delivered to the spinal cord, directly addressing the posterior roots projecting to the leg flexor and extensor motor pools timed to the stepping cycle (Fig. 3). This spatiotemporal motor stimulation was triggered based on the foot trajectory to directly control the swing and stance phases during stepping. A key difference in this paradigm was that the individual leg movements and stepping were directed by the targeted EES. Notably, during targeted EES the movement could be influenced by the conscious thought of the person. After training with an over-ground robotic device with EES, walking improved. Continuous EES was reported to block proprioception and was purported to prevent walking in those with severe SCI [37]. However, with tonic scES proprioception is not blocked with independent stepping achieved indicating key differences in the electrical field generation in these two approaches.

Both EES [36], and scES [22,30,31,39■] showed the emergence of voluntary leg movements consistent with an early case study report in one individual with motor and sensory incomplete [40] and another with motor complete SCI [22]. Fourteen individuals in three studies diagnosed with clinically motor complete spinal cord injury enabled by scES were able to move their legs voluntarily immediately [22,26,30,31,39■]. Two of the three with motor incomplete SCI [36] and one initially motor complete SCI voluntary motor activity [28] improved even without stimulation indicating long-term neuromuscular adaptation. The amount and location of spared spinal cord tissue at the lesion site were not shown to be related to the ability to generate volitional leg movements indicating differing spared spinal cord regions across individuals contributing to recovery [30]. The ability to stand was recovered using scES and although in some cases occurred immediately the extent was dependent on specific task specific training [27–29] indicating the role of the spinal circuitry integrating sensory cues driving activity-dependent plasticity.

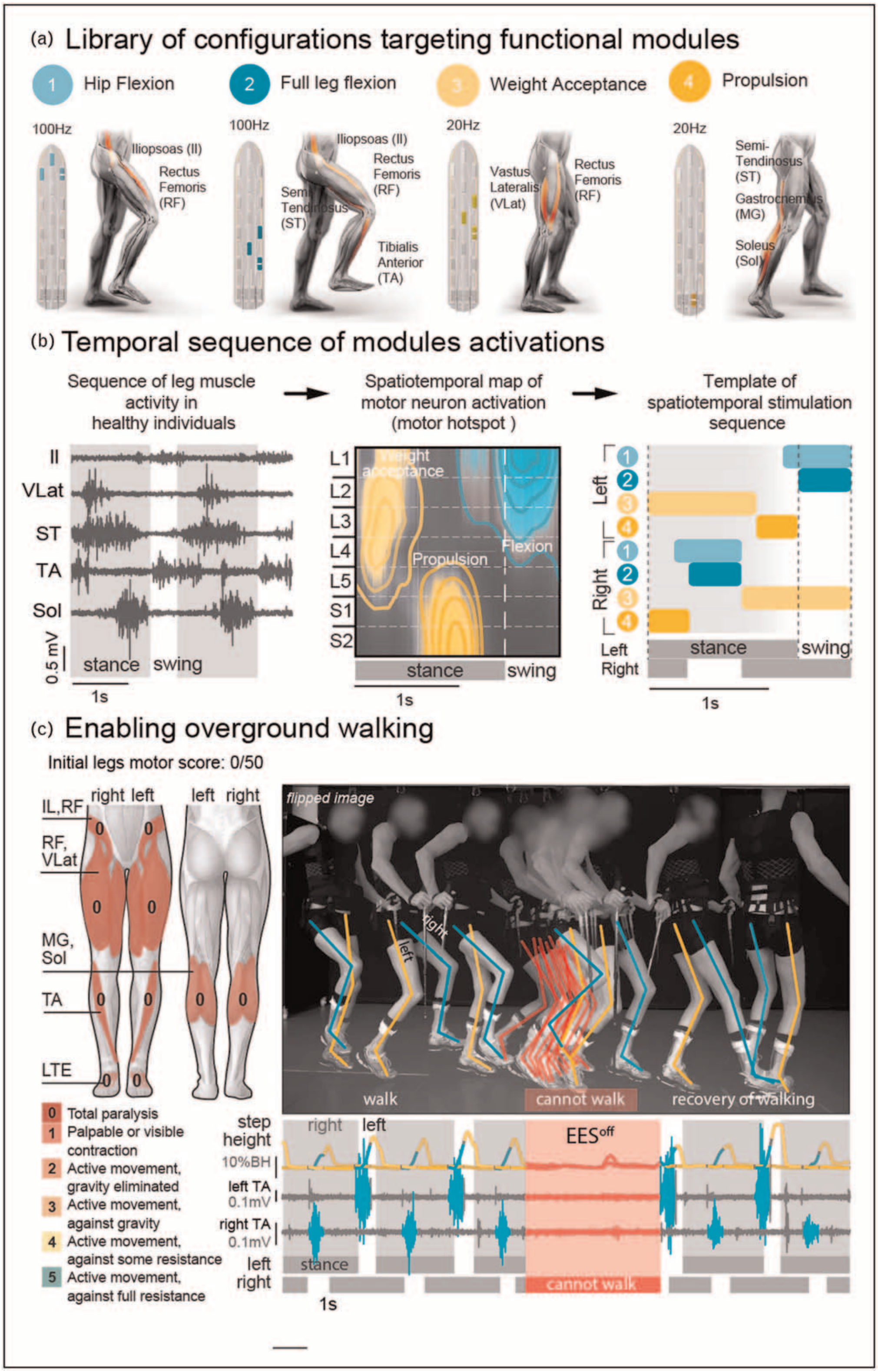

FIGURE 3. Spatiotemporal epidural electrical stimulation induces stepping after paralysis. (a) Each configuration targets a specific muscle group/function. (b) Sequential alternating bursts aim to reproduce the natural muscle activity. (c) Flexor muscle, tibialis anterior activity, and foot vertical position during overground stepping while EESS is switched ON/OFF/ON 5 days after onset of therapy. EESS, epidural electrical spinal stimulation. Reproduced by courtesy of Drs Courtine and Bloch.

Darrow *et al.* begins to address the generalizability of the SCI population without standardized rehabilitation using scES with two individuals with clinically complete SCI (5 and 10 years postinjury) [41▪,42]. Left tibialis anterior, right gastrocnemius, and right anterior tibialis EMG bursts occurred during attempted sequential bilateral flexion and extension with the same relative amplitude and timing in each muscle. The stimulation cathode electrodes were caudal and the anodes rostral both on the left and midline. The emergence of EMG activity only with stimulation during the attempted movement confirms the earlier findings of clinically motor complete individuals able to elicit motor activation in the presence of tonic scES. However, these movements were described as nonfunctional, without an alternating EMG pattern among flexors and extensors differing from the previous reports [22,26,30,31,36,39▪]. The observation of higher EMG activity at each joint in both participants during these attempted maneuvers, regardless of coordination pattern, supports the ability of neuromodulation to facilitate spinal network excitation that leads to a movement that was not possible prior for up to 10 years.

The authors [41▪] suggest that the specific contribution of epidural stimulation in voluntary movement in previous studies [22,26] was unknown because prerehabilitation had occurred. However, the design of the previous studies was to standardize the activity-based recovery training (ABRT) and provide this rehabilitation alone and then using scES. In all cases, standing and stepping ABRT without scES yielded no improvements in voluntary movement, standing, or stepping. Only following the implantation, when scES was provided motor activation emerged and continued to improve when combined with ABRT specific for the motor task. In addition, the standardized ABRT program did not include targeted voluntary movement. Thus, another interpretation would be that the studies that have ABRT as a control intervention provide evidence for the role of neuromodulation given that ABRT is provided in both paradigms with only motor recovery following the addition of neuromodulation. These varied approaches to neuromodulation in chronic SCI motor activation many years after injury, even decades collaboratively support the continued study and appropriate translation of spinal cord stimulation into clinical therapies.

AUTONOMIC RECOVERY WITH EPIDURAL STIMULATION

Disruption of motor and autonomic pathways induced by SCI leads to persistent dysfunction in cardiovascular, respiratory, and bladder function. Early reports of improvement in autonomic dysfunction were reported with ABRT alone [43,44▪] and ABRT with tonic epidural stimulation that specifically targeted improvement in motor function [22,45,46▪,47]. Subsequently, proof of principle studies designed to specifically target cardiovascular (CV-scES) and urinary bladder-scES [44▪,46▪,48–50] functions indicated that the autonomic effects could be directly targeted. Low arterial blood pressure (BP) and orthostatic intolerance have been mitigated by tonic CV-scES of the lumbosacral spinal cord [51–56]. Darrow *et al.* [41▪] showed stimulation in this same spinal cord region more rostrally improved BP in an individual with deficits but did not affect an individual who did not have significant autonomic dysfunction. One individual provided with EES at a higher level (thoracic) of the spinal cord also reported improvement in low BP when a postural challenge was given [57▪▪]. Darrow *et al.* reported standard bladder scores from questionnaires in two participants, who reported minor improvement in the storage and voiding subdomain and the incontinence subdomain [41▪,42]. Respiratory function has also been targeted with some success [58]. These findings demonstrate that autonomic function can improve with neuromodulation, further, specifically targeting cardiovascular and bladder function can further improve autonomic control even with a significant postural challenge.

ADVANCEMENT OF EPIDURAL STIMULATION: TECHNOLOGY AND FUTURE STUDIES

Future scientific investigations should focus on understanding the observation that the supraspinal and spinal interneurons seem to reform functionally seamless networks that can generate motor tasks. Studies using voluntary intent to move and walk as well as imagining performance in the presence of spinal stimulation applied to the cervical as well as to the lumbar spinal cord could be performed to understand the pathways and neural mechanisms [59]. Such experiments would be directed to improve brain–spinal cord interaction as well as to modulate the functional state of spinal locomotor-related neuronal networks.

Future studies also need to explore the mechanisms of the different stimulation paradigms presented and consider how the initial state of excitability of the spinal networks and the extent of the residual supraspinal connections interact to identify the potential for neuromodulation as an effective treatment for a broad population of those with spinal cord injury and other types of paralysis using this *brain–spinal integration* paradigm. New strategies of neurorehabilitation should focus on the combined spinal cord stimulation and optimal task specific training and enhance brain–spinal integration and design these to understand effectiveness related to severity and time since injury. As these clinical studies of neuromodulation proliferate, it will be important to report the specific stimulation configurations (anode and cathode selection, pulse width, frequency, and amplitude) and the timing of the stimulation to continue to understand the specific fields that provide the best modulation for each motor task and autonomic function both for the understanding of the mechanisms and the best approach for each subpopulation.

CONCLUSION

Epidural stimulation may inevitably provide an innovative treatment for paralysis, as importantly, is a valuable tool for understanding the complexity and plasticity of the human circuitry and integration of the entire nervous system. Research and technological advances need to continue to move forward considering the possibility of recovery of walking in a large population of paralyzed persons using spinal neuromodulation. The time has arrived for evidenced-based findings to elevate to clinical trial and be translated into treatments to change the daily lives of those living with chronic spinal cord injury. However, technology must be adapted specifically for use in the paralysis population in the home and community to be effective and for clinical trials to be successful. For the first time, opportunities exist for treatments after spinal cord injuries to focus on recovery rather than compensation, moving beyond maintenance therapy and adaptations to life in a wheelchair. The benefits for improved health, quality of life, community participation, and long-term lower medical costs are immense.

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Conflicts of interest

YG holds shared interest in Cosyma Inc. and Onward.

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