american physiological society

JNP JOURNAL OF NEUROPHYSIOLOGY

J Neurophysiol 126: 1843–1859, 2021.
First published October 20, 2021; doi:10.1152/jn.00020.2021

NEURO FORUM

Spinal Networks and Spinal Cord Injury: A Tribute to Reggie Edgerton

Epidural spinal cord stimulation as an intervention for motor recovery after motor complete spinal cord injury

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Abstract

Spinal cord injury (SCI) commonly results in permanent loss of motor, sensory, and autonomic function. Recent clinical studies have shown that epidural spinal cord stimulation may provide a beneficial adjunct for restoring lower extremity and other neurological functions. Herein, we review the recent clinical advances of lumbosacral epidural stimulation for restoration of sensorimotor function in individuals with motor complete SCI and we discuss the putative neural pathways involved in this promising neurorehabilitative approach. We focus on three main sections: review recent clinical results for locomotor restoration in complete SCI; discuss the contemporary understanding of electrical neuromodulation and signal transduction pathways involved in spinal locomotor networks; and review current challenges of motor system modulation and future directions toward integrative neurorestoration. The current understanding is that initial depolarization occurs at the level of large diameter dorsal root proprioceptive afferents that when integrated with interneuronal and latent residual supraspinal translesional connections can recruit locomotor centers and augment downstream motor units. Spinal epidural stimulation can initiate excitability changes in spinal networks and supraspinal networks. Different stimulation parameters can facilitate standing or stepping, and it may also have potential for augmenting myriad other sensorimotor and autonomic functions. More comprehensive investigation of the mechanisms that mediate the transformation of dysfunctional spinal networks to higher functional states with a greater focus on integrated systems-based control system may reveal the key mechanisms underlying neurological augmentation and motor restoration after severe paralysis.

electro-enabling motor control; epidural stimulation; functional restoration; neurorestoration; spinal cord injury

INTRODUCTION

Spinal cord injury (SCI) commonly results in permanent loss of sensorimotor and autonomic function which can impact quality of life, functional independence, physical and psychological health, and social and economic participation. In the United States, ~18,000 SCI occur annually, and an estimated 1,300,000 people are living with SCI-related neurologic deficits (1, 2). SCI more commonly afflicts younger individuals, resulting from traffic accidents, falls, and other recreational or occupational trauma (1, 3). Injury grade is most commonly stratified by the American Spinal Injury Association (ASIA) Impairment Scale: i.e., motor and sensory complete (AIS-A), motor complete-sensory incomplete (AIS-B), and gradations of motor incomplete (AIS-C to AIS-E). Almost half of SCIs result in complete sensorimotor paralysis where significant recovery is rare (1–3). Restoration of neurologic function is of paramount importance and a meta-analysis across twenty-four studies has identified consistent neurorestorative priorities. Bladder, bowel, and sexual function are always considered a high priority (4, 5). In terms of motor function, individuals with paraplegia identified restoration of ambulation as the most critical priority followed by standing (6), whereas tetraplegic individuals prioritized restoration of hand/arm function ahead of lower limb function (4, 5, 7). Although attempts to treat SCIs are

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Submitted 13 January 2021 / Revised 19 August 2021 / Accepted 12 October 2021

underway using, for example, cell replacement strategies (e.g., stem cells, progenitor cells, Schwann cells), implantable polymer scaffolds, and various other agents (e.g., growth factors, axon-guidance molecules, and gliosis-inhibiting molecules), significant functional recovery has remained elusive and there is still no cure. Individuals with incomplete SCI who have residual ability to generate volitional muscle activation may benefit from certain neurorehabilitative regimens involving activity-based therapies to promote network reorganization with modest functional gains. However, this does not usually occur in the setting of complete motor paralysis (8–12). Assistive technologies such as exoskeletons and weight-support devices exist for the purpose of rehabilitation (13, 14), however, are far from replacing the wheelchair for everyday mobility.

Recent studies have shown that epidural stimulation may restore functional and volitional lower extremity movements after SCI, even in the setting of chronic complete paralysis (15–27). Herein, we review the recent advances in epidural stimulation for restoration of locomotion after clinically defined complete motor paralysis. We discuss putative neuronal networks and pathways modulated by epidural stimulation. We provide an overview of the motor control systems, review the concept of central pattern generators (CPG) for locomotion, and discuss the current views on electrical recruitment and epidural motor system neuromodulation.

EMERGENCE OF SPINAL EPIDURAL STIMULATION FOR LOCOMOTOR RECOVERY

Epidural stimulation emerged in the late 1960s when neurosurgeon Norman Shealy and engineering graduate student Thomas Mortimer developed the "dorsal column stimulator," the first implantable use of spinal cord stimulation (28, 29). After initial applications for chronic pain based on Melzack and Wall's "gate control" theory (30), Cook (31, 32) and Dooley (33) then independently described observations of motor system modulation (34). Further investigations for restoring motor function sparked in the 1980s and 1990s, when during efforts to ameliorate multiple sclerosis-related spasticity several investigators serendipitously observed anecdotal improvements in voluntary motor, bladder, and bowel function (35–37). In 1998, Dimitrijevic and colleagues (38, 39) reported that lumbar stimulation at 25–60 Hz generated rhythmic flexion/extension patterns in six paraplegic individuals and proposed this finding as functional evidence of central pattern generators (CPGs) in humans. Based on key observations in animal studies by Grillner and Zangger (40, 41), Herman and coworkers were the first to demonstrate that spinal epidural implants commonly used to treat chronic pain could also be used to facilitate improvements of motor function in humans after spinal cord injury. They reported that two subjects with incomplete injuries who were able to ambulate but with considerable difficulty, could step more effectively and with less metabolic stress during active epidural stimulation. The participants also noted more ease with stepping during active stimulation (42–44). The decades of preceding preclinical studies provided the stimulus for the proof of concept in humans with incomplete injuries which ultimately provided the incentive for investigating this approach in individuals with more severe spinal cord injuries and motor-complete paralysis.

Epidural stimulation applies electrical fields to the dorsal surface of the spinal cord via electrodes implanted on the dorsum of the dura, typically either via cylindrical linear multicontact electrodes implanted percutaneously or multicolumn paddle arrays implanted via laminotomy. Each contact provides an individually programmable conductive surface resulting in flexible combinations of mono-, bi-, or multipolar stimulation. Lead wires are tunneled to a remote subcutaneous implantable pulse generator that can be modulated electronically and is often rechargeable. The aforementioned studies have mostly implemented paddle-type electrodes over the lumbosacral enlargement of the spinal cord (variably reported as spinal levels T11-L1, T10-L1, or T10-T12) (15–21, 23–27, 45).

In 2011, Harkema et al. (21) showed for the first time that epidural stimulation in individuals with motor complete paralysis can restore functional lower limb movements, stepping, and weight-bearing standing in humans. The study had enrolled a 23-yr-old participant with chronic high-thoracic motor complete sensory incomplete SCI (AIS-B). Prior to implantation, the participant first underwent 26 mo of physical locomotor rehabilitation with 170 body weight supported training sessions. The participant then underwent surgical implantation of a 16-contact epidural paddle electrode array (5-6-5 Specify, Medtronic, Minneapolis, MN) placed over the posterior surface of the lumbosacral enlargement together with an implantable pulse generator (Restore ADVANCED, Medtronic, Minneapolis, MN). Stimulation in conjunction with targeted proprioceptive input (e.g., passive leg positioning and joint support by trainers) enabled the participant to perform weight-bearing standing over short periods up to 4.25 min. Using weight- and balance support and subjected to treadmill proprioceptive inputs, the participant was further capable of generating rhythmic locomotor-like stepping patterns, albeit not sufficient for independent ambulation. Standing was evoked at lower lumbosacral segments at 15 Hz, whereas stepping was facilitated at higher frequencies in the 30–40 Hz range. Motor outputs were dependent on sensory inputs: standing required bilateral axial loading and stepping required dynamic load alteration with appropriate leg positioning. Surprisingly, after 7 mo of physical rehabilitation and epidural stimulation, the subject recovered volitional control over lower extremity motor functions during active stimulation. Secondary findings also included improvements in blood pressure control, thermoregulatory function, bladder, bowel, and sexual function (21).

Angeli et al. (15) subsequently reported the findings of three additional study participants: a second subject with AIS-B and two individuals with AIS-A SCI. Electrophysiological testing via transcranial magnetic stimulation and somatosensory evoked potentials (SSEP) were obtained to confirm injury classification and showed absence of lower extremity motor-evoked potentials (MEPs) in all subjects, as well as either delayed (AIS-B) or absent (AIS-A) lower extremity cortical SSEPs. These subjects also underwent preceding physical rehabilitation with >80 locomotor sessions before implantation. Only the subject with sensory incomplete SCI was anticipated to regain volitional control while the

participants with motor and sensory complete injuries were not expected to achieve volitional control due to the nature of their complete injury. However, voluntary motor control was restored in all three subjects and occurred relatively quickly (within 1 mo), which was probably at least partially attributable to the lessons learned from the initial pilot participant. All subjects regained the ability to generate visual- or auditory-cued volitional lower limb movements (e.g., ankle dorsiflexion or knee flexion in supine position) with graded contraction force proportionate to volitional effort. Contraction force, accuracy, and reliability all increased throughout the training period suggesting that spinal motor circuitry under epidural stimulation conditions can undergo task-specific adaptation. Several subjects, however, also experienced stimulation side effects, e.g., clonic muscle activity that limited motor outcome (15).

Rejc et al. (24) later reported full weight-bearing overground standing with only handrail balance assist in these study participants. Stimulation parameters needed to be individualized and higher frequencies (range 25–60 Hz) at more caudal contacts resulted in more effective standing performance. The authors also found that higher frequencies (25–50 Hz) eventually triggered rhythmic bursting patterns at greater stimulus amplitudes. Rejc et al. reported effects of differential task-specific training paradigms (i.e., stand-training vs. step-training) on stimulation-augmented motor performance. Although the authors reported beneficial effects of stand-training on stance performance in all participants, they reported that subsequent step-training had detrimental effect on standing in three of the four participants. The authors suggested that motor learning and network plasticity may be task-specific and that certain task-specific rehabilitation modalities may be suboptimal for or even impair different motor tasks (25).

One AIS-B participant eventually gained volitional independence of the epidural stimulation with the ability to maintain volitional command independent of continued active stimulation, i.e., the subject could continue performing volitional task-specific motor control during periods with the stimulator turned off. This functional progression suggests engagement of adaptive neural plasticity effects triggered by the combined intervention (26).

Similar findings have since been reproduced and further advanced by Lee, Zhao, Grahn, and coworkers (17, 19, 20, 45). The Mayo Clinic group initially enrolled a 26-yr-old male with chronic thoracic AIS-A SCI. Motor- and somatosensory-evoked potentials were absent to/from the lower extremities. The participant underwent 22 wk of neurorehabilitation (61 motor training sessions) followed by lumbosacral implantation of a 16-contact epidural electrode array (Specify 5-6-5, Medtronic, MN) and pulse generator (RestoreSensor SureScan MRI, Medtronic, MN). Intraoperative low-frequency (1 Hz) volleys and segmental electromyogram (EMG)-responses were used to facilitate electrode positioning. Within eight stimulation sessions (2 wk), the participant achieved volitional task- and joint-specific muscle control during active stimulation: volitional rhythmic stepping-like patterns in side-lying position, independent weight-bearing standing with balance support in the range of minutes, and partial weight-bearing volitional stepping. Consistent with previous reports (see Table 1), stepping patterns were augmented at 40 Hz whereas standing was facilitated at 15 Hz. Throughout the 43-wk period of combined dynamic neurorehabilitation and epidural stimulation, motor performance continued to improve (19). Conversely to Rejc et al. (25), the Mayo Clinic group found uniformly positive effects of dynamic task-specific training (combination of step- and stand-training) on both stand and gait performance, respectively. They did, however, observe reduced standing stability and emergence of rhythmic patterns while using the stepping program (i.e., higher frequency ranges). Implementing an interleaved program geared toward alternating leg control, the subject was able to perform independent treadmill stepping without harness or trainer support and independent overground stepping with front-wheel walker and some trainer balance assistance. Stepping performance and speed gradually improved from 0.05 m/s (*week 25*) to 0.20 m/s (*week 42*). Maximal single-session distance was reported as 102 m via 331 steps. Intraoperative protocol for electrophysiology-guided electrode implantation has been reported (45). Angeli et al. have also reported progression to functional overground walking with assistive devices in two subjects after 15 and 85 wk, respectively, with up to 90.5 continuous meters and maximal speed of 0.19 m/s. Both subjects had AIS-B injuries, while the AIS-A participants remained limited to partially weight-supported treadmill-stepping. Of note, a spontaneous (nontraumatic) hip fracture occurred in one of the subjects during treadmill training (16).

Recently, Darrow et al. (18) reported initial results of the *E-STAND* trial ("epidural stimulation after neurologic damage"). These participants did not undergo dedicated preceding neurorehabilitation before device implantation. This study initially enrolled two female participants with thoracic AIS-A SCI at relatively more advanced ages compared with previous studies (48- and 52 yr, respectively) and relatively longer chronicity interval from injury (5- and 10-yr post-injury, respectively). These participants also received lumbosacral epidural paddle leads and implantable generators. The authors reported restoration of volitional control on the first instance of application of epidural stimulation. Interestingly, the authors also observed restoration of volitional micturition in one participant (albeit incomplete with residual postvoid-volume), amelioration of orthostatic hypotension in one participant, and improved sexual function. Peña Pino et al. (23) since reported follow-up results of total seven participants and found restoration of volitional control in all subjects (six AIS-A and one AIS-B). Following chronic stimulation, four of seven participants eventually sustained volitional control, even during periods of stimulation cessation. Nonetheless, magnitude and fidelity of motor activation remained higher with stimulation ON than OFF. Finally, Gorgey et al. reported a pilot study harnessing the putative benefits of epidural stimulation for augmenting exoskeletal-assisted walking (EAW). In a single participant with C7 AIS-A SCI, the authors found gradual improvements in gait performance with decreased swing assistance, improved EMG patterns, and up to 573 unassisted steps (50% of total steps) while using the EAW (14).

Table 1. *Epidural stimulation for motor restoration in humans with spinal cord injury*

References	Subjects	Key Findings
Dimitrijevic et al. (38)	*n* = 6 (AIS-A)	Rhythmic locomotor-like flexion/extension patterns in the lower limbs (25–60 Hz)
Jilge et al. (57)	*n* = 6 (AIS-A/B)	Sustained extension of the lower extremities (5–15 Hz)
Minassian et al. (58)	*n* = 10 (AIS-A/B)	Monosynaptic reflex activation (2.2 Hz) with short-latency muscle contraction and sustained tonic extension (5–15 Hz); stepping-like flexion/extension patterns via longer-latency polysynaptic pathways (25–50 Hz)
Minassian et al. (59)	*n* = 15 (AIS-A)	Location-dependent segmental motor responses at low-frequency (2.2 Hz), e.g., upper segments adductors/quadriceps vs. lower segments (tibialis anterior and triceps surae), amplitude-dependent EMG responses
Harkema et al. (21)	*n* = 1 (AIS-B)	Supine lower limb movements (15 Hz) and stepping (30–40 Hz), weight-bearing standing and assisted stepping; improved EMG patterns (e.g., increased muscle activation) and eventual restoration of volitional control in AIS-B participant
Minassian et al. (22)	*n* = 7 (AIS-A/B)	Supine rhythmic lower extremity activity (29.5 ± 4.85 Hz); stimulation-evoked augmentation of assisted stepping EMG patterns and differential EMG response between absence (supine) or presence (treadmill) of proprioceptive inputs
Angeli et al. (15)	*n* = 4 (AIS-A/B)	Lower extremity motor control; restoration of volitional motor control, even in AIS-A subjects; individuals with motor complete paralysis conceptually processed auditory and visual input to regain voluntary fine motor control over paralyzed muscles
Danner et al. (60)	*n* = 10 (AIS-A/B)	Stimulation-evoked rhythmic EMG activity (29.5 ± 4.85 Hz); synergistic locomotor-like patterns with coactiviated muscle groups
Hofstoetter et al. (61)	*n* = 8 (AIS-A/B)	Monosynaptic lower extremity reflex activation of lower extremity muscles (2 Hz) and rhythmic burst-like activity (22–60 Hz)
Rejc et al. (24)	*n* = 4 (AIS-A/B)	Overground weight-bearing standing without external assistance; functional reliance on proprioceptive input for effective motor activation (e.g., sufficient muscle activation only in standing position); improved standing with more caudal stimulation at higher frequencies (25–60 Hz)
Rejc et al. (25)	*n* = 4 (AIS-A/B)	Stand training improved stimulation-augmented standing performance; pretraining EMG patterns more variable and bursting and associated with poorer performance/more assistance requirement; posttraining EMG patterns more stable and correlated with improved standing performance; step training impaired stimulation-augmented standing performance
Rejc et al. (26)	*n* = 1 (AIS-B)	Continued volitional motor control of task-specific motor activity and weight-bearing standing, independent of continued epidural augmentation
Grahn et al. (20)	*n* = 1 (AIS-A)	Volitional motor control over task- and joint-specific muscle activity, in side-lying and harness-supported upright position; independent unassisted weight-bearing standing (with balance support rails); rhythmic locomotor-like activity, both in side-lying and upright position; volitional motor control
Gill et al. (19)	*n* = 1 (AIS-A)	Independent weight-bearing standing and independent treadmill stepping without harness or trainer support; independent overground stepping with front-wheel walker and some trainer balance assistance; improved performance with interleaved EES program
Angeli et al. (16)	*n* = 4 (AIS-A/B)	Recovery of functional overground walking in two of four subjects after combined multimodal rehabilitation (after 15 and 85 wk, respectively, both AIS-B) with assistive devices
Wagner et al. (27)	*n* = 3 (AIS-C/D)	Establishment of "targeted spinal cord stimulation"/"biomimetic stimulation" (spatiotemporal dynamic stimulation coordinated with gait cycle via real-time feedback triggers; restoration of volitional lower extremity control and balance-assisted or independent weight-bearing ambulation in individuals with chronic SCI; progressive locomotor improvements during training; emergence of continued volitional control during episodes of stimulation cessation; volitional walking and cycling in ecological environments
Calvert et al. (45)	*n* = 2 (AIS-A)	Intraoperative electrophysiological protocol for array placement; stimulation-evoked stepping-like patterns within first week of testing
Darrow et al. (18)	*n* = 2 (AIS-A)	Restoration of volitional motor control immediately after stimulation onset without prior rehabilitation; restoration of volitional micturition; amelioration of cardiovascular autonomic dysfunction; improvement of sexual function (restoration of orgasm)
Beck et al. (17)	*n* = 2 (AIS-A)	Increase in lean body mass; worsening bladder compliance and increased urinary incontinence in one participant using standing/stepping epidural stimulation program
Peña Pino et al. (23)	*n* = 7 (AIS-A/B)	Restoration of volitional command in all study participants; sustained volitional control in the absence of active stimulation in four of seven participants after prolonged chronic epidural stimulation
Gorgey et al. (14)	*n* = 1 (AIS-A)	Combination of exoskeletal-assisted walking with epidural stimulation resulting in decreased swing assistance, improved EMG patterns, and up to 573 unassisted steps (50% of total steps) using the EAW

Secondary findings of improved autonomic function have consistently been reported in multiple studies across centers including improvements in bladder and bowel control, sexual function, blood pressure regulation, thermoregulatory function, increased muscle mass, and improved body composition (15, 17, 18, 21, 46–54). Additional applications for other neurological functions such as restoration of respiratory and cough function are also being investigated and are reviewed elsewhere (55, 56).

APPROACHES TO EPIDURAL STIMULATION: TARGETED EPIDURAL STIMULATION

Targeted neurotechnology is designed for delivering targeted stimulation in a phase-dependent manner as opposed to continuous nonpatterned stimulation. "Targeted spinal cord stimulation" or "biomimetic stimulation" has been proposed by Courtine and coworkers (27) and Bloch and coworkers (62–64) based on spatially and temporally dynamic

activation of targeted subsets of nerve roots coordinated with the phases of the gait cycle with the goal of achieving more natural activation patterns and relatively smoother and more coordinated motor activation. Compared with nonselective stimulation focused on enhancing global excitability levels, the concept of targeted spinal cord stimulation is based on the modular and dynamic activation of selective dorsal rootlets that represent and interact with certain "motor hotspots" within the spinal cord. The authors developed a flexible multielectrode array for the research setting (65) and clinically available paddle electrode arrays (27) to allow more spatial selectivity along the longitudinal extent of the lumbosacral enlargement. To this end, more proximal lumbar spinal segments are generally associated with hip flexor and knee extensor myotomes, whereas more distal lower lumbar and sacral segments are more predominantly associated with extensor motor groups. Similarly, reciprocal laterality of contacts may allow alternating activation patterns between the two lower extremities with the goal to synchronize electrical stimuli with the phases of the natural gait cycle (e.g., stance, swing, propulsion phase). This could potentially leverage physiological spinal circuit synergisms while minimizing simultaneous coactivation of potentially antagonistic contralateral inhibitory circuits. Dynamic temporal patterning of the stimulus algorithms can be flexibly adjusted to coincide with phases of the gait cycle and task-specific participant training can further augment the appropriate timing of volitional effort with the neural prosthesis. For example, coordinated and selective sequential dorsal roots excitation to activate the hip flexors and ankle dorsiflexors to initiate forward swing phase, followed by activation of the knee extensors to promote weight-acceptance and stance phase, followed by hip and ankle extensors to promote propulsion. Studied initially in rodents (64, 66, 67) and nonhuman primates (62), this approach has shown to be able to restore functional lower extremity movement and stepping motion using treadmill- and gravity-assisted support devices, as well as trigger facilitative neuronal network reorganization and axonal sprouting (68). In a recently published human clinical study, Courtine, Bloch, and coworkers (27) enrolled three individuals with chronic motor incomplete mid-/low-cervical SCI of 4–6 years duration post-injury. Importantly, unlike the other studies discussed earlier, this study has focused on subjects with less severe AIS-grades (2 AIS-C, 1 AIS-D). The subjects underwent implantation of epidural paddle electrodes (Specify 5-6-5, Medtronic, Minneapolis, MN) in combination with implantable pulse generators (Activa RC IPG, Medtronic, Minneapolis, MN) using a combination of fluoroscopic guidance and electrophysiological guidance using intramuscular EMG electrodes and targeted trial stimulation. The authors found immediate improvement of volitional control, even over previously paralyzed muscle groups, progressive locomotor improvements with graduated muscle activation, and improved volitional control throughout the course of the training period. Notably, although the participants had motor incomplete SCI, they did have severe motor impairments, with one participant ("P1") showing strength *grade 0* throughout one entire lower limb that improved by multiple strength grades and improvement by one AIS-grade from AIS-C to AIS-D with epidural stimulation. Across participants, the authors reported restoration of volitional lower extremity control evoking single-joint movements, full weight-bearing standing, and functional coordinated compound movement patterns such as treadmill ambulation up to 1,200 steps and 1 h duration, and even weight-bearing balance-assisted overground ambulation (27, 69). The authors found superior motor coordination and performance using their dynamic targeted stimulation paradigm when compared with continuous tonic stimulation. This finding is overall consistent with results from the Mayo Clinic group who also reported enhanced motor performance with a more selective interleaved stimulation program (45). Wagner et al. (27) also reported eventual emergence of continued volitional command despite periods of stimulation cessation, as well as functional lower extremity mobility in ecological environments including cycling or volitional walker-assisted independent overground ambulation. This study has since enrolled additional participants, including several subjects with motor complete spinal cord injury; however, the results of the full patient cohort have not been published, to date.

MECHANISMS OF EPIDURAL STIMULATION FOR MOTOR RESTORATION

Electrical Recruitment and Activation of Large-Diameter Afferent Fibers

Primary electrical neuronal/axonal recruitment is a function of the anatomical location (i.e., spinal segments), shape and properties of the electrodes (i.e., lead geometry, conductive properties, and stimulus parameters), and regional tissue properties for current spread and electrical depolarization (e.g., membrane resistance and capacitance). Epidural electrodes apply a relatively broad electrical field, impacting multiple tissue types at levels that are largely determined by the specific conductivity properties of each tissue type. The cerebrospinal fluid (CSF) is a highly conductive medium allowing the electrical current to spread across some distance (70–72). One of the excitable elements when stimulated epidurally can be the dorsal root afferents, particularly at the level of the vertical projections of the dorsal root entry zones (58, 63, 71, 73–80). The lumbosacral dorsal nerve roots have a prominent intrathecal component placing them near the stimulating electrodes with favorable membrane properties for electrical depolarization (59, 81,82). According to classical cable theory, axon diameter is directly proportional to membrane capacitance and inversely proportional to membrane resistance (83). Large-diameter myelinated axons are therefore generally more excitable by electrical current (84, 85), predominantly comprised of proprioceptive A-α fibers followed by other mechanoreceptive A-β fibers (86). This hypothesis is supported by computational modeling (73, 76, 78). The accuracy of the description of the anatomical and physiological features of the spinal dorsal roots noted is not in question.

However, isolated focus on axon diameter/fiber size as the single driving factor for electrical neuromodulation to explain the vastly complex motor behavioral effects of epidural stimulation (and other neuromodulation techniques) does not appropriately account for the complex underlying physiological mediators. For example, electrical neuromodulation can

alter physiological states of dendrites and soma in other characteristics short of triggering an action potential. Moreover, can it be assumed that the conduction properties of an axon are functionally analogous to a network of neurons under in vivo conditions? Little is known of the basic physiology of network dynamics, particularly under in vivo conditions. In short, there are abundant reasons for caution in assuming that axon size is the single critical factor in explaining the behavioral outcomes of spinal networks when being neuromodulated across a wide range of stimulation parameters and spinal lesions that can vary widely. Moreover, larger stimulus intensities may result in sufficient electrical field expansion to enclose the dorsal aspects of the spinal cord and evoke neuromodulatory changes of the dorsal column fibers directly. Neuromodulation can alter excitability and activity states of intrinsic spinal and supraspinal networks that change their physiological states to lower or higher levels of excitability, even without generating an immediate motor output (72, 87).

To discuss this topic in a broader perspective there are many "targets" or strategies being pursued by different laboratories for optimizing functional outcomes of epidural spinal cord stimulation. With respect to technological strategies, site of electrical stimulation, details of the design of the electrodes, and a long list of stimulation parameters and the temporal patterns that are used have differing points of focus. It is noteworthy that the physiological impact of each of these variables are highly interdependent, that is, changing one parameter is highly likely to change the response of the other parameters so that the overall outcome cannot be easily predicted in any given subject or setting. From a physiological perspective, the mechanisms impacted by each of the variables noted, in our view, remain poorly defined. It remains unclear how tightly the technological variables noted are linked to the physiological mechanisms that account for a given motor output. For example, placement of the electrodes only vaguely defines the pathways and neuronal types that are modulated. Electrical activation of large-diameter dorsal root afferent fibers as the sole physiological mechanism driving complex and volitional motor patterns may fall short of the comprehensive mechanisms involved in evoking the observed motor patterns. The mechanism for the improved coordination among motor pools in response to epidural stimulation remains largely undefined. How fine motor control of movement is modulated within the spinal circuitry, e.g., which mechanisms provide the activation patterns of multiple motor pools and to some a lesser extent, the level of recruitment of motor units within a single motor pool, remains incompletely understood. The latter mechanism, the size principle, is a rather automatic process, i.e., the level of recruitment of motor units that determines the force and power generated by that single motor pool. The mechanisms of modulating the dynamics of a constantly changing combination of multiple motor pools remain to be determined. For these reasons, we think that as technology advances in concert with a more detailed understanding of the neurophysiological mechanisms at the network and systems level, it can become increasingly possible to intervene in the intrinsic control strategies among spinal networks more successfully. Perhaps, from a bioengineering perspective, the goal should be to match the functional design that is intrinsically natural to the spinal networks. Magnitude of stimulation can be regulated to directly induce versus enable motor function. Most of the strategies employed, to date, appear to engage both techniques, largely, stimulation greater than the immediate "passive" motor threshold versus facilitation of "active" motor control via subthreshold network modulation. We suggest that the effects of epidural stimulation on movement control consist of modulating the physiological activity states of selected networks, i.e., the proximity of the excitable level (relative to the motor threshold of a network) before the activating signal as being as important in defining the output movement. Although currently the predominant impact has been placed on the recruitment of proprioceptive afferents, evoked movement patterns appear to incorporate a wide range of specific motor behaviors likely beyond the scope of simple electrical all-or-none activation of any single afferent receptor/fiber type.

Spinal Motor Networks

Understanding the topography and organization of motor circuits is critical for optimizing spinal neuromodulation approaches. The spinal cord originates in continuity with the brain and descends within the spinal canal and gives of 31 segmental spinal nerves. The spinal cord contains two enlargements: the cervical enlargement for innervation to the upper limbs and the lumbar enlargement for innervation to the lower limbs, respectively. Spinal motor neurons are somatotopically organized into elongated cigar-shaped functional clusters termed motor neuron pools that can span one or multiple spinal levels (88, 89). Topographical organization of motor neurons and networks are evolutionary conserved within and across species (90–93). Lower motor neurons are capable of powerful functional signal integration and modulation (94). There are also complex interneuronal networks, such as the propriospinal system, that connect different neuron clusters, spinal segments, and hemicords for effective and efficient signal integration and motor coordination (95–97). Additional pathways that synapse within the ventral gray matter include descending cerebrospinal projections, notably the pyramidal system (corticospinal tracts) and extrapyramidal tracts (e.g., reticulospinal, vestibulospinal, rubrospinal, and tectospinal tracts). Ultimately, all motor signals exit the spinal cord via the efferent limb of the motor network via effector motor neurons traveling via the ventral rootlets to the neuromuscular junction of the musculoskeletal system.

Under physiologic conditions, load-bearing postures such as stance and ambulation are geared to maintain equilibrium in the upright position while withstanding gravitational forces and external perturbation (72, 98). Certain aspects of these processes are integrated directly within the spinal motor networks. Increased load-bearing generally enhances extensor tone, while inhibiting the flexor compartment. Proprioceptive feedback signals, such as axial loading and baseline joint angle, are integrated in real time within the spinal circuitry for coordinating phases of the locomotor cycle and are integrated into dynamic spatiotemporal activation patterns of motor neuron populations that facilitate progression through the gait cycle (27, 99–102). Similarly, a host of SCI studies in rodents (74, 75, 81, 103–114), cats (115–117),

rabbits (118), and humans (see Table 1) have consistently demonstrated that lumbosacral motor networks (subjected to epidural stimulation) are capable of adjusting muscle tone in response to dynamic load-bearing alterations (e.g., changes in treadmill speed or direction). Recently, Courtine and coworkers (119, 120) reported evidence from mouse models of SCI that epidural activates proprioceptive neurons within the dorsal root ganglion and that muscle spindle proprioceptive afferents are critical for mediating epidural stimulation-evoked motor effects showing that genetic knockdown can abolish motor recovery.

Neuronal Networks and Signal Transduction

Certain spinal reflex pathways may be involved in mediating some of these signals and several prominent examples have been characterized at an intrasegmental, intersegmental, and commissural level (121–123). Well-described reflex pathways include the Ia- (muscle spindle, myotactic reflex), Ib- (Golgi tendon organ, inverse myotatic reflex/autogenic inhibitory reflex), II-reflex (polysynaptic myotactic), and flexor-reflex-afferent (FRA, withdrawal reflex, nocifensive reflex) (124). Ia-fibers have expansive intra- and intersegmental connections with homonymous and synergistic motor neuron pools via direct synapses, and negative inhibitory connections to antagonistic motor pools via interneurons (125, 126). Ia and Ib inputs may be involved in postural stability and enhancing extensor contraction during stance (127–129). The flexor-reflex-afferent (FRA) pathway may be involved in the swing phase of gait and for maintaining postural balance during sudden gravity shifts via ipsilateral excitatory interneurons to the flexors (and extensor inhibition) together with decussating contralateral excitatory interneurons to the extensors (and flexor inhibition) (124). Mono- and polysynaptic pathways may be involved in a phase-dependent manner (72, 81, 130, 131). Different muscle groups appear to show different activation patterns: extensors seem to be more directly activated via monosynaptic connections, whereas flexors appear to be activated via more indirect polysynaptic pathways (58, 132). In addition, proprioceptive inputs are paramount for priming, shaping, and aligning task-specific motor outputs. For example, under constant epidural stimulation parameters, responses appear to favor flexor patterns in supine position, while positional shift into upright and weight-supporting posture shifts balance toward extensor tone (72). Similarly, under constant stimulation settings, continuous predominant extensor EMG-signals are recorded during weight-bearing, whereas only negligible extensor patterns occur during sitting posture (24).

In addition, evoked motor patterns are also stimulus parameter dependent: low frequency (e.g., 2–5 Hz), high amplitude stimulation typically evokes short-latency segmental muscle contractions, believed to be mediated via monosynaptic integration from large-diameter afferents, termed posterior root muscle reflex (PRMR) response. These short-latency compound action potentials are segment-dependent with higher lumbar spinal levels recruiting more proximal hip and thigh muscles, whereas more caudal locations recruit distal leg and calf muscle groups. Intermediate frequency ranges (e.g., 5–15 Hz) result in more continuous motor tonicity patterns favoring extensor motor groups, before at higher frequencies (e.g., 25–50 Hz) activation shifts toward flexor patterns and rhythmic alternating locomotor-like patterns emerge. Even higher frequencies (e.g., greater than 70–100 Hz) can result in deceleration and eventual cessation of rhythmic patterns (57, 59–61, 72, 79, 133, 134). Importantly, polysynaptic interneuronal integration may be the primary mechanism for invoking the long-latency muscle responses (72) associated with the generation of stepping patterns (38, 72, 114, 131). Limited evidence has been reported on how chronic epidural stimulation may result in electrophysiological changes within the spinal and supraspinal-spinal pathways.

Central Pattern Generators

The concept of "central pattern generators" (CPG) dates to the early 1900s. CPGs have been hypothesized as an intrinsic feature of the spinal circuitry involved in a breadth of stereotypical motor patterns across invertebrates and vertebrates including breathing, mastication, swallowing, micturition, ejaculation, scratching, crawling, swimming, flying, and locomotion (124, 135–137). These hypothesized specialized neuronal networks can autonomously generate oscillatory action potentials for initiating and maintaining certain rhythmic motion patterns, without immediate oscillatory inputs. The hallmark feature is the ascribed capability of generating coordinated movements in repeatable and recognizable patterns that mimic locomotion, thus referred to as fictive locomotion, in the absence of supraspinal and/or sensory inputs from neuronal networks (41, 138–142). Sir Charles Sherrington and his student Thomas Graham Brown studied the concept of locomotor CPGs in the early twentieth century in decerebrate and spinally transected cats and dogs (97, 124, 135, 136, 143, 144). The "half-center" model was proposed, consisting of two reciprocally organized opposing groups of spinal interneurons (an extensor and a flexor half-center) in an alternating-dominant pattern of mutual inhibition resulting in rhythmic stepping. Supported by additional research from Anders Lundberg and Elzbieta Jankowska in the 1960s (97, 145, 146), these half-centers are sometimes referred to as CPGs. At that time there was little understanding of the neural basis of this rhythmic output, but an obvious question was whether this rhythmicity was derived within the intrinsic spinal neurons or a mere function of rhythmic sensory inputs from the periphery. Another important question was which spinal neurons, if any, could generate this rhythmicity. A series of experiments using dorsal root sectioning and/or curare injections (paralytic agent to prevent muscular contractions) showed that rhythmic output could be generated in the absence of sensory and supraspinal inputs.

There remains controversy as to whether rhythm generation and patterning are mediated via different mechanisms (96, 147–151). From our perspective there is no compelling reason why the same interneuron networks would not be controlling both these highly interlinked features of locomotion. Both rhythmic initiation and stereotypic patterning are key parameters that define the character of every movement. The essential functions of the proposed locomotor CPGs within the mammalian lumbosacral region remains a point of

contention and to what degree different rhythms and coordination patterns rely on specific interneuronal subtypes remains unknown. Numerous spinal reflexes have been implicated in the task-dependent modulatory functions during spinal locomotion and have been proposed as part of the locomotor CPG (97). There is a large number of studies investigating candidate CPG neurons including anatomical, electrophysiological, biochemical, pharmacological, and genetic studies (124, 135, 136, 152–155). Candidate CPG neurons have been identified near the central canal and within the medial intermediate zone along the lumbar spinal segments to be functionally linked to locomotor rhythms (156, 157). Although there have been several knockout models that have shown alterations in movement patterns, none have been identified as being uniquely accountable for rhythmic motor neuron excitation in vivo. Following the renewed interest in the concept of central pattern generation largely from Grillner and coworkers (124, 151, 158–162) in the mid-1960s, there have since been hundreds of papers published attempting to answer the questions noted earlier.

From a systems perspective of the biology of CPGs, it seems improbable that there is a single type or even group of cell types to perform even fictive locomotion nor does it seem that the biological function can or should be assumed to be an all-or-none function. The common outcome that might be expected in such efforts is that during experimental systematical elimination of cell types or groups of neurons or networks, there will be an increasing decline in the robustness of the redundant cyclic activity. The interpretation of these experimental approaches is even more complex, given that it is unlikely that any mammalian behavior that is cyclic will yield an all-or-none result under in vivo conditions.

Importantly, although there are evolutionary-conserved locomotor principles across invertebrates and vertebrates (163), human gait is characterized by several unique features that distinguish it from invertebrates or even other vertebrates (164, 165). A key question is how the neural control of locomotion in humans has adapted given the inevitably added complexities in fully integrating the sensory-motor behaviors that are unique to humans. It is rather clear that the locomotor CPG phenomenon persists in humans. A key question is, how the neural control of CPGs has changed in a nervous system that has acquired the ability to control the unique behaviors of humans. Although facilitated stepping can be achieved via a relatively nonspecific tonic lumbosacral stimulation, functional and balanced gait restoration in humans has been more challenging. Although the functional importance of CPGs in humans thus remains topic of debate, its ability to generate fictive locomotion, that is, rhythmic pattern activation of motor pools that approximates in vivo locomotion is unlikely to be its essential feature in the control of actual physiological locomotion.

Motor System Modulation during Weight-Bearing and Ambulation

One hypothesis of SCI is that loss of descending corticospinal connections disrupts downstream spinal motor networks from their "movement trigger" resulting in functional depression into a latent state that impedes volitional and functional motor production (21, 113). In addition, aberrant and dysfunctional plasticity changes and maladaptive network remodeling occur that can itself present a hindrance to motor activation via residual connections. Tonic epidural neuromodulation below the motor threshold combined with task-specific sensory input may facilitate shifting neuronal balance from a latent inactivity state toward generation of certain task-specific "movement programs." Under certain conditions, this mechanism can evoke muscle contractions forceful enough to sustain full weight-bearing, generate stereotypic stepping patterns capable of achieving short-distance treadmill and overground ambulation, and even restore volitional control (16, 17, 19, 23, 24, 27). The current understanding places paramount importance on functional integration of proprioceptive signals within the inherent capacities of spinal motor circuits. Electrical stimulation of these dormant functionally incompetent motor circuits may thus enhance excitability states and decrease activation thresholds from residual connections priming them for task-specific propriospinal and/or supraspinal activation. Functional plasticity and facilitative network reorganization may further shift the neural balance toward volitional motor promotion by reactivating residual (yet clinically latent) signal transmission from spared supraspinal connections to reinstate volitional command (21, 105) (Fig. 1). Moreover, the ability to sustain volitional command after prolonged epidural stimulation, even during periods of stimulation cessation, serves as further indication that long-term plasticity effects may be capable of "reawakening" underlying latent neuronal networks and restoring enhanced functionality (23, 26, 27).

CHALLENGES AND LIMITATIONS

Study Design

Selection criteria for most studies reviewed in Table 1 have focused on clinically classified motor complete paralysis (i.e., only AIS-A or AIS-B participants) with injury chronicity greater than 1 yr. The 1-yr requirement was selected because it is generally accepted that spontaneous recovery does not typically occur beyond 6–12 mo postinjury. Therefore, any observed effect could be attributed to the stimulation paradigms in concert with the locomotor training. Notably, the initial clinical reports incorporated large-scale preceding and concomitant neurorehabilitative efforts (15, 16, 19–21, 25, 26).

Prolonged periods of very low levels of neuromuscular activity result in physical deconditioning, muscle atrophy, and changes in bone composition. In the setting of trials involving rigorous physical activity, these factors are important considerations. Therefore, a preconditioning period was also included to optimize the level of physical activity before imposing higher levels of activity-induced stress on muscle, connective tissues, neural tissues, and bones induced by stimulation and locomotor training combined. The long-term effects of prolonged periods of inactivity may exert on the individuals' musculoskeletal system and neural circuits remain unclear. Careful attention to this issue must be continuously present throughout the study, since participants with SCI-

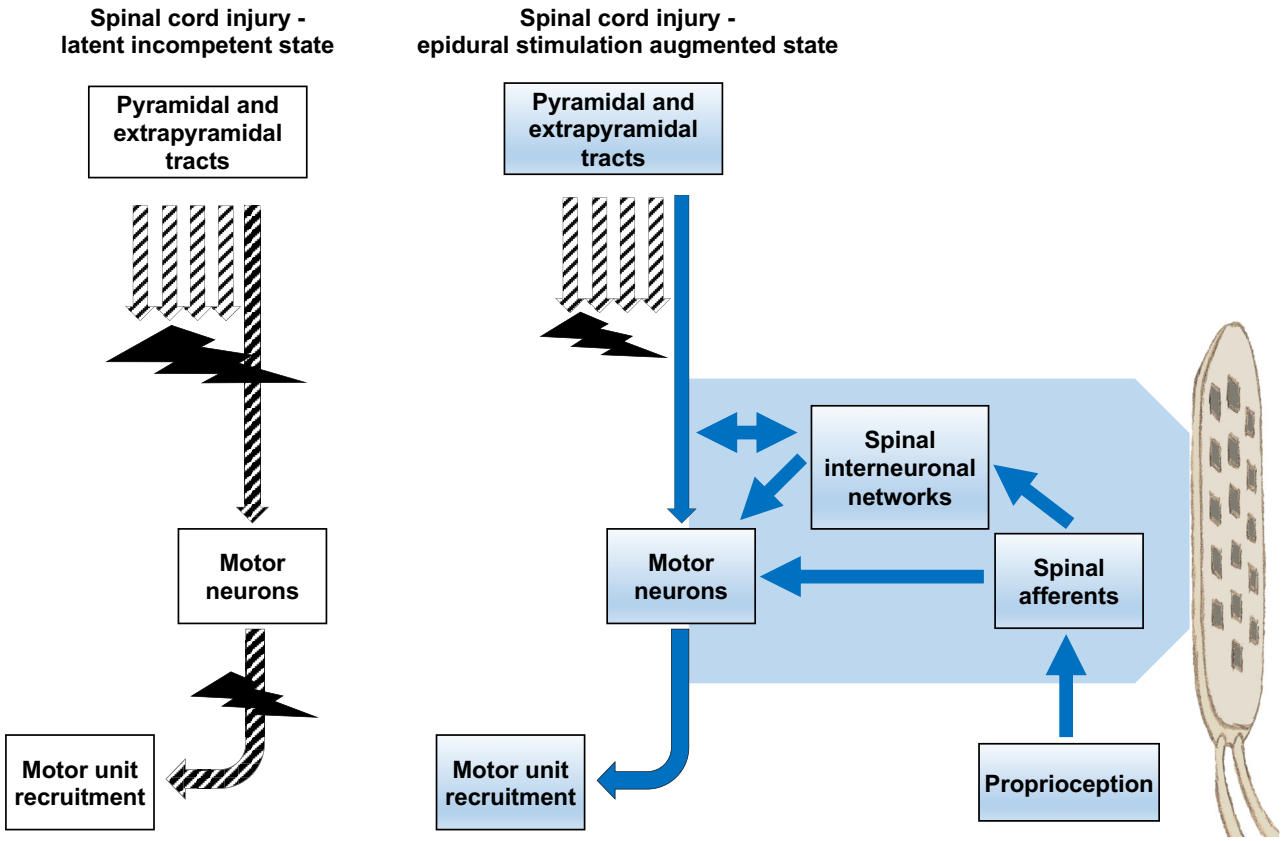

Figure 1. Lumbosacral epidural stimulation for augmenting lower extremity function and restoration of volitional motor control. Spinal cord injury results in disruption of corticospinal and extrapyramidal tracts that may result in complete motor paralysis. Residual latent supraspinal connections may persist in a clinically dormant state and the intrinsic lumbosacral spinal motor networks also remain, albeit functionally suppressed. Lumbosacral epidural stimulation may exert local electrical field effects to enhance neural excitability levels toward motor promotion. Stimulation may modulate proprioceptive afferents at the dorsal root level and recruit higher-order synaptic effects for integration with intrinsic interneuronal networks and residual supraspinal inputs to recapture volitional motor unit recruitment. Together with synergistic proprioceptive signals, epidural stimulation may enable task-specific volitional motor control and restore compound motor functions such as weight-bearing standing and treadmill or overground ambulation, even in settings of clinically complete spinal cord injury.

related neurologic deficits may not perceive conscious signals of exertion or neurological or physical injury.

Preceding locomotor training before initiation of epidural stimulation also raises a question regarding the synergistic or even independent effects of the neurorehabilitative efforts on the spinal motor networks. To this end, there is abundant evidence that subjects with severe, but incomplete injury can regain some locomotor function with task-specific locomotor training alone (8, 166–169). Recently, the E-STAND trial (18, 23) has included participants with even longer periods of injury chronicity and without any preceding physical conditioning. This preliminary data indicate that similar functional outcomes may be possible without as extensive preceding or simultaneous physical rehabilitation. However, potential implications on physical stress and associated risks for musculoskeletal injury related to deconditioning remains to be determined.

Understanding the Neural Pathways and Stimulation Control Challenges

Although there is mounting evidence that the neuromodulatory effects of epidural stimulation can be mediated by activating the dorsal root afferents, less is known about the effects of motor subthreshold modulation of spinal interneuronal networks that are modulated into different physiological states. This type of modulation prepares networks for activation triggered by multimodal sensory ensembles. To this end, further investigation will be necessary to characterize these pathways and networks further. Putative modulators of motor augmentation include a variety of inputs including descending pathways from the cortex, subcortical centers, and cerebellum, and proprioceptive/sensory afferents (and/or central pattern generators) for controlling posture, coordination, gait, and locomotor speed. However, most data related to mechanisms, to date, are still based on anatomical, often preclinical studies, and sometimes computer modeling studies, and little is known about the real-time effects and network changes in vivo in humans. Furthermore, understanding the circuitry changes in the setting of spinal cord injury and the dynamic plasticity effects of neuromodulation will further aid treatment optimization of neuromodulatory interventions. In addition, identifying the most effective spinal stimulation targets, developing dynamic controllers to optimally recruit the key mediating pathways while limiting nonbeneficial or detrimental co-

activations, and developing interleaved and adaptable stimulation programs to best facilitate differential motor functions will likely be necessary to improve functional gains. Fluoroscopic imaging can provide macroscopic information for device implantation; intraoperative neurophysiological testing via evoked monosynaptic segmental myotomal EMG-response patterns can be used to complement and guide appropriate array placement, both in rostrocaudal and mediolateral orientations along the three-dimensional neuroaxis (45). However, the feasibility of reliably activating these optimal stimulation locations in the awake, behaving state remains to be established. Once the neural prosthetic is delivered successfully, device programming has proven challenging requiring extensive trial-and-error evaluation. Optimal stimulation configuration and parameters, including cathode and anodes orientations, exact combinations of pulse durations, frequencies and amplitude of the current are still elusive. The most effective electrode configurations and stimulator settings can vary, are subject-specific, and may even show task-dependent and dynamic temporal variability (15–17, 19–21, 24, 26). Design and geometrical properties of the electrode (e.g., size, shape, contact arrangement, and orientation) may be a beneficial adjunct to favorably adapt spatial features of the electrical field such as distance between activated contacts and targeted neural structures. Dynamic selection of stimulation parameters (e.g., amplitude, frequency, pulse widths, electrode contact setup, and polarity) may be useful for finetuning neural recruitment with spatial optimization (86).

Finally, it remains unknown where the ceiling for functional gains using an epidural approach may be. Epidural stimulation as a technology has inherent limitations with regards to electrical field specificity. Undirected stimulation spillover to functionally unrelated or even antagonistic motor groups is likely an inherent limitation of widespread current dispersion and may be dose-limiting. Clonic activity, spasticity, or generalized contractions have been reported in several studies, especially using high amplitude and wide-field stimulation settings (15, 21, 72). Such effects have also similarly been observed with thoracic epidural stimulation for restoration of cough. Stimulation of the lower thoracic spinal cord at intermediate frequencies and higher amplitudes evoked stimulation side effects including unintended spasms of the trunk and thigh muscles resulting in back or leg jerks, as well as autonomic dysreflexia (170–173).

Therefore, it remains to be seen what degree of accuracy, reliability, and effectiveness of motor outputs can be achieved. Different programs may likely be required to optimally augment either stance or ambulatory performance, especially in the setting of interindividual or plastic network differences. Furthermore, conventional nonpatterned continuous waveforms may not be optimal for recruiting spinal circuitry and may, in fact, be detrimental by creating antidromic block of proprioceptive afferent inputs that are critical for successful signal integration. Bidirectional depolarization of proprioceptive axons, especially tonic continuous stimulation, may create antidromic block of these vital afferent inputs during depolarization volleys. Although antidromic block may mediate some of the positive effects on spasticity, it may hinder functional signal integration for neuroaugmentation. Recent computational models by Formento et al. (76) have suggested that neurophysiological differences between rodents and humans may render occurrence of "antidromic collisions" more probable in humans (especially for distal muscle groups). In addition to inherent interspecies differences in neural circuitry, this factor may contribute to the current limitations in locomotor performance in humans compared with rodent stepping recovery (76, 174). Phasic (rather than tonic) stimulation programs may prove more efficacious for motor restoration by facilitating synergistic integration with these crucial proprioceptive afferent inputs (17, 19, 27, 76).

Open-Loop versus Closed-Loop Controllers

Open-loop controllers are not capable of performing real-time device adaptations to compensate for variability in motor recruitment. During activity, the human vertebral column and spinal cord can undergo certain types of mechanical deformation including flexion/extension, axial compression/elongation, rotation, and torsion. To this end, although an epidural electrode array becomes relatively affixed and static within the epidural space due to engulfing scar tissue, the spinal cord itself, being suspended relatively freely within the cerebrospinal fluid, has a moderate degree of mobility and flexibility within the thecal sac. In turn, the spinal cord can yield to the substantial degree of spinal mobility, and in the setting of postural changes (e.g., supine vs. upright) or dynamic motion patterns such as gait, it can undergo a certain degree of shift along its three-dimensional neural axis within the thecal sac. Shift between the posterior spinal surface and critical dorsal root entry zones relative to the electrode contacts, both regarding distance and spatial orientation, can present an important challenge for stable neural interfacing. In addition, open-loop algorithms are incapable of adapting for unexpected external or internal perturbations or other dynamic system changes. Lack of feedback integration of positional signals from the musculoskeletal and propriospinal system into the neuroprosthetic controller remains a major challenge for many neural prosthetic approaches and can limit postural stability and balance, and result in unsteady, turbulent, and clumsy motion. Conversely, closed-loop controllers are, by definition, distinguished by their capacity of performing internal feedback signal integration to perform real-time stimulus corrections aligned toward planned motor output (27). To this end, muscle recruitment typically does not follow linear recruitment characteristics. Muscle fatigue can gradually diminish contraction force, and external perturbations (e.g., uneven surfaces) can present important challenges for maintaining stability and equilibrium, especially in the absence of supraspinal corrective inputs from pyramidal and extrapyramidal neurons. Feedback signal recording and implementation of control algorithms may have potential for offsetting progressive muscle fatigue (175, 176) and modulating gait performance (177). As surmised by McCloskey and Prochazka (178): "one can only control what one senses." Integration of control systems with biomimetic sensors monitoring proprioceptive information such as position in space or evoked torque and force transduction has significant potential to

facilitate superior motor performance. Several approaches have been suggested including external or peripherally implantable sensors (179). In addition, recording of electrophysiological activity from the dorsal root ganglia (DRG) has been reported as a putative approach for detecting and integrating proprioceptive input (177, 180). For example, DRG microrecordings in walking cats have been shown to correlate with limb position and velocity with high fidelity and precision (181). Anatomical proximity may render DRG recordings beneficial for integration with epidural stimulation. A feedback controller loop may thus improve smoothness, reliability, stability, and endurance of the evoked motor output, whereas a volitional loop (e.g., brain computer interface) may augment intention control for appropriate "program" selection in real-time while potentially augmenting residual translesional control. Recently, Courtine, Bloch, and coworkers have successfully integrated certain feedback triggers into their epidural stimulation technology including devices such as inertial measurement units attached to the feet to provide motion feedback, walker clickers to indicate initiation of reciprocal alternating stepping, together with elements of user control via voice activation or tablet control into their paradigm of targeted spinal cord stimulation to allow the study participants independent use of the stimulator program within ecological settings outside of the research environment (27). This promising endeavor and following next-generation iterations will likely be critical for more widespread utilization and larger scale clinical trials, as well as allow the individuals ease of use and independent implementation in their home and public environments.

Based on the current rate of development of technological capabilities to merge with the intrinsic control capabilities of the neural control networks remaining after an injury, it seems inevitable that the availability of that technology, in the short run, will be limited to a small segment of the severely injured by its cost in technological support and the duration of the development time. But the more important point in the technological development is to begin to be aware of future possibilities. And finally, regarding technological solutions, its potential can be amplified by smoothly interfacing with the basic biological principles of locomotor control that persists after an injury.

Integrative Motor and Neurological Restoration

There remain numerous challenges to enhance functional mobility with meaningful day-to-day improvements. Widespread implementation will require devices to be practical, feasible, user-friendly, and adaptable, as well as durable and reliable for stable day-to-day performance over the lifetime with minimal risk and maintenance (182). Aesthetics and cosmesis are of obvious and important concern. The majority of individuals with SCI would prefer a fully implanted neuroprosthesis over externally visible devices that may be cosmetically displeasing and/or uncomfortably stigmatizing for the users (6). Electrodes and implantable pulse generators for epidural stimulation (although not specifically designed for motor restoration) are available in clinical practice with good safety profile. Often, however, the electrode designs are adapted from pain applications and are not specifically designed for neurorestorative purposes.

Epidural stimulation has shown promise for evoking graded, controlled, and moderately specific motor functions, restoring volitional control, and for augmenting full weight-bearing stance, cycling, treadmill, and overground stepping, even in cases of complete SCI. Challenge remains to facilitate more durable and reliable responses and improve degree of motor control toward more independent and unassisted functional gains outside of the research setting. Fidelity of evoked motor responses is inconsistent, variable between participants, and may be hindered by limited degrees of freedom. Although most studies of epidural stimulation for motor restoration, to date, have targeted the lumbar enlargement for augmentation of gait, exploratory studies targeting the cervical enlargement for restoration of upper extremity function such as reach and grasp are also emerging (183–187). Investigative efforts implementing thoracic epidural stimulation for augmentation of respiratory function and cough are similarly underway (55, 56). Beneficial effects on autonomic cardiovascular function, thermoregulatory function, body weight composition, bowel function, sexual function, and bladder function including restoration of volitional micturition have consistently been observed in these studies and are being increasingly investigated as either secondary endpoints, and also being investigated as primary endpoints in dedicated studies (17, 18, 46, 47, 49–54, 105). In principle, it appears that spinal cord stimulation holds substantial potential to restore multiple neurological functions via a single neuroprosthetic device to achieve more comprehensive functional gains.

GRANTS

This work is currently supported by the U.S. Department of Defense-Congressionally Directed Medical Research Programs clinical trial program award number W81XWH-20-1-0845 (SC190107 CDMRP W91ZSQ), Department of Veterans Affairs-SPiRE Program (B3456-P) to Ashraf S. Gorgey.

DISCLOSURES

V.R.E. holds shareholder interest in spineX, Inc. and holds certain inventorship rights on intellectual property licensed by the Regents of University of California and serves as chair of the scientific advisory board at spineX and on the scientific advisory board of in vivo Therapeutics and ArianRF. V.R.E. holds shareholder interest in ONWARD and holds certain inventorship rights on intellectual property licensed by the Regents of University of California to ONWARD.

AUTHOR CONTRIBUTIONS

J.T.H. conceived and designed research; J.T.H. and A.Y. prepared figures; J.T.H., A.Y., J.J.W., and A.S.G. drafted manuscript; J.T.H., A.Y., J.J.W., P.N.G., V.R.E., and A.S.G. edited and revised manuscript; J.T.H., A.Y., J.J.W., P.N.G., V.R.E., and A.S.G. approved final version of manuscript.

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