Enabling Task-Specific Volitional Motor Functions via Spinal Cord Neuromodulation in a Human With Paraplegia

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Abstract

We report a case of chronic traumatic paraplegia in which epidural electrical stimulation (EES) of the lumbosacral spinal cord enabled (1) volitional control of task-specific muscle activity, (2) volitional control of rhythmic muscle activity to produce steplike movements while side-lying, (3) independent standing, and (4) while in a vertical position with body weight partially supported, voluntary control of steplike movements and rhythmic muscle activity. This is the first time that the application of EES enabled all of these tasks in the same patient within the first 2 weeks (8 stimulation sessions total) of EES therapy.

It is well accepted that severe spinal cord injury (SCI) leads to functional disconnection of ascending and descending spinal pathways, impairing neural circuitry through and below the SCI. However, in clinically complete SCI, defined as American Spinal Injury Association Impairment Scale (AIS) level A, a portion of neural tissue commonly remains intact across the injury site and may provide nonspecific supraspinal influence on sublesional spinal circuitry. This injury profile is defined as “discomplete.” An emerging therapy for recovering function after SCI, which may be more effective in injuries identified as discomplete, is epidural electrical stimulation (EES). In patients with SCI diagnosed as having AIS-A or AIS-B (in the latter, some sensory function remains intact), EES of the lumbosacral spinal cord has been shown to drive nonvolitional rhythmic motor circuitry. In a recent paramount study, EES facilitated volitional control of joint-specific muscles and independent standing after months of training with EES (Supplemental Table, available online at http://www.mayoclinicproceedings.org).

Although these findings were powerful, they have yet to be reported by other research teams, a necessary milestone before these treatments can be widely adopted by the medical community. Therefore, the initial goal of this study was to replicate the findings from work performed at the University of Louisville that reported that (1) EES enabled volitional control of motor activity and (2) EES enabled independent standing. In addition to the initial goal of replication, we set out to determine whether EES could enable volitional control over rhythmic, steplike activities.

METHODS

Participant Description

All the procedures for this study were performed with the approval of the Mayo Clinic Institutional Review Board and with an Investigational Device Exemption from the US Food and Drug Administration. The participant was a 26-year-old man who sustained a traumatic T6 AIS-A SCI 3 years before study enrollment. Immediately after his injury, he...
underwent a spinal fusion of the fifth to eleventh thoracic vertebrae and participated in in-patient physical rehabilitation for approximately 2 months to achieve independence during activities of daily living from a wheelchair. Once discharged from in-patient rehabilitation, the patient underwent 5 weeks of outpatient SCI rehabilitation. After those 5 weeks, he performed only self-directed upper limb strengthening and general lower limb stretching without any other form of formal neuromuscular training until enrollment in this study.

**Study Timeline**

On enrollment, the patient’s motor and sensory characteristics were documented by clinical examination and electrophysiologic measures. The American Spinal Injury Association Examination as defined by the International Standards for the Classification of Spinal Cord Injury was used to determine the extent of the SCI, including the neurologic level and the “completeness” of the injury. Electrophysiologic measures included upper and lower limb somatosensory evoked potentials and transcranial magnetic motor evoked potentials recorded over select upper and lower limb muscles. This was followed by 22 weeks of motor training. An EES system was then implanted in the region of the lumbar enlargement, followed by 3 weeks of postoperative recovery and 8 sessions of volitional motor performance testing in the presence of EES over a 2-week period (Figure 1A).

**Electrophysiologic Assessment of Translesional Neural Connectivity**

To test for potentially intact translesional neural connectivity below the threshold for standard clinical electrophysiologic recordings, we applied separate conditioning stimuli before spinally evoked motor potentials elicited via transcutaneous stimulation over the region of the lumbar spinal cord enlargement. These evoked potentials were recorded over select lower limb muscles. The conditioning stimuli were applied in an attempt to activate (1) long propriospinal tracts via ulnar nerve stimulation, (2) descending white matter via cervical spinal cord stimulation, or (3) the corticospinal tract via transcranial magnetic stimulation of the motor cortex. The conditioning stimuli were followed 5 to 200 milliseconds later by test stimuli delivered to the lumbosacral spinal cord to elicit spinally evoked motor potentials in lower limb muscles.

**Motor Training Paradigm**

Before implantation of the EES system, the patient underwent 61 motor training sessions (approximately 3 sessions per week for 22 weeks) performed by a team led by a physical therapist (M.L.G.) and a kinesiologist (M.B.L.), both of whom had extensive locomotor education from the NeuroRecovery Training Institute (http://www.neurorti.com). Sessions consisted of approximately 15 minutes of lower extremity stretching to ensure optimal kinematics, 45 minutes of locomotor training on a treadmill with body weight support and trainer assistance at the legs and pelvis, and 30 minutes of balance and task-specific strengthening exercises during sitting and while standing in custom-built standing bars with trainer assistance at the knees and pelvis (Supplemental Figure 1A-D, available online at http://www.mayoclinicproceedings.org). During select sessions at approximately 4-week intervals, the patient was instructed to first attempt whole-leg, then knee, and then ankle flexion/extension of each leg while side-lying with the top leg positioned on a smooth, low-friction surface to allow detection of slight movements with minimal influence of gravity (Supplemental Figure 1E). Tasks included attempts to continuously modulate leg muscle activity while following a digitally displayed sinusoidal wave, as well as volitionally increasing muscle activity when cued by a 3-step audio tone. Visual feedback was provided by mirrors reflecting the lower limbs and by real-time streaming surface electromyography (EMG).

**Data Processing**

Muscle activity was recorded via surface EMG electrodes (LabChart and PowerLab, ADInstruments). Data were sampled at 4 kHz and were exported from LabChart software and analyzed using MATLAB software (The MathWorks Inc). The EMG data were filtered using a 60-Hz notch filter and a bandpass filter of 20...
to 1000 Hz. Additional analyses included full-wave rectification on the filtered EMG signal after subtraction of the mean background signal, and then the root mean square of the EMG activity was calculated as the square root of the mean square averaged over a window length of 4000 samples (sliding overlap of 3000 samples).

FIGURE 1. The patient’s spinal cord injury (SCI) profile. A, Experimental timeline. Assessments were performed at enrollment, before surgery, and after 3 weeks of surgical recovery. B, Shaded regions depict American Spinal Injury Association motor, pinprick, and light touch scores across assessments. C, Evoked potential latencies were within reference ranges when recorded over the spine below the level of injury during bilateral tibial nerve stimulation. Green squares and red diamonds represent right and left tibial nerve stimulation, respectively. There were no detectable responses at the cortical level (black x’s and blue circles). D, Motor evoked potentials were not observed from any leg muscle during transcranial magnetic stimulation of the motor cortex. Recordings from the right arm flexor carpi radialis (R FCR) indicate that stimulation intensity adequately evoked responses. Bold trace represents an average of 5 responses. E, Conditioning stimuli applied to the motor cortex, ulnar nerve, or cervical spine were followed by a stimulus delivered to the lumbosacral spinal cord. Conditioned depression or potentiation of spinally evoked motor potentials was not observed. Traces represent an average of 5 responses. Blue vertical lines indicate timing of conditioning stimuli before the onset of lumbosacral stimuli (black dashed line). Top and bottom traces are unconditioned evoked potentials. F, Evidence of discomplete SCI and progressive increases in muscle activation observed at weeks 8 and 16 of presurgical motor training during 2 attempts (white and gray panels) of maximal volitional contraction. Red dashed lines indicate start of volitional attempt. Mean ± SD area under the curve (AUC) was extracted from the root mean square envelope of rectified electromyographic recordings from left leg muscles and averaged for the 2 trials. L = left limb; MG = medial gastrocnemius; MH = medial hamstrings; ms = milliseconds; NR = no response; R = right limb; RF = rectus femoris; SOL = soleus; TA = tibialis anterior; µV = microvolts; VL = vastus lateralis.
EES System Implantation
After the 61 presurgical motor training sessions, an EES device (RestoreSensor Sure-Scan MRI, Medtronic) was surgically implanted and connected to a 16-contact electrode array (Specify 5-6-5, Medtronic) positioned on the dorsal epidural surface of the lumbosacral spinal cord. Intraoperative radiography (Supplemental Figure 2, available online at http://www.mayoclinicproceedings.org) and epidurally evoked motor responses (0-5.5 V, 0.5 milliseconds, 1 Hz) were used to confirm array position over the lumbosacral enlargement of the spinal cord.\(^{23,24}\)

Identification of EES Parameters That Enable Volitional Control of Motor Functions
After 3 weeks of postsurgical recovery, volitional activation of leg muscles was attempted in the presence of EES while the patient was positioned side-lying or upright (with and without body weight support). The EES parameters that enabled voluntary control of rhythmic lower limb muscle activity were identified while in the side-lying position with the top leg suspended using nonelastic nylon fabric support slings to allow free limb movement.\(^{25,26}\) While the patient was in an upright position, with trainer assistance or while in a body weight support harness, EES settings were identified that allowed either independent standing or volitional control of steplike muscle activity and limb movements.

Over 2 weeks (8 sessions, 5-7 hours each), active electrode configurations and stimulation parameters were adjusted to allow volitional control of the muscles of interest. A systematic approach was used to determine the best parameter settings. Previous reports were reviewed to provide starting points for stimulation.\(^{8,10,11,27,28}\) We chose frequencies (25 and 40 Hz for volitional control and stepping and 15 Hz for standing) and a pulse duration (0.21 milliseconds) based on previous reports. The electrode configuration was adjusted based on an algorithm where we initially evaluated the effect of wide-field (via electrodes most distal from each other) vs local-field (via electrodes most proximal to each other) stimulation, with both cathode and anode electrodes tested (ie, reversing polarity) for each configuration. The effect of right vs left lateralized electrode location was also assessed. For each configuration, we incrementally increased voltage intensity from 0 to 6 V. Voltage intensity was reduced to a comfortable level or was turned off if the patient reported any signs of discomfort. Once volitional control was achieved, that EES setting was held constant for further repetitions of the intended task.

RESULTS
Clinical Assessment Outcomes
Presurgical and postsurgical clinical assessments showed no change in motor or sensory scores on the AIS (Figure 1B). Tibial somatosensory evoked potentials showed normal latencies at peripheral and lumbar spine sites, but there were no detectable cortical responses (Figure 1C). Transcranial magnetic stimulation elicited normal motor evoked potentials in the upper extremities, but there were no responses observed from lower extremity muscles (Figure 1D). These assessments were performed on several occasions during the pre- and post-EES implant periods with no changes identified.

Electrophysiologic Assessment of Translesional Neural Connectivity
There was no significant difference between spinally evoked motor potentials that were elicited after conditioning and those evoked independent of conditioning pulses (Figure 1E). In summary, neural connectivity across the injury site was not detectable during clinical or electrophysiologic examinations at the time of enrollment into the study, before EES surgical implantation, or after surgery.

Motor Training Outcomes
Throughout the presurgical motor training sessions, no volitional EMG modulation or control of lower limb movement was observed. When in side-lying, some prolonged attempts (lasting 10-15 seconds) of maximal volitional flexion of all joints of the leg while contracting the anterior trunk muscles resulted in nonspecific coactivation of agonist and antagonist lower leg muscles over the course of motor task training (Figure 1F). This EMG activity was first recognizable in the second month of motor training and was
observed on multiple testing sessions over the course of motor training before surgery. The EMG recordings showed delayed muscle activation that occurred in a generalized, co-contractile mass activation pattern. The patient did not volitionally target the muscles activated below the level of injury; rather, this observed activity was the result of his maximal efforts to flex all the joints of his leg and contract anterior trunk muscles. This observation is similar to descriptions in the literature of a discomplete SCI profile.2-5,29

Intraoperative Positioning of the Epidural Electrode Array
Intramuscular EMG recordings were gathered from select lower limb muscles. Spinally evoked motor potentials via the implanted epidural electrode were used to position the array to allow recruitment of either distal or proximal lower limb musculature bilaterally. Recruitment of distal or proximal muscles at low voltage intensity depended on active electrode location (Supplemental Figure 3, available online at http://www.mayoclinicproceedings.org). At high voltage intensity, coactivation of both distal and proximal leg muscles was observed.

EES Enabled Volitional Control of Task-Specific Muscle Activity
In a side-lying position with the top leg positioned on a smooth, low-friction surface, stimulation intensities that were at the threshold for evoking nonvolitional muscle activity were identified for each EES configuration. The EES at subthreshold intensities, in which stimulation alone did not directly elicit muscle activity, facilitated volitional production of motor activity only when the patient attempted to move his leg (Figure 2A, left panel). At EES intensities that were at the threshold for eliciting muscle activity, the EMG amplitude of muscles involved in the task performed increased, but limb movements were minimal (eg, flexor muscles such as the medial hamstrings could be activated during knee flexion attempts, but minimal knee flexion was observed) (Figure 2A, center panel). The EES settings that facilitated volitional control of movement enabled control of muscle groups involved in producing joint-specific movement (Figure 2A, right panel) (Supplemental Video 1, available online at http://www.mayoclinicproceedings.org). This volitional control could be modulated in an increasing and decreasing manner using either visual cuing that consisted of a digitally displayed scrolling sinusoidal wave (Figure 2B) or audio cuing as a tone consisting of 3 increasing intensities (Figure 2C). In contrast, without EES, muscle activity was either absent or unorganized and could not be controlled with respect to timing, intensity, or duration (Figure 2B and C).

EES Enabled Volitional Control of Rhythmic Motor Activity to Produce Steplike Movements in the Side-Lying Position
The EES settings that enabled volitional rhythmic activity were also identified (Figure 3A). Lateralizing electrode configurations facilitated ipsilateral control of rhythmic activity, and shifting active electrodes contralaterally on the array attenuated EES facilitation of ipsilateral EMG activity (Figure 3B). Once a subset of parameters was identified that enabled volitional control of rhythmic activity, with the top limb suspended using a fabric support sling, the patient was able to initiate and then modulate the amplitude of steplike movements, as well as volitionally terminate rhythmic steplike activity (Supplemental Video 2 and Supplemental Figure 4, available online at http://www.mayoclinicproceedings.org).

EES Enabled Independent Standing
Without EES, the patient was unable to stand without trainer assistance. In the presence of EES, he was able to stand independently for more than 1.5 minutes, using his arms to maintain balance (Figure 4) (Supplemental Video 3, available online at http://www.mayoclinicproceedings.org). While independently standing, he was able to shift his weight forward, backward, and laterally using his arms to assist. During standing sessions performed in the presence of EES, multiple factors contributed to the patient requesting a brief break from standing, including changes in blood pressure and heart rate when transitioning from sitting to standing, arm muscle fatigue from maintaining balance, and cardiovascular fatigue. The duration of standing was not limited by a decrease in efficacy of
stimulation during a session. However, as stimulation parameters were adjusted to find settings that enabled independent standing, the patient did report bouts of trunk paresthesia, trunk muscle discomfort, and feeling short of breath, which required brief periods of rest lasting approximately 5 minutes with EES turned off.

**EES Enabled Steplike Movements in the Upright Position**

While in an upright position, with body weight partially supported, the participant was able to voluntarily generate leg flexion of 1 leg with coordinated contralateral leg extension in the presence of continuous EES. He was able to volitionally alternate this activity in the legs to produce steplike movements (Figure 5, Supplemental Video 4, available online at http://www.mayoclinicproceedings.org).

**DISCUSSION**

In this report, a patient diagnosed as having sensory and motor complete (AIS-A) SCI was identified to have a discomplete SCI during motor task training before EES implantation. After EES implantation and surgical recovery, EES enabled (1) volitional control of task-specific lower limb muscle activity in a
side-lying position; (2) voluntary initiation, modulation, and termination of rhythmic muscle activity to produce steplike movements while side-lying; (3) full weightbearing independent standing; and (4) volitional control of muscle activity to produce steplike movements while in a vertical position with body weight partially supported. For the first time, all of these functions, which were absent before EES, were enabled in the presence of EES during the first 2 weeks (8 sessions total) in the same participant. During these training sessions, in the presence of EES, the patient regained volitional control of paralyzed muscles and was able to control rhythmic steplike motor activity, both in side-lying and while standing with body weight partially supported. In addition, EES facilitated independent standing using his arms placed on support bars for balance only. Without EES, the patient was unable to perform any of these tasks.

Early reports of evidence of central pattern generators in the human spinal cord led to the development of strategies to engage spinal networks that drive locomotor activity after SCI.6,30-34 Since then, numerous studies have shown that step training on a treadmill can improve locomotor performance after incomplete SCI.35-38 Several reports of EES of the lumbosacral enlargement after SCI previously described that locomotor spinal networks could be facilitated to produce nonvolitional steplike patterns of limb movement with rhythmic muscle activity.6-8 A later study described a series of 4 cases of chronic loss of motor function due to SCI, where EES combined with motor rehabilitation enabled volitional control of motor activity in the lower limbs.11 However, EES-enabled independent standing did not occur for at least 17 weeks. In addition, to date, there are no reports in the literature of recovery of volitional control of EES-facilitated rhythmic activity to allow initiation, modulation, and termination of steplike activity and volitional control of task-specific muscle activity (eg, flexion and extension) in the same patient.

The results of this case report, combined with previous reports of spinal cord neuromodulation restoring function after motor complete paralysis,10,11,25,39 suggest that subfunctional neural connections are likely present in some cases of clinically motor complete (AIS-A or AIS-B) SCI, and these neural connections can be identified and used for
enabling volitional control of motor function via EES. In this study, we used multiple techniques to attempt to diagnose residual fibers across the injury level; however, no detectable connections were observed. Still, before EES, nonspecific muscle activity (ie, coactivation of agonist and antagonist lower leg muscles) during maximal volitional flexion of all joints

FIGURE 4. Epidural electrical stimulation (EES)—facilitated independent standing. Without EES, trainer support was required at the pelvis and knees, with the patient using arm support to maintain upright posture. Electromyographic (EMG) recordings from lower limb muscles show no muscle activity during trainer-assisted standing without EES. During threshold EES (1.5 V, 15 Hz, 210 microseconds), trainer assistance was required at the knees with minimal support at the pelvis. The EMG records indicate activity in the left vastus lateralis (L VL) and bilaterally in the medial hamstrings. At increased EES voltage intensity (2.2 V, 15 Hz, 210 microseconds), independent standing was achieved for more than 1.5 minutes. Trainers provided no assistance but remained in position to assist if needed. Active electrode positions on the EES array are displayed as cathodes (black) and anodes (red). Bottom panels show area under the curve (AUC) values from rectified EMG as percentage maximum of the left vastus lateralis during independent standing. Black bars represent EMG activity in microvolts and time in seconds. Hz = hertz; L = left; MG = medial gastrocnemius; MH = medial hamstrings; R = right; RF = rectus femoris; s = seconds; SOL = soleus; TA = tibialis anterior; µV = microvolts; V = volts.
of the leg and simultaneous contraction of anterior trunk muscles was observed, indicating that this patient has discomplete SCI. At the same time, the observed EMG activity increased in amplitude during presurgical motor training, suggesting that motor training may have influenced the overall excitability of spinal motor circuitry via unidentified residual fibers that cross the injury site.

Although the present data suggest that patients found to have discomplete SCI could be potential candidates for EES therapy, we recognize that the indication of discomplete SCI currently provides only general information about the injury status and lacks a specific definition that characterizes specific ascending or descending spinal pathways. This lack of a distinct definition is due to limited diagnostic approaches that can be used to identify the pathways transmitting residual, yet subfunctional, descending and ascending signals across the injury in AIS-A patients. Therefore, the neural substrates underlying the phenomenon of discomplete SCI and the extent to which these substrates contribute to EES-enabled functional recovery described in the present study remains to be determined.

In summary, these results provide evidence of successful replication of a previous clinical trial using EES therapy and altogether provide further evidence that spinal cord neuromodulation strategies combined with intense motor rehabilitation can facilitate functional recovery even when initiated years after the occurrence of a motor complete spinal injury.

**CONCLUSION**

This report provides evidence of successful replication of previously reported results that (1) EES enabled volitional control of motor activity and (2) EES enabled independent standing after several months of training in 2 AIS-A and 2 AIS-B patients. In addition, this is the first report of EES-facilitated volitional control

**FIGURE 5.** Bilateral steplike electromyographic (EMG) activity in an upright position with partial body weight supported. The EMG recordings from the left and right legs are shown for 5 cycles of volitional extension and flexion bilaterally in the presence of epidural electrical stimulation (EES). Active electrode positions on the EES array are displayed as cathodes (black) and anodes (red). Red and blue bars represent the period when the patient was attempting leg extension and flexion activity. EXT = leg extension; FLX = leg flexion; Hz = hertz; L = left; MG = medial gastrocnemius; MH = medial hamstrings; r = right; RF = rectus femoris; SOL = soleus; TA = tibialis anterior; μs = microseconds; μV = microvolts; V = volts; VL = vastus lateralis.
of task-specific motor activity and control of rhythmic steplike movements in a single patient with clinically complete chronic SCI during the first 2 weeks of EES.

ACKNOWLEDGMENT

We thank Penelope S. Duffy, PhD, for editorial expertise; Beth A. Cloud, PhD, DPT, Daniel D. Veith, MS, Deborah E. Hare, MS, and Yulun Li, BS, for assistance during motor task training; Andrew Schmeling, BSEE, for guidance on stimulation programming; Carlos Cuellar Ramos, PhD, and Riazul Islam, MS, for assistance with data processing; and Amanda Turner, BS, Cynthia J. Stoppel, AAS, Elizabeth M. Mosier, BA, Marc N. Shaft, BA, and Terri A. Gardner for administrative support.

Drs Grahn and Lavrov contributed equally to this work.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: AIS = American Spinal Injury Association Impairment Scale; AUC = area under the curve; AVG = root mean square average; EES = epidural electrical stimulation; EMG = electromyography; EXT = leg extension; FLX = leg flexion; L = left limb; MG = medial gastrocnemius; MH = medial hamstrings; NR = no response; R = right limb; RF = rectus femoris; R FCR = right flexor carpi radialis; SCI = spinal cord injury; SOL = soleus; TA = tibialis anterior; VL = vastus lateralis

Grant Support: This study was supported by the Broccoli Foundation, the Christopher and Dana Reeve Foundation, Mayo Clinic Center for Clinical and Translational Sciences, Mayo Clinic Rehabilitation Medicine Research Center, Mayo Clinic Transform The Practice, The Craig H. Neilsen Foundation, The Bell’3ve in Miracles Foundation, and The Grainger Foundation.

Potential Competing Interests: Drs Gad, Gerasimenko, and Edgerton are shareholders in NeuroRecovery Technologies; Dr Edgerton is president and chair of the company’s board of directors; and Drs Gad, Gerasimenko, and Edgerton hold investorship rights on intellectual property licensed by the regents of the University of California to NeuroRecovery Technologies and its subsidiaries.

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