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Effect of Epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: a case study

Susan Harkema, Ph.D.,

Department of Neurological Surgery, Kentucky Spinal Cord Research Center, University of Louisville. Frazier Rehab Institute, Louisville KY, 220 Abraham Flexner Way, Louisville KY 40202 - USA

Yury Gerasimenko, Ph.D.,

Pavlov Institute of Physiology, St. Petersburg, Russia. Department of Integrative Biology and Comparative Physiology, University of California, Los Angeles USA, Los Angeles, CA 90095 - USA

Jonathan Hodes, M.D.,

Department of Neurological Surgery, Kentucky Spinal Cord Research Center, University of Louisville, 401 East Chestnut Street – Suite 580, Louisville, KY 40202 - USA

Joel Burdick, Ph.D.,

Division of Engineering and Applied Sciences, California Institute of Technology, Pasadena, CA 91125 - USA

Claudia Angeli, Ph.D.,

Frazier Rehab Institute, Louisville KY. Department of Neurological Surgery, Kentucky Spinal Cord Research Center, University of Louisville, 220 Abraham Flexner Way, Louisville KY 40202 - USA

Yangsheng Chen, Ph.D.,

Department of Neurological Surgery, Kentucky Spinal Cord Research Center, University of Louisville. Frazier Rehab Institute, Louisville KY, 220 Abraham Flexner Way, Louisville KY 40202 - USA

Christie Ferreira, B.S.,

Department of Neurological Surgery, Kentucky Spinal Cord Research Center, University of Louisville. Frazier Rehab Institute, Louisville KY, 220 Abraham Flexner Way, Louisville KY 40202 - USA

Andrea Willhite, B.S.,

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Corresponding Author: vre@ucla.edu, 310-825-1910.

Contributors

RE, SH, YG, JB and CA were responsible for the study concept and design. JH performed surgical implant, SH, YC, CA and CF conducted the electrophysiological testing during surgery. SH, CA, CF, AW conducted all data collections and figure development. YC designed the data collection system. YG and ER also contributed to figure development. SH and RE were responsible for supervision of the study. All authors contributed to data interpretation and writing of the manuscript.

Conflicts of interest

No authors have any conflicts of interest.

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Department of Neurological Surgery, Kentucky Spinal Cord Research Center, University of Louisville. Frazier Rehab Institute, Louisville KY, 220 Abraham Flexner Way, Louisville KY 40202 - USA

Enrico Rejc, M.S.,

Department of Biomedical Sciences and Technologies, University of Udine, P.le Kolbe 4, 33100, Udine, Italy

Robert G. Grossman, M.D., and

Department of Neurosurgery, The Neurological Institute, The Methodist Hospital, Texas USA, 6560 Fannin, Suite 944, Houston, TX 77030 - USA

V. Reggie Edgerton, Ph.D.

Department of Integrative Biology and Comparative Physiology, Department of Neurobiology and Brain Research Institute, University of California, Los Angeles, Los Angeles, CA 90095 - USA

Summary

Background—Repeated periods of stimulation of the spinal cord and training seems to have amplified the ability to consciously control movement.

Methods—An individual three years post C7-T1 subluxation presented with a complete loss of clinically detectable voluntary motor function and partial preservation of sensation below the T1 cord segment. Following 170 locomotor training sessions, a 16-electrode array was surgically placed on the dura (L1-S1 cord segments) to allow for chronic electrical stimulation. After implantation and throughout stand retraining with epidural stimulation, 29 experiments were performed. Extensive stimulation combinations and parameters were tested to achieve standing and stepping.

Findings—Epidural stimulation enabled the human lumbosacral spinal circuitry to dynamically elicit full weight-bearing standing with assistance provided only for balance for 4.25 minutes in a subject with a clinically motor complete SCI. This occurred when using stimulation at parameters optimized for standing while providing bilateral load-bearing proprioceptive input. Locomotor-like patterns were also observed when stimulation parameters were optimized for stepping. In addition, seven months after implantation, the subject recovered supraspinal control of certain leg movements, but only during epidural stimulation.

Interpretation—Even after a severe low cervical spinal injury, the neural networks remaining within the lumbosacral segments can be reactivated into functional states so that it can recognize specific details of ensembles of sensory input to the extent that it can serve as the source of neural control. In addition, newly formed supraspinal input to this same lumbosacral segments can re-emerge as another source of control. Task specific training with epidural stimulation may have reactivated previously silent spared neural circuits or promoted plasticity. This suggests that these interventions could be a viable clinical approach for functional recovery after severe paralysis.

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Introduction

The mammalian spinal cord can generate locomotor output in the absence of input from the brain¹⁻³ by central pattern generation.⁴⁻⁶ Cats with complete spinal cord transection can execute standing and stepping when sensory input is provided to the lumbosacral pattern generator circuitry.⁷⁻⁹ Spinal cats can learn to stand, fully supporting their hindquarters, and to step over a range of speeds and load-bearing levels with task specific training. Adult spinally transected rats generate stepping only with combined interventions of locomotor training, pharmacological intervention and/or epidural stimulation.^{10,11} This evidence leads

to the hypothesis that if similar spinal circuits exist in humans, then electrically stimulating the lumbosacral spinal cord epidurally coupled with intense training can facilitate standing and stepping in an individual with a clinically motor complete spinal cord injury (SCI).

Improvements in walking have been achieved with intense locomotor training in individuals who have detectable voluntary movement of the legs after SCI^{12–14} but not in those classified as clinically motor complete.^{15–17} Rhythmic efferent activity timed to the step cycle can occur during manually facilitated stepping, and bilateral tonic activity can occur during partial weight-bearing standing after a clinically complete SCI. Rhythmic and tonic motor patterns of the legs have been induced with^{18–22} and without^{23–25} epidural stimulation in humans after motor complete SCI while lying supine. This suggests that spinal circuitry for locomotion is present in the human but cannot functionally execute these tasks without some critical level of excitability from supraspinal centers present after incomplete SCI.

We hypothesized that tonic epidural spinal cord stimulation can modulate the human spinal circuitry into a physiological state that enables sensory input, derived from standing and stepping movements, to serve as a source of neural control to perform these tasks. We observed that the spinal circuitry was able to generate full weight-bearing standing with balance assistance in response to task specific sensory cues in the presence of epidural stimulation. This occurred in a paraplegic subject with a clinically motor complete SCI. Stepping-like patterns were also generated with epidural stimulation during manually facilitated stepping on a treadmill using body weight support. The subject also regained some supraspinally mediated control of the legs after intense stand training with epidural stimulation. Unexpectedly, clinical assessments indicated improvements in other physiological functions including bladder, sexual function, and temperature regulation. One possible explanation for this recovery is that residual supraspinal connections that existed but could not be detected clinically were reactivated or that new supraspinal connections to the spinal networks were formed.

Methods

Clinical characteristics prior to implantation

A 23-year-old male struck by a motor vehicle 3-4 years prior to implantation was enrolled in this study. Neurological examination revealed paraplegia from a C7-T1 subluxation with injury to the lower cervical and upper thoracic spinal cord. The triceps and intrinsic hand muscles exhibited weak voluntary contraction. He had no contraction of trunk or leg muscles. He was treated emergently, subluxation was reduced by anterior interbody fusion and instrumentation. MRI of the injury site obtained prior to implantation revealed myelomalacia and atrophy of the cord segment adjacent to the T1 vertebral body (supplemental figure 1a).

Prior to implantation, his neurological deficit on the American Spinal Injury Association (ASIA) impairment scale (AIS)²⁶ as AIS B (pinprick and light-touch present below the lesion). He had no motor function of trunk or leg muscles, a flaccid anal sphincter, and no voluntary bladder contraction (supplemental figure 1b). Sensation was abnormal below C7.

Somatosensory evoked potentials showed bilateral delay of cortical responses from posterior tibial nerve stimulation. Lower extremity nerve conduction studies were normal. Motor cortex transcranial magnetic stimulation elicited no response from leg muscles. He was unable to stand or walk independently or voluntarily move his legs despite standard-of-care rehabilitation and additional intensive locomotor training. The research subject signed an informed consent for electrode implantation, stimulation, and physiological monitoring

studies approved by the University of Louisville and the University of California, Los Angeles Institutional Review Boards.

Prior to the electrode implantation, the participant received 170 locomotor training sessions¹⁴ over a period of 26 months using body weight support on a treadmill with manual facilitation resulting in 108 hours of step training and 54 hours of stand training with no detectable change in electromyographic (EMG) activity (figure 1). During manually facilitated stepping, sporadic EMG activity was observed in the lower leg muscles, most often in the medial hamstrings. No improvement was observed in EMG over the course of the training.

Surgical Implantation of electrode array and stimulator

An epidural spinal cord stimulation unit (RestoreADVANCED, Medtronic) was used to electrically stimulate the lumbosacral enlargement. A 16-electrode array (5-6-5 Specify, Medtronic) was implanted under fluoroscopic control at T11-L1 over spinal cord segments L1-S1 (supplemental figure 2a). The electrode array was positioned over the midline of the exposed dura. The location of the array was evaluated during surgery with thresholds and amplitudes of EMG recorded from leg muscles²¹ elicited by stimulation at 2 Hz. Multiple stimulations were tested using a midline stimulation configurations, with each electrode pair being 6 mm apart. Symmetry was tested by using left and right side electrodes within the array. The electrode lead was tunneled to a subcutaneous abdominal pouch where the pulse generator was implanted. Two weeks after implantation, the position of the array was reconfirmed using the same stimulation protocols while the subject was lying supine (supplemental figure 2c–d).

Experimental Design

Varying combinations of stimulation were systematically evaluated to elicit optimal efferent patterns for standing and stepping. Spinal cord stimulation was conducted during sessions lasting up to 250 minutes. During these sessions, stimulation duration ranged from 40 to 120 minutes. Stimulation amplitudes and frequencies ranged from 0.5 to 10.0V and 5 to 40 Hz, respectively, using either a 210 or 450 μ s pulse width. The optimal standing configurations evoked sustainable tonic co-activation specifically when standing; stepping configurations evoked rhythmic activity with alternation of right and left leg and intralimb flexors and extensors. EMG activity of 14 lower extremity muscles and hip, knee, and ankle joint angles were measured.

During experimental sessions on the treadmill, three trainers provided manual facilitation, when needed. Two trainers provided facilitation by placing their hands distal to the patella during the stance phase and at the popliteal fossa and anterior distal tibia for foot clearance during the swing phase.¹⁴ The third trainer held the pelvis for stabilization and weight shifting during stepping. Stand training was performed using a device comprised of vertical and horizontal bars surrounding the individual allowing him to assist balance. Bungees were attached to the device to provide support only if the knees or hips flexed beyond the normal standing posture (supplemental note). The total duration of stimulation averaged 54 ± 13 minutes per session. Epidural stimulation was not provided outside laboratory sessions.

Data Acquisition

EMG, joint angles, footswitch, ground reaction forces and body weight support (Innoventor, St. Louis, MO) data were collected at 2,000 Hz using a custom-written acquisition software (National Instruments, Austin, TX). Bilateral EMG (Motion Lab Systems, Baton Rouge, LA) from the soleus, medial gastrocnemius, tibialis anterior, medial hamstrings, quadriceps, and gluteus maximus muscles was recorded using bipolar surface electrodes with fixed

inter-electrode distance.¹⁶ Bilateral EMG from the iliopsoas was recorded with fine-wire electrodes. Two surface electrodes placed symmetrically lateral to the electrode array incision site over the paraspinal muscles were used to record the stimulation artifact. Hip, knee, and ankle joint angles were acquired using a high-speed optical motion capture system (Motion Analysis, Santa Rosa, CA). Ground reaction forces were collected using shoe-insole pressure sensors (TEKSCAN, Boston, MA).

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The sponsors of this study had no role in study design, data collection, data analysis and interpretation, or writing of the manuscript. All authors had full access to all the data reported in the manuscript. All authors had responsibility for the decision to submit the manuscript.

Results

The patient was always cognizant of the presence of the stimulation. The most common sensation was a tingling feeling localized to the electrode implantation site and in those muscles that were targeted for activation. Parasthesias were also routinely perceived in the trunk, hips, and legs and varied according to the stimulation intensity; however, these sensations never reached a level of significant discomfort or pain and never precluded the use of epidural stimulation.

Standing with epidural stimulation

Epidural stimulation (15 Hz, 8V) of the caudal segments (L5-S1) of the spinal cord combined with sensory information related to bilateral extension and loading was sufficient to generate standing without manual facilitation when first attempted (figure 2) with 65% (585/900N) body weight support (figure 2a, supplemental video 1). The subject was able to sustain standing without manual facilitation while the level of body weight support was progressively reduced to full weight-bearing (figure 2b, supplemental video 1).

Transitioning from sitting to standing without body weight support altered the EMG activity during epidural stimulation even though the stimulation parameters remained constant (figure 3). When loading of the legs was initiated, the EMG activity increased dramatically and was sufficient to support the subject's body weight with minimal assistance required by the trainers (supplemental note). During this transition, the stimulation remained constant using the same location, frequency and intensity parameters (figure 3b–e). The EMG activity was also modulated by the site and intensity of stimulation. The caudal (L5-S1) stimulation at higher intensities resulted in a more optimal motor pattern for standing (figure 3a–c). During caudal stimulation, there was a greater increase in the EMG amplitude bilaterally in the more proximal muscles compared to that of the more distal muscles which were initially markedly reduced (figure 3c and e, supplemental video 2). Once standing was achieved, there was more co-contraction of both flexors and extensors and proximal and distal muscles.

Postural responses with epidural stimulation

Postural responses were observed in the leg EMG activity when the subject shifted his center of gravity sagittally while standing with epidural stimulation and intermittent manual facilitation (figure 4a). The EMG burst of the medial gastrocnemius increased with forward deviation, whereas backward deviation induced EMG bursts in the tibialis anterior. Standing bouts with tonic bilateral EMG activity routinely occurred for several continuous minutes and increased in frequency and duration as training progressed (figure 4b). After 80 sessions (supplemental note), the subject could initiate and maintain continuous full weight-bearing

standing without manual facilitation (maximum 4.25 min) with bilateral tonic EMG activity (figure 4b, supplemental video 3). Oscillatory patterns, often clonic-like, emerged and then were followed by little or no EMG activity, requiring a return to manually facilitated standing. This sequence occurred repeatedly during the 60 minute standing sessions.

Locomotor patterns with epidural stimulation

Epidural stimulation at 30–40 Hz and task specific sensory cues were needed to generate locomotor-like patterns. Sensory cues from manually facilitated stepping included load alternation and leg positioning with appropriate kinematics of the hips, knees, and ankles timed to the step cycle. Without epidural stimulation, manually facilitated stepping produced little or no EMG activity (figure 5a). The EMG activity in the legs was dramatically different depending on the loading and kinematic patterns when using identical stimulation parameters. Consistent oscillatory EMG patterns did not occur when the legs were extended and bilaterally loaded, but emerged with alternating loading and flexion and extension of the legs (figure 5b and c).

Supraspinal control of movements with epidural stimulation

Supraspinal control of toe extension and ankle and leg flexion emerged only with epidural stimulation. This occurred after 80 stand training sessions (seven months after implantation) (figure 6 and supplementary videos 4 and 5). Voluntary movement was observed in both lower extremities, although the stimulation parameters were different. Technical limitations of the stimulator prevented simultaneous movements of the legs. When the subject was instructed to flex (draw the leg upward), the toe extended, the ankle dorsi-flexed and the hip and knee flexed with the appropriate muscle activation. When instructed to dorsi-flex the ankle, the foot moved upward with tibialis anterior activation. When instructed to extend the great toe, the toe moved upward with activation of the extensor hallucis longus. The subject could consciously activate the appropriate muscles for the intended movement, and the timing of activation was closely linked to the verbal commands (figure 6e).

Clinical Impressions

With training and epidural stimulation, the subject had functional gains in bladder and sexual function and temperature regulation (supplemental note). The subject has been able to voluntarily void with minimal residual volume and reports improved sexual response and performance. The subject regained diaphoretic capability and ability to tolerate temperature extremes. In addition, a sense of well being and increased self-esteem enabled more frequent social interactions. An eighteen percent weight gain was associated with increased appetite and relative increase in lean body mass and decrease in total body fat as measured using a DEXA scan.

Discussion

We have used an epidurally implanted electrode array to modulate the physiological state of the spinal circuitry to enable full weight-bearing standing in a human with a chronic clinically motor complete SCI. This phenomenon was observed with the first attempt at standing. The epidural stimulation did not induce standing by directly activating motor pools, but enabled motor function by stimulating afferent fibers in the dorsal root and engaging populations of interneurons that integrated load-bearing related proprioceptive input to coordinate motor pool activity. Although motor pool activity in the presence of epidural stimulation could occur during sitting in some cases, the activity needed for effective standing required the proprioceptive information associated with load-bearing positional changes. Dynamic changes in position during standing were accompanied by motor patterns needed to maintain upright posture without changes in the epidural

stimulation parameters. Intensive task specific training combined with epidural stimulation extended the duration of periods of full weight-bearing standing that could be initiated by the subject.

Robust, consistent rhythmic stepping-like activity emerged during manually facilitated stepping only when tonic epidural stimulation and stepping-associated proprioception (alternating weight-bearing and flexion and extension of the legs) was present. When standing, the same stimulation parameters elicited primarily tonic bilateral activity; however, when stepping, the parameters evoked rhythmic alternating activity. Presumably, the epidural stimulation activates the dorsal root afferent fibers and, more likely at higher intensities, dorsal columns and additional spinal structures. The continuous stimulation modulated the physiological state of the spinal cord which enabled sensory information processing that was closely linked to the functional task. This is of great clinical importance, because the intended task can be driven and controlled via the spinal sensorimotor circuitry rather than by an external control system.

Previous studies have shown that epidural stimulation can induce rhythmic activity in clinically complete subjects lying supine.¹⁸⁻²¹ Also, different sources of sensory input, e.g. hip extension and pinching of skin, can elicit rhythmic activity in the trunk and legs in subjects with clinically complete SCI.^{18,22-24} Manually facilitated standing¹⁷ and stepping^{15,16,27} can elicit bilateral tonic EMG and rhythmic oscillatory EMG, respectively, in many individuals with clinically complete SCI demonstrating the importance of providing task specific sensory cues. Our study provides evidence that, when enabled by epidural stimulation, the sensory input may serve as a spinal circuitry controller during standing and manually facilitated stepping in the absence of clinically detectable supraspinal input in humans.

The individual in this study was eventually able to voluntarily execute toe extension, ankle dorsi-flexion, and leg flexion in the presence of epidural stimulation. In subjects with a motor incomplete SCI who have some ability to voluntarily move their legs, a common phenomenon is the loss of specificity of control of selected muscles.²⁷ In this study, the activated motor pools were appropriate for the intended movement. Two possible mechanisms are: 1) epidural stimulation provided excitation of lumbosacral interneurons and motoneurons²⁸ which, combined with the weak excitatory activity of residual descending axons, achieved a level of excitation that was sufficient to activate motoneurons; and/or 2) axonal regeneration or sprouting may have been induced via activity-dependent mechanisms over a period of months. It is highly significant from a neurobiological, as well as a clinical perspective, that this supraspinal control was manifested only in the presence of continuous tonic epidural stimulation. Seemingly, conscious control was regained by elevating the level of spinal interneuronal excitability with stimulation to a critical, but sub-threshold level, allowing control via descending pathways.

These same mechanisms may also explain the improved autonomic function in bladder, sexual and thermoregulatory activity that has been of significant benefit to the subject. The areas of lumbosacral spinal cord stimulated included at least parts of the neural circuits that regulate these autonomic functions and may have also resulted in activity-dependent changes.

The evidence supports the proof of principle that humans have conserved spinal locomotor circuitry as found in other mammals including the ability to: 1) transition from a low level activity state to one that can generate active standing in the presence of tonic epidural stimulation; 2) gate tonic electrically evoked responses to coordinate motor pools to elicit patterns consistent with the task specific sensory input; 3) control the level and timing of

neural excitation sufficient to generate standing and facilitate stepping through the use of appropriate task specific sensory input; and 4) mediate voluntarily initiated movement of the legs in the presence of epidural stimulation. These results indicate that epidural stimulation has potential as a clinical intervention in combination with task specific training for the recovery of function after SCI and other neurologic disorders.³⁰ Improvements in the array and stimulation technology will be needed for practical application, and the addition of pharmacological agents may result in greater degrees of functional recovery.

PANEL: Research in Context

Systematic Review—The search strategy for evidence that epidural stimulation of the spinal cord could be used to improve motor function in humans consisted of identifying all published literature listed in PubMed that related to electrical, pharmacological and electromagnetic stimulation of the spinal cord. This search included studies ranging from *in situ* isolated spinal cord of the lamprey to humans with implanted epidural electrodes. Each listed publication was assessed relative to the animal species, whether the spinal injury was motor complete or incomplete, details of the stimulation parameters relative to the motor responses, the specific experimental model used in the study, i.e. *in vivo* versus *in situ*, and utilization of proprioceptive input. In addition, our research team sponsored an international 2-day workshop consisting of scientists and clinicians with knowledge of electrical stimulation of the spinal cord and the neural control of posture and locomotion. Study design for implantation and training of a spinal motor complete human subject was discussed and evaluated extensively. In the most closely related studies, it was shown that epidural stimulation of the lumbosacral spinal cord of spinally complete (AIS A) subjects could induce an oscillatory movement in the legs, and the pattern of movement changed with different stimulation parameters.^{20–21}

Interpretation—While it has been clear that the human spinal cord circuitry can be induced to generate cyclic movements of the legs without supraspinal input in response to tonic stimulation of peripheral afferents or directly stimulating the spinal cord, the significance of these observations have been uniformly interpreted as providing evidence for central pattern generation i.e. oscillations induced without input from the brain or from peripheral afferents. The present data demonstrate three new concepts regarding the spinal control of movement. First, that the human spinal cord circuitry for posture and locomotion can be “controlled” by the peripheral sensory input, thus, emphasizing this key role of sensory input in posture and locomotion rather than its independence from sensory input. Secondly, we show the “enabling” phenomenon of epidural stimulation whereby modest levels of stimulation do not “induce” stepping or standing, but when stimulated with the appropriate parameters the sensory input can serve as the “controller”, as occurs in cats and rats. And most dramatically, after months of stimulation and training, voluntary control of leg movement emerged, but only when enabled by modest levels of epidural stimulation. None of these observations have been demonstrated previously in a human with chronic (more than 3 years post lesion) paralysis. These observations open the possibility of a paradigm shift in the perception of possible interventions that could be used to improve function for a range of neuromotor disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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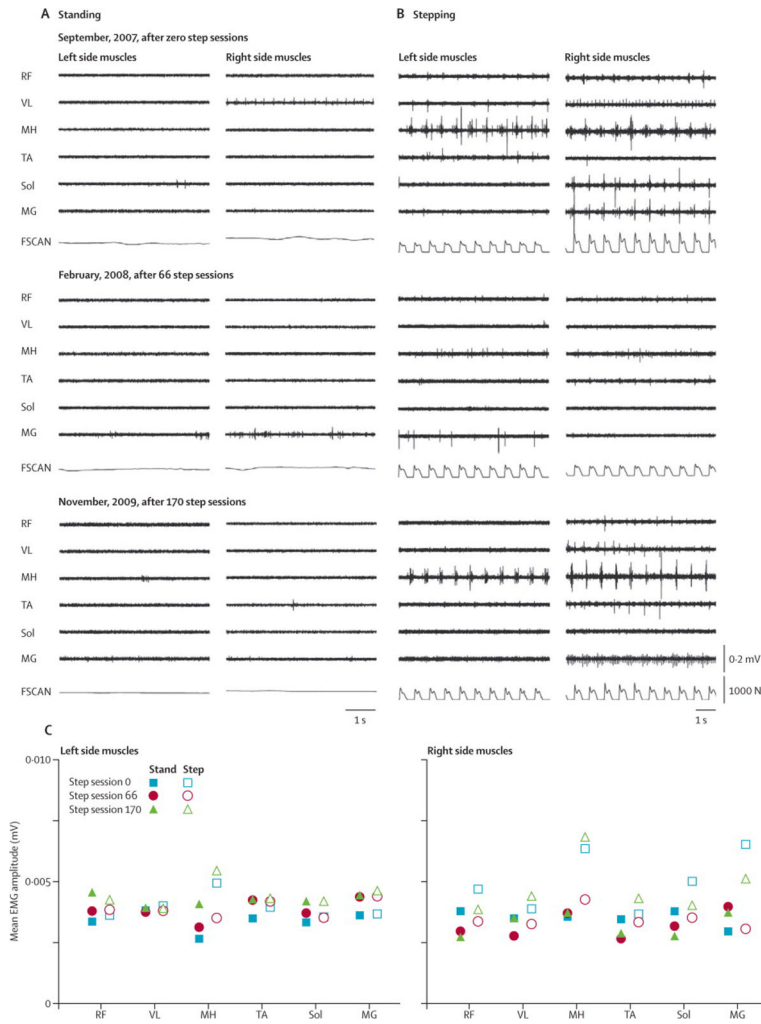


Figure 1. Lower extremity EMG activity during standing and stepping with body weight support prior to implantation

These data demonstrate that intensive training did not result in significant changes in efferent motor patterns. (a) Standing and (b) stepping with body weight support and manual facilitation on a treadmill prior to implantation. (c) Mean EMG amplitude for standing (solid symbols) and stepping (open symbols) across three different time points (0, 66, and 170 step training sessions). Left (L) and right (R) side muscles: rectus femoris (RF), vastus lateralis (VL), medial hamstrings (MH), tibialis anterior (TA), soleus (Sol), and medial gastrocnemius (MG). FSCAN is ground reaction force data.

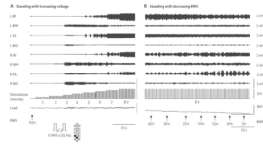


Figure 2. Lower extremity EMG activity with epidural stimulation of the lumbosacral segments during standing

These data demonstrate that the output of the spinal circuitry is modulated by the proprioceptive input during standing without manual facilitation when sufficient epidural stimulation is present. **(a)** EMG activity increases in amplitude and becomes more constant bilaterally in most muscles as stimulation is increased in strength from 1–8V (15Hz) with a constant level of body weight support (65% BWS; 585/900N BWS). **(b)** Reducing body weight support from 45% to 5% (405/900 N to 45/900N) and with constant stimulation (8V, 15Hz) changed the EMG amplitudes and oscillatory patterns differently among muscles. Array diagram illustrates the stimulation configuration; anode electrodes are black and cathode electrodes are gray. Left (L) and right (R) side muscles: rectus femoris (RF), medial hamstrings (MH), tibialis anterior (TA), and medial gastrocnemius (MG). Stim indicates the stimulation intensity. Interpulse interval depicting stimulation frequency is shown at the bottom of graph **a**. Refer to Supplementary Video 1.

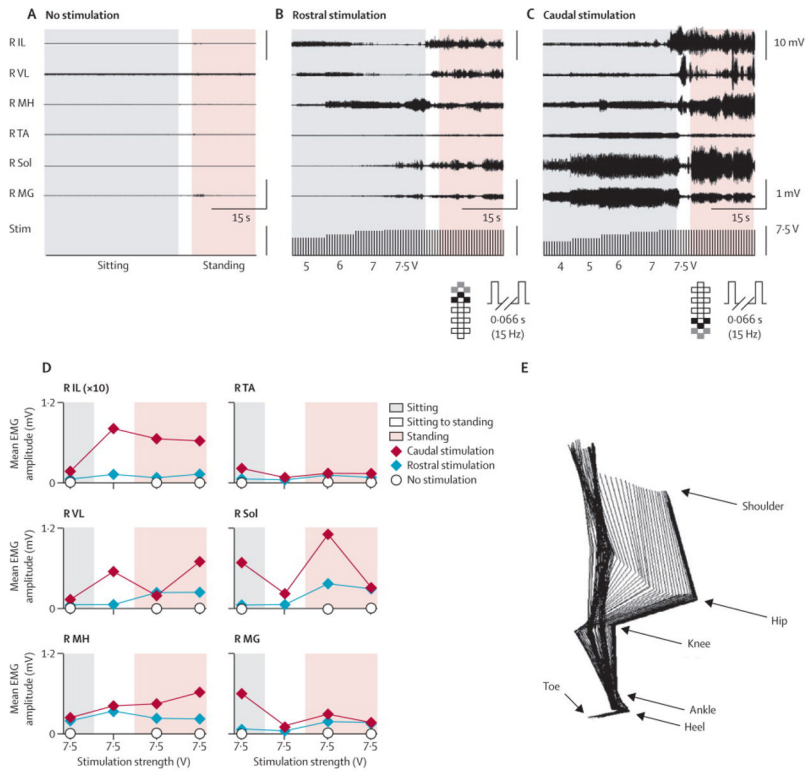


Figure 3. Lower extremity EMG activity during sitting and standing with and without epidural stimulation

There was little or no EMG activity without stimulation during sitting or standing. With increasing levels of epidural stimulation, EMG amplitudes were modulated in a tonic pattern while the subject remained sitting. During the transition from sitting to standing, amplitudes and patterns of EMG were modulated in all recorded muscles. Transition (white) from sitting (gray) to standing (yellow) with (a) no stimulation, (b) rostral (spinal segments L₁-L₂) stimulation (4–7.5V, 15Hz), and (c) caudal (spinal segments L₄-S₁) stimulation (4–7.5V, 15Hz). (d) Averaged mean EMG amplitude responses on the right side during sitting and standing with no stimulation (○), and rostral (♦) and caudal (◆) stimulation at 7.5V, 15Hz. (e) Kinematic representation of sitting to standing transition with caudal stimulation (illustration at 10 frames per sec) (Supplementary Video 2). Array diagram illustrates the stimulation configuration; anode electrodes are black and cathode electrodes are gray. Right (R) side muscles: fine wire: iliopsoas (IL); surface EMG: vastus lateralis (VL), medial hamstrings (MH), tibialis anterior (TA), soleus (Sol), and medial gastrocnemius (MG). Stim indicates the stimulation intensity. Interpulse interval depicting stimulation frequency is shown at the bottom of graphs b and c.

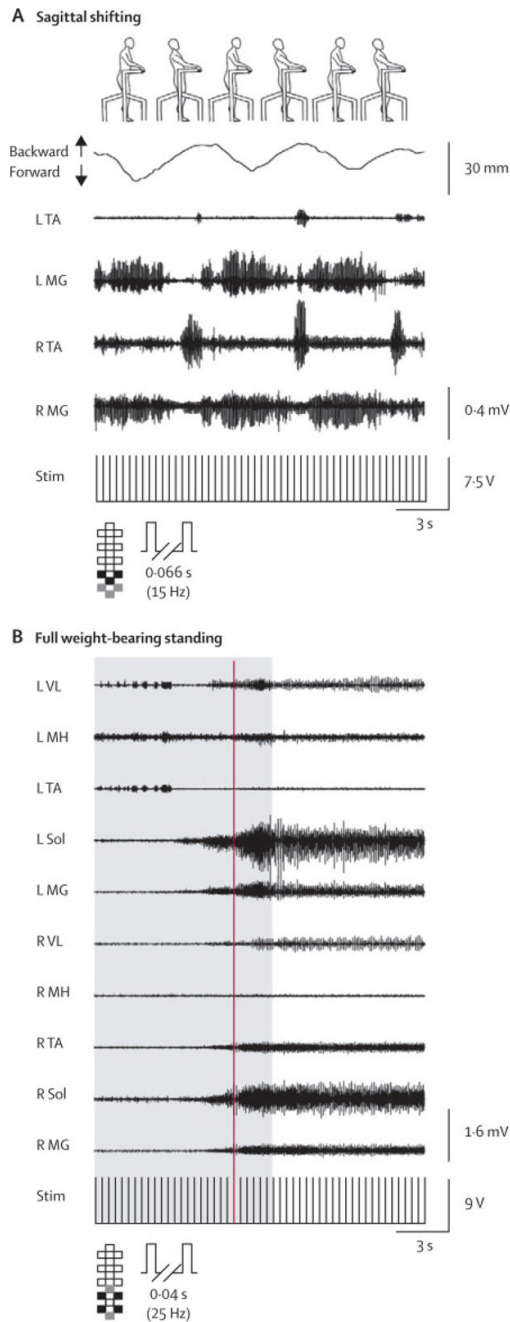


Figure 4. Lower extremity EMG activity with epidural stimulation during continuous full weight-bearing standing

(a) EMG activity with epidural stimulation (7.5V, 15Hz) of the lumbosacral segments during weight shifting. Center of gravity displacement in the sagittal plane depicting backward (B) and forward (F) shifts shown under the schematic diagram of the movement. (b) EMG activity with epidural stimulation (9V, 25Hz) during the transition from manually facilitated weight-bearing standing (gray) to full weight-bearing standing without manual facilitation (white). Red line indicates 3 second count down by the subject to initiation of standing without manual facilitation (Supplementary Video 3). Left (L) and right (R) side muscles: vastus lateralis (VL), medial hamstrings (MH), tibialis anterior (TA), soleus (Sol),

and medial gastrocnemius (MG). Array diagram illustrates the stimulation configuration; anode electrodes are black and cathode electrodes are gray. Stim indicates the stimulation intensity. Interpulse interval depicting stimulation frequency is shown at the bottom of each graph.

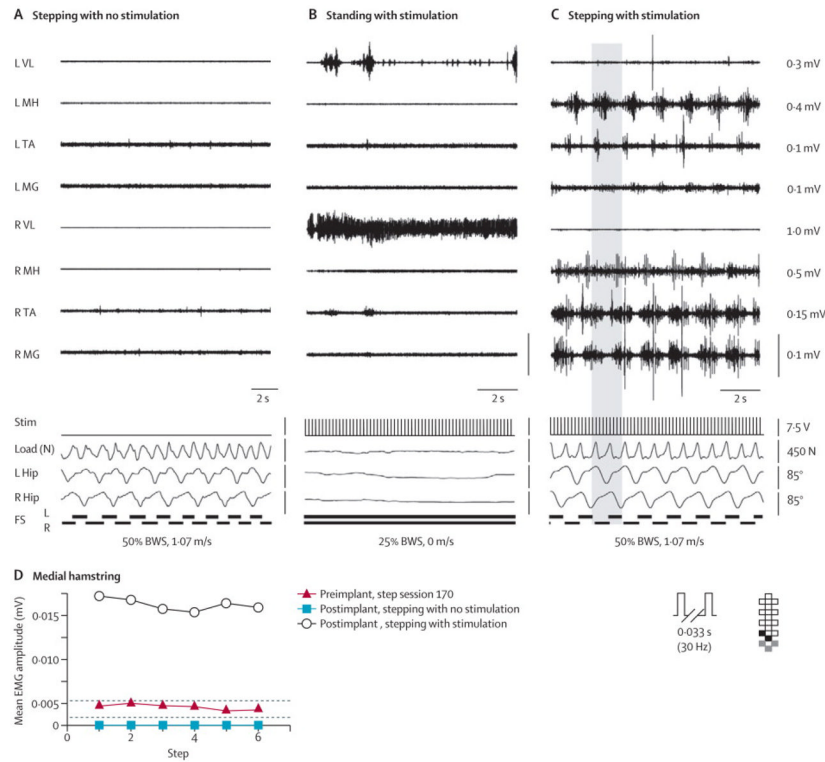


Figure 5. Lower extremity EMG activity during standing and stepping with body weight support and manual facilitation with and without epidural stimulation of lumbosacral segments

The EMG patterns were modified by stimulation and by different patterns of sensory input. EMG activity during (a) manually facilitated stepping (50% BWS, 450/900N, 1.07 m/s) without stimulation, (b) standing with 25% BWS (225/900N) and with epidural stimulation (7.5 V, 30 Hz) and (c) manually facilitated stepping (50% BWS, 450/900N, 1.07 m/s) with epidural stimulation (7.5V, 30 Hz). Shaded area indicates one full step of the right leg. (d) Mean EMG activity for the medial hamstrings (MH) during stepping without stimulation (□) and with stimulation (○) (a and c respectively) and stepping after 170 step training sessions prior to implantation (△) (Figure 1b). The horizontal lines represent the baseline variation in the noise of each signal. Left (L) and right (R) side muscles: vastus lateralis (VL), medial hamstrings (MH), tibialis anterior (TA), and medial gastrocnemius (MG). Load is load cell reading in Newtons (N). Sagittal joint angles for the left (L Hip) and right (R Hip) hip joint. Stance phase represented by left (L FS) and right (R FS) footswitches. Array diagram illustrates the stimulation configuration; anode electrodes are black and cathode electrodes are gray. Stim indicates the stimulation intensity. Interpulse interval depicting stimulation frequency is shown at the bottom of graph c.

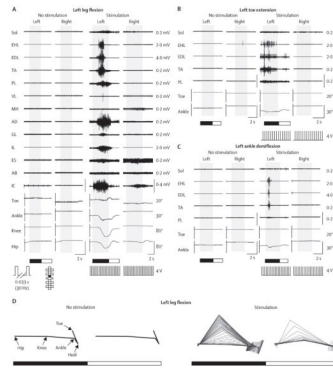


Figure 6. EMG activity during voluntary leg movements in a supine position

Supraspinal control of leg movements only occurred during epidural stimulation. EMG and kinematics are shown for three different movement commands with (4V, 30Hz) and without stimulation. At the bottom of each graph the black bar (and gray shading within graph) indicates the “up” command for (a) left leg flexion, (b) left toe extension, and (c) left ankle dorsiflexion. The white bar (and no shading within graph) indicates the command to relax. Left and right EMG are shown to emphasize the isolated control of the left side following the command. There was a delay observed between the onset of the EMG activation in some muscles relative to the “up” command, while the termination of the activation often occurred prior to the command to relax. Intercostal (IC) EMG activation occurred as the subject inhaled during the performance of the voluntary leg movement. (d) Kinematic representation of leg movement (graph a) with and without epidural stimulation (illustrated at 10 frames per second). Left (L) and right (R) side muscles: fine wire: extensor hallucis longus (EHL), extensor digitorum longus (EDL), iliopsoas (IL); surface EMG: soleus (Sol), tibialis anterior (TA), peroneus longus (PL), vastus lateralis (VL), medial hamstrings (MH), adductor magnus (AD), gluteus maximus (GL), erector spinae (ES), rectus abdominus (AB), and intercostals (IC). Sagittal joint angles for the toe (1st metatarsal relative to foot), ankle, knee and hip joints. Array diagram illustrates the stimulation configuration; anode electrodes are black and cathode electrodes are gray. Stim indicates the stimulation intensity. Interpulse interval depicting stimulation frequency is shown at the bottom of graph a. Supplementary Videos 4 and 5 show voluntary control attempts with and without stimulation, respectively.