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

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Summary

Background **Repeated periods of stimulation of the spinal cord and training increased the ability to control movement in animal models of spinal cord injury. We hypothesised that tonic epidural spinal cord stimulation can modulate spinal circuitry in human beings into a physiological state that enables sensory input from standing and stepping movements to serve as a source of neural control to undertake these tasks.**

Methods **A 23-year-old man who had paraplegia from a C7–T1 subluxation as a result of a motor vehicle accident in July 2006, presented with complete loss of clinically detectable voluntary motor function and partial preservation of sensation below the T1 cord segment. After 170 locomotor training sessions over 26 months, a 16-electrode array was surgically placed on the dura (L1–S1 cord segments) in December 2009, to allow for chronic electrical stimulation. Spinal cord stimulation was done during sessions that lasted up to 250 min. We did 29 experiments and tested several stimulation combinations and parameters with the aim of the patient achieving standing and stepping.**

Findings **Epidural stimulation enabled the man to achieve full weight-bearing standing with assistance provided only for balance for 4·25 min. The patient achieved this standing during stimulation using parameters identified as specific for standing while providing bilateral load-bearing proprioceptive input. We also noted locomotor-like patterns when stimulation parameters were optimised for stepping. Additionally, 7 months after implantation, the patient recovered supraspinal control of some leg movements, but only during epidural stimulation.**

Interpretation **Task-specific training with epidural stimulation might reactivate previously silent spared neural circuits or promote plasticity. 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 brain[1–3] by central pattern generation.[4–6] Cats with complete transection of the spinal cord (spinal cats) can stand and step 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 at a range of speeds and load-bearing levels with task-specific training. Adult spinally transected rats can step only with a combination of interventions of locomotor training, pharmacological intervention, and epidural stimulation.[10,11] This evidence led to the hypothesis that if similar spinal circuits exist in human beings, then electrically stimulating the lumbosacral spinal cord epidurally coupled with intense training could facilitate standing and stepping in patients with a clinically motor complete spinal cord injury (SCI).

Improvements in walking have been achieved with intense locomotor training in patients with SCI who have detectable voluntary movement of the legs[12–14] but not in those with clinically motor complete SCI.[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 motor complete SCI. Rhythmic and tonic motor patterns of the legs have been induced with[18–22] and without[23–25] epidural stimulation in patients with clinically motor complete SCI while lying supine. This finding suggests that spinal circuitry for locomotion is present in human beings but that human beings cannot functionally complete these tasks without some crucial level of excitability from supraspinal centres that are present after incomplete SCI.

We hypothesised that tonic epidural spinal cord stimulation can modulate spinal circuitry in human beings into a physiological state that enables sensory input from standing and stepping movements to serve as a source of neural control to undertake these tasks. We tested this hypothesis by epidural stimulation of the dura of a man with paraplegia who had clinically motor complete SCI.

Methods

Clinical characteristics before implantation

A 23-year-old man, who was hit by a motor vehicle in July 2006, 3·4 years before implantation in December 2009,

was included in this study. Neurological examination at hospital admission revealed paraplegia from a C7–T1 subluxation with injury to the lower cervical and upper thoracic spinal cord. The patient was able to do weak voluntary contraction of the triceps and intrinsic hand muscles but he had no contraction of trunk or leg muscles. He received emergency treatment after the accident; subluxation was reduced by anterior interbody fusion and instrumentation. Before implantation, MRI of the injury site was done, which revealed myelomalacia and atrophy of the cord segment adjacent to the T1 vertebral body (webappendix p 1).

Before implantation, the patient's neurological deficit on the American Spinal Injury Association impairment scale[26] was grade B (pinprick and light-touch sensation present below the lesion). He had no motor function of trunk or leg muscles, a flaccid anal sphincter, and no voluntary bladder contraction (webappendix p 1). Sensation was abnormal below C7.

Somatosensory evoked potentials showed bilateral delay of cortical responses from posterior tibial nerve stimulation. Leg nerve conduction studies were normal. Motor cortex transcranial magnetic stimulation elicited no response from leg muscles. The patient was unable to stand or walk independently or to voluntarily move his legs despite standard-of-care rehabilitation and additional intensive locomotor training.

The patient signed an informed consent for electrode implantation, stimulation, and physiological monitoring studies, which were approved by the University of Louisville (KY, USA) and the University of California, Los Angeles (CA, USA) institutional review boards.

Procedures

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. The study design for implantation and training of a patient with clinically motor complete SCI was discussed and assessed.

Before electrode implantation, the patient received 170 locomotor training sessions[14] over 26 months from Oct 19, 2007, to Nov 23, 2009, with bodyweight support and manual facilitation on a treadmill, resulting in 108 h of step training and 54 h of stand training, with no detectable change in electromyography (EMG) activity (figure 1). During manually facilitated stepping, sporadic EMG activity was noted bilaterally in the lower leg muscles most often in the medial hamstrings. No improvement was observed in EMG over the course of the training.

We used an epidural spinal cord stimulation unit (RestoreADVANCED, Medtronic, Minneapolis, MN, USA) to electrically stimulate the lumbosacral enlargement. A 16-electrode array (Specify 5-6-5, Medtronic) was implanted under fluoroscopic control at T11–L1 over spinal cord segments L1–S1 (webappendix p 2). We positioned the electrode array over the midline of the exposed dura. The location of the array was assessed during surgery with thresholds and amplitudes of EMG recorded from leg muscles[21] elicited by stimulation at 2 Hz. Multiple stimulations were tested using midline stimulation configurations, with each electrode pair 6 mm apart. Symmetry was tested by left and right side electrodes within the array. The electrode lead was tunnelled to a subcutaneous abdominal pouch where the pulse generator was implanted. 2 weeks after implantation, the position of the array was confirmed by the same stimulation protocols while the patient was lying supine (webappendix p 2).

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Varying combinations of stimulation were systematically assessed to obtain optimum efferent patterns for standing and stepping. Spinal cord stimulation was done during sessions that lasted up to 250 min. During these sessions, stimulation duration ranged from 40 to 120 min. Stimulation amplitudes ranged from 0·5 to 10·0 V and frequencies from 5 to 40 Hz, with either a 210 μs or 450 μs pulse width. The optimum 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. We measured the EMG activity from 14 leg muscles and hip, knee, and ankle joint angles.

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 stabilisation and weight shifting during stepping. Stand training was done with a device that comprised of vertical and horizontal bars surrounding the patient, which helped him to balance. Bungees were attached to the device to provide support only if the knees or hips flexed beyond the normal standing posture (webappendix p 3). Epidural stimulation was not provided outside laboratory sessions.

EMG, joint angles, foot switch, ground reaction forces, and bodyweight support (Innoventor, St Louis, MO, USA) data were collected at 2000 Hz with custom-written acquisition software (National Instruments, Austin, TX, USA). We recorded bilateral EMG (Motion Lab Systems, Baton Rouge, LA, USA) from the soleus, medial gastrocnemius, tibialis anterior, medial hamstrings, quadriceps, and gluteus maximus muscles bilaterally by 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. We recorded hip, knee, and ankle joint angles with a high-speed optical motion capture system (Motion Analysis, Santa Rosa, CA, USA). Ground

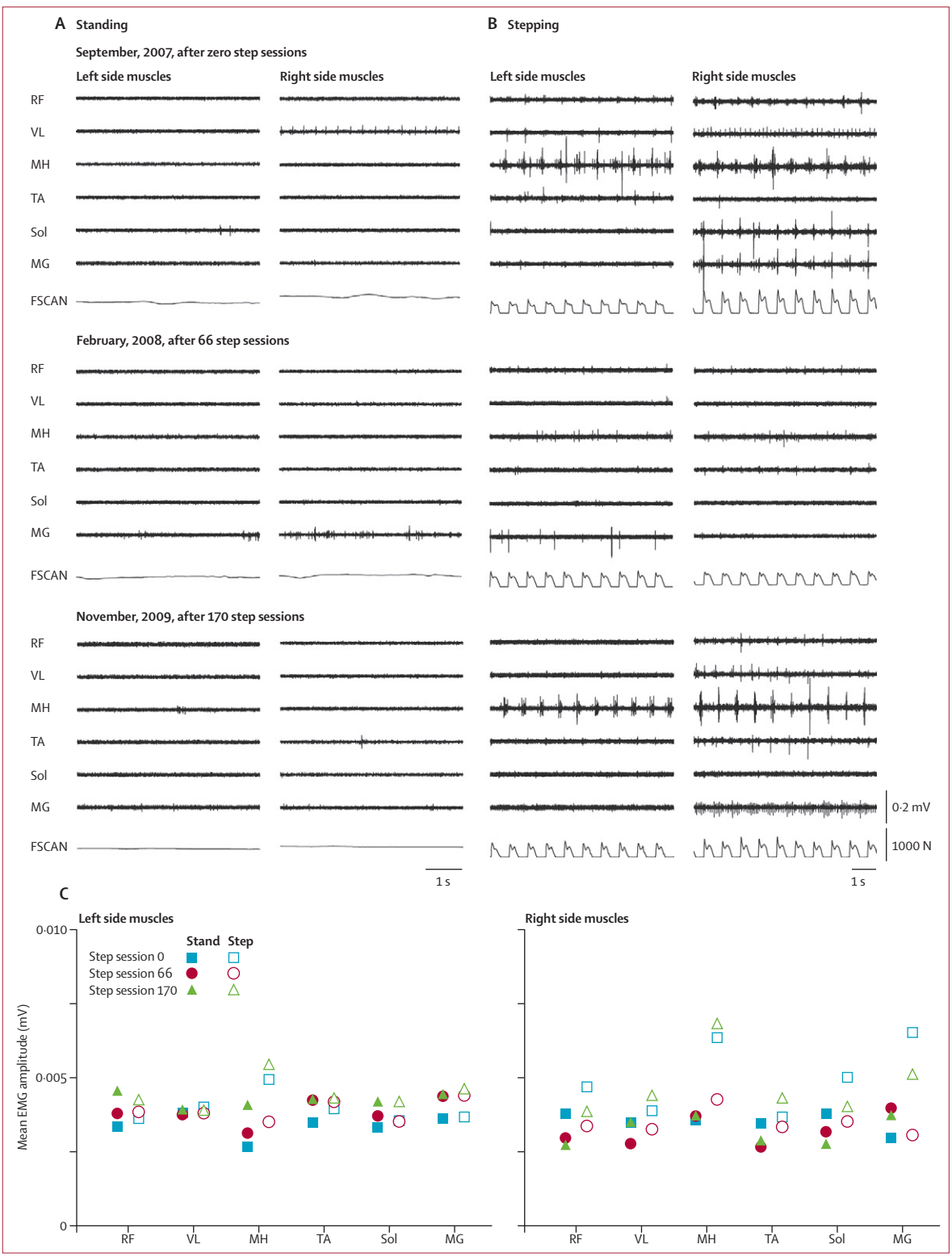

Figure 1: **Leg EMG activity during standing and stepping with bodyweight support before implantation**
EMG activity while standing (A) and stepping (B) with bodyweight support and manual facilitation on a treadmill before implantation. (C) Mean EMG amplitude for standing (solid symbols) and stepping (open symbols) at three timepoints (0, 66, and 170 step training sessions). EMG=electromyography. RF=rectus femoris. VL=vastus lateralis. MH=medial hamstrings. TA=tibialis anterior. Sol=soleus. MG=medial gastrocnemius. FSCAN=ground reaction force data.

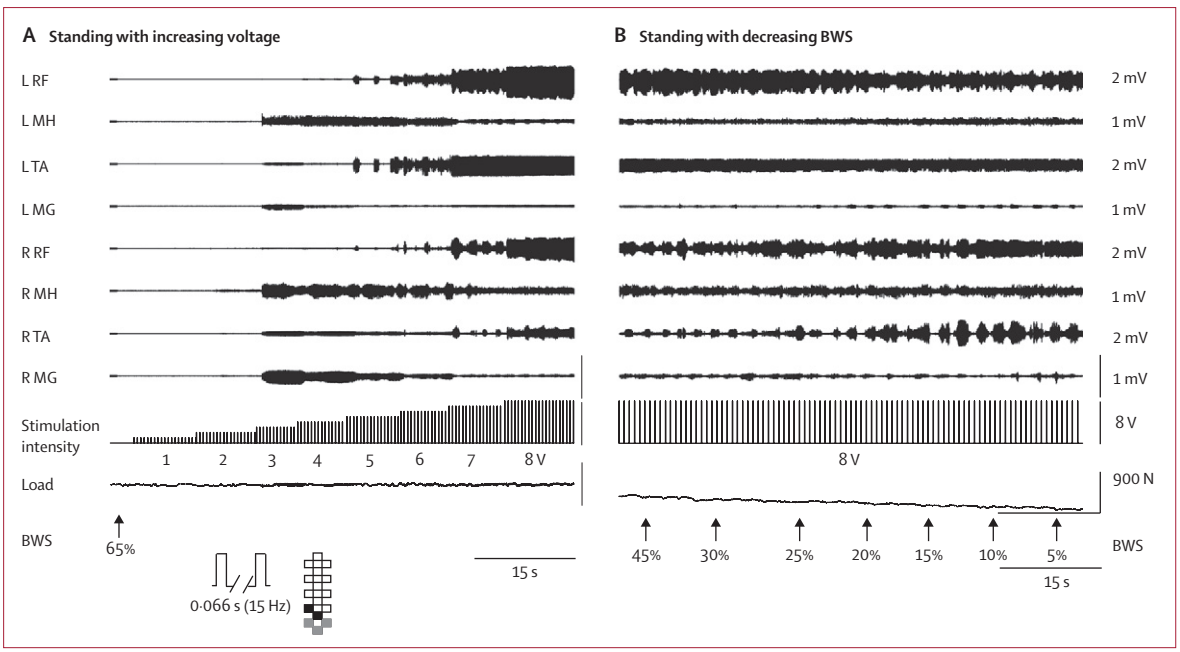

Figure 2: **Leg EMG activity with epidural stimulation of the lumbosacral segments during standing**
Please also see webvideo 1. (A) EMG activity increases in amplitude and becomes more constant bilaterally in most muscles as stimulation is increased in strength from 1 to 8 V (15 Hz) with a constant level of BWS (585/900 N [65%]). (B) Reduction of BWS from 45% to 5% (405/900 N to 45/900 N) and with constant stimulation (8 V; 15 Hz) changed the EMG amplitudes and oscillatory patterns differently among muscles. The array diagram at the bottom of (A) shows the stimulation configuration: anode electrodes are black and cathode electrodes are grey. The interpulse interval, which shows the stimulation frequency, is also shown at the bottom of (A). EMG=electromyography. BWS=bodyweight support. L=left. R=right. RF=rectus femoris. MH=medial hamstrings. TA=tibialis anterior. MG=medial gastrocnemius.

reaction forces were collected with shoe-insole pressure sensors (Tekscan, Boston, MA, USA).

Role of the funding source

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

Results

The mean total duration of stimulation was 54 min (SD 13) per session. The patient was always aware of the presence of the stimulation. The most common sensation was a tingling feeling localised to the electrode implantation site and in those muscles that were targeted for activation. Paraesthesia also routinely occurred in the trunk, hips, and legs and varied according to the stimulation intensity; however, these sensations never reached a level of substantial discomfort or pain and never precluded the use of epidural stimulation.

Epidural stimulation (15 Hz, 8 V) 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 with 65% (585/900 N) bodyweight support (figure 2; webvideo 1). The patient was able to sustain standing without manual facilitation while the amount of bodyweight support was progressively reduced to full weight bearing.

Transitioning from sitting to standing without bodyweight support altered the EMG activity during epidural stimulation even though the stimulation parameters remained constant (figure 3). When loading of the legs was initiated, EMG activity increased markedly and was sufficient to support the patient's bodyweight with minimum assistance needed from the trainers (webappendix p 3). During this transition, the stimulation remained constant with the same location, frequency, and intensity parameters (figure 3). The EMG activity was also modulated by the site and intensity of stimulation. The caudal (L5–S1) stimulation at higher intensities resulted in an optimal motor pattern for standing (figure 3). During caudal stimulation, there was a greater increase in the EMG amplitude bilaterally in the more proximal muscles than the more distal muscles, which were initially markedly reduced (figure 3; webvideo 2). Once the patient was standing, there was greater contraction of both flexors and extensors and proximal and distal muscles than when the patient was in transition from sitting to standing.

When the patient received epidural stimulation and intermittent manual facilitation during standing, postural responses occurred in leg EMG activity when he shifted his centre of gravity sagittally (figure 4). The EMG burst of the medial gastrocnemius increased with

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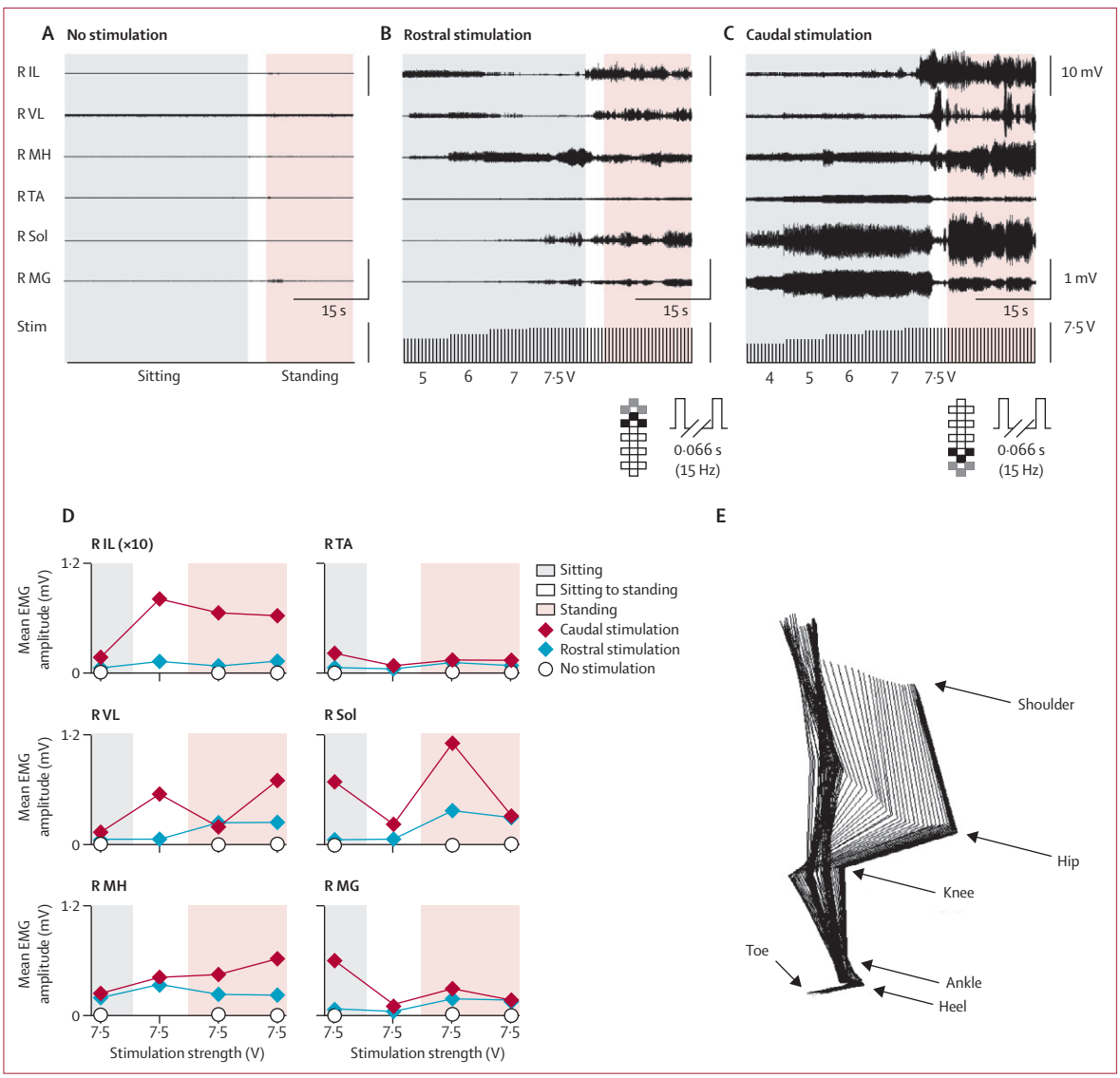

Figure 3: **Leg EMG activity during sitting and standing with and without epidural stimulation**
Transition (white) from sitting (grey) to standing (orange) with (A) no stimulation, (B) rostral (spinal segments L1–L2) stimulation (5–7·5 V, 15 Hz), and (C) caudal (spinal segments L4–S1) stimulation (4–7·5 V, 15 Hz). With increasing levels of epidural stimulation, EMG amplitudes were modulated in a tonic pattern while the patient remained sitting. During the transition from sitting to standing, amplitudes and patterns of EMG were modulated in all recorded muscles. (D) Mean EMG amplitude responses on the right side during sitting and standing with no stimulation, and rostral and caudal stimulation at 7·5 V (15 Hz). (E) Kinematic representation of sitting to standing transition with caudal stimulation (illustration at 10 frames per s; webvideo 2). Array diagrams at the bottom of (B) and (C) show the stimulation configurations; anode electrodes are black and cathode electrodes are grey. The interpulse interval, which shows the stimulation frequency, is shown at the bottom of (B) and (C). IL was measured with fine-wire electrodes. VL, MH, TA, Sol, and MG were measured with surface EMG. EMG=electromyography. R=right. IL=iliopsoas. VL=vastus lateralis. MH=medial hamstrings. TA=tibialis anterior. Sol=soleus. MG=medial gastrocnemius. Stim=stimulation intensity.

forward deviation, whereas backward deviation induced EMG bursts in the tibialis anterior. Standing bouts with tonic bilateral EMG activity routinely occurred for several minutes and increased in frequency and duration as training progressed (figure 4). After 80 sessions (webvideo 3), the patient could start and maintain continuous full weight-bearing standing without manual facilitation (maximum 4·25 min) with bilateral tonic EMG activity (figure 4; webvideo 3). Oscillatory patterns, often clonic-like, emerged and then were followed by little or no EMG activity, at which point the patient needed manual facilitation to maintain standing. This sequence occurred repeatedly during the 60-min standing sessions.

Epidural stimulation at 30–40 Hz and task-specific sensory cues were needed to generate locomotor-like patterns. Sensory cues for 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,

manual facilitation for stepping produced little or no EMG activity (figure 5). The EMG activity in the legs was markedly 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 5).

Supraspinal control of toe extension and ankle and leg flexion emerged only with epidural stimulation. This occurred after 80 stand training sessions (7 months after implantation; figure 6; webvideos 4 and 5). Voluntary movement was observed in both legs, although the stimulation parameters were different. Technical limitations of the stimulator prevented simultaneous movements of the legs. When the patient was instructed to flex (draw the leg upward), the toe extended, the ankle dorsiflexed and the hip and knee flexed with the appropriate muscle activation. When instructed to dorsiflex the ankle, the foot moved upward with tibialis anterior activation. When instructed to extend the hallux (big toe), the toe moved upward with activation of the extensor hallucis longus. The patient could consciously activate the appropriate muscles for the intended movement, and the timing of activation was closely linked to the verbal commands (figure 6).

After training and epidural stimulation, the patient also had functional gains in bladder and sexual function and temperature regulation (webappendix pp 3–4). The patient is now able to voluntarily void with minimum residual volume of urine and has reported improved sexual response and performance. The patient regained diaphoretic capability and the ability to tolerate extremes of temperature. Additionally, the patient reported that a sense of wellbeing and increased self-esteem enabled more frequent social interactions. The patient increased in weight by 18%, which was a result of an increased appetite and relative increase in lean body mass and decrease in total body fat, as measured with a dual-emission x-ray absorptiometry scan.

Discussion

With an epidurally implanted electrode array, we modulated the physiological state of the spinal circuitry to enable full weight-bearing standing in a patient with a chronic clinically motor complete SCI. This phenomenon was observed on the first attempt at standing. Epidural stimulation did not induce standing by directly activating motor pools, but enabled motor function by stimulating afferent fibres 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 occurred during sitting on some occasions, proprioceptive information associated with load-bearing positional changes was needed for effective standing. Dynamic changes in position during standing were accompanied by motor patterns that were needed to maintain upright posture without changing the epidural stimulation parameters. Intensive task-specific training combined with epidural stimulation extended the duration of periods of full weight-bearing standing that the patient could achieve.

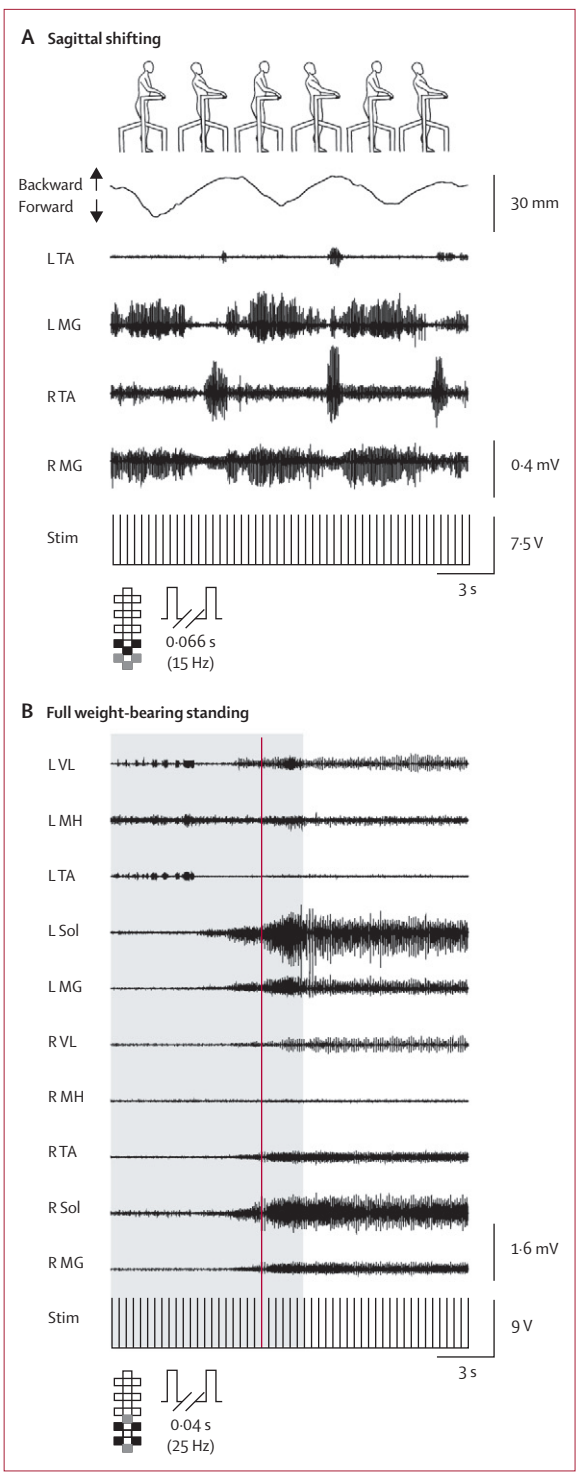

Figure 4: **Leg EMG activity during continuous full weight-bearing standing with epidural stimulation**
(A) EMG activity with epidural stimulation (7·5 V, 15 Hz) of the lumbosacral segments during weight shifting. Centre of gravity displacement in the sagittal plane showing backward and forward shifts is shown under the schematic diagram of the movement. (B) EMG activity with epidural stimulation (9 V, 25 Hz) during the transition from manually facilitated weight-bearing standing (grey) to full weight-bearing standing without manual facilitation (white). The red line shows the 3 s countdown by the patient to initiation of standing without manual facilitation (webvideo 3). Array diagrams at the bottom of (A) and (B) show the stimulation configuration; anode electrodes are black and cathode electrodes are grey. The interpulse interval, which shows stimulation frequency, is also shown at the bottom of each graph. L=left. R=right. TA=tibialis anterior. MG=medial gastrocnemius. VL=vastus lateralis. MH=medial hamstrings. Sol=soleus. Stim=stimulation intensity.

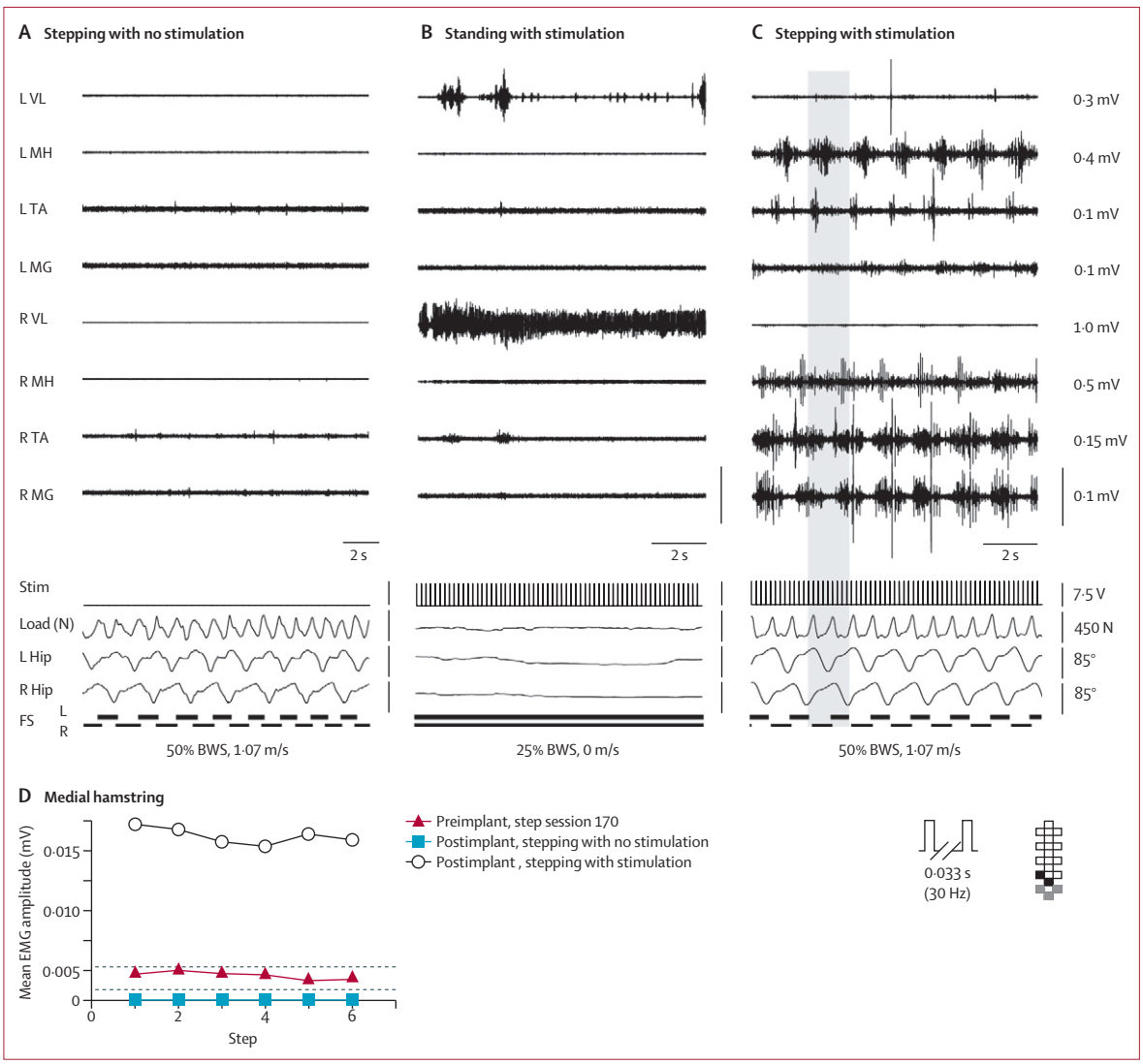

Figure 5: **Leg EMG activity during standing and stepping with bodyweight support and manual facilitation with and without epidural stimulation of lumbosacral segments**

The EMG patterns were modified by stimulation and by different patterns of sensory input. EMG activity during (A) manually facilitated stepping (450/900 N [50% BWS], 1·07 m/s) without stimulation, (B) standing (225/900 N [25% BWS], 0 m/s) with epidural stimulation (7·5 V, 30 Hz), and (C) manually facilitated stepping (450/900 N [50% BWS], 1·07 m/s) with epidural stimulation (7·5 V, 30 Hz). The grey shaded area shows one full step of the right leg. (D) Mean EMG activity for the MH during stepping after 170 step training sessions before implantation (see figure 1B), and during stepping after implantation with (C) and without (A) stimulation. The horizontal lines represent the baseline variation in the noise of each signal. The array diagram at the bottom of (C) shows the stimulation configuration; anode electrodes are black and cathode electrodes are grey. The interpulse interval, which shows stimulation frequency, is also shown at the bottom of (C). EMG=electromyography. L=left. R=right. VL=vastus lateralis. MH=medial hamstrings. TA=tibialis anterior. MG=medial gastrocnemius. Load=load cell reading. L Hip=left hip sagittal joint angle. R Hip=right hip sagittal joint angle. FS=footswitches. Stim=stimulation intensity.

The patient managed robust, consistent rhythmic stepping-like activity 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, epidural stimulation activates the dorsal root afferent fibres and, more likely at higher intensities, dorsal columns and additional spinal structures. Continuous stimulation modulated the physiological state of the spinal cord, which enabled sensory information processing that was closely linked to the functional task. This finding is of 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 reported that epidural stimulation can induce rhythmic activity in patients with clinically

motor complete SCI when lying supine.[18–21] Also, different sources of sensory input, such as hip extension and pinching of skin, can elicit rhythmic activity in the trunk and legs in patients with clinically motor complete SCI.[18,22–24] Manually facilitated standing[17] and stepping[15,16,27] can cause bilateral tonic EMG and rhythmic oscillatory

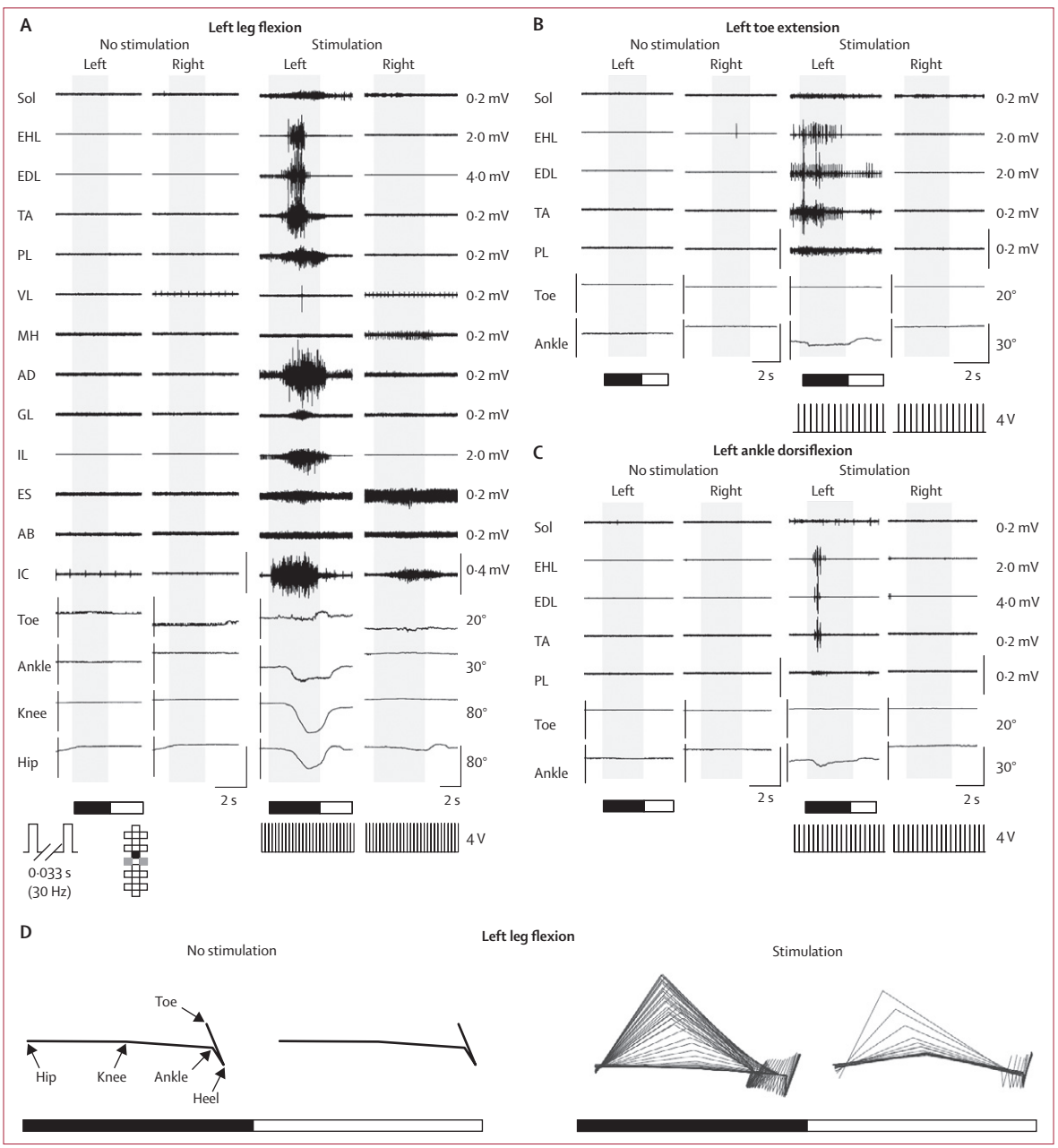

Figure 6: **EMG activity during voluntary leg movements in a supine position**

EMG and kinematics are shown for three different movement commands with (4 V, 30 Hz) and without stimulation. At the bottom of each graph the black bar (and grey shading within the graphs) shows the up command for (A) left leg flexion, (B) left toe extension, and (C) left ankle dorsiflexion. The white bar (and no shading within the graphs) shows the command to relax. Left and right EMG show the isolated control of the left side after the command. There was a delay between the onset of the EMG activation in some muscles after the up command, whereas the termination of the activation often occurred before the command to relax. IC EMG activation occurred as the patient inhaled during voluntary leg movement. The array diagram at the bottom of (A) shows the stimulation configuration: anode electrodes are black and cathode electrodes are grey. The interpulse interval, which shows stimulation frequency, is also shown at the bottom of (A). (D) Kinematic representation of leg movement (from graph A) with and without epidural stimulation (shown at 10 frames per s). Sagittal joint angles were measured for the toe (first metatarsal relative to foot), ankle, knee, and hip joints. EHL, EDL, and IL were measured with fine-wire electrodes. Sol, TA, PL, VL, MH, AD, GL, ES, AB, and IC were measured with surface EMG. Webvideos 4 and 5 show voluntary control attempts with and without stimulation, respectively. EMG=electromyography. EHL=extensor hallucis longus. EDL=extensor digitorum longus. IL=iliopsoas. Sol=soleus. TA=tibialis anterior. PL=peroneus longus. VL=vastus lateralis. MH=medial hamstrings. AD=adductor magnus. GL=gluteus maximus. ES=erector spinae. AB= rectus abdominus. IC=intercostals. Stim=stimulation intensity.

Panel: Research in context

Systematic review

We searched PubMed with no date restrictions set for studies on electrical, pharmacological, or electromagnetic stimulation of the spinal cord. This search identified studies ranging from in-situ isolated spinal cord of the lamprey to people with implanted epidural electrodes. Each 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 (in vivo *vs* in situ), and use of proprioceptive input. In the studies that are most closely related to this study, epidural stimulation of the lumbosacral spinal cord of spinally complete (American Spinal Injury Association impairment scale grade A) patients induced an oscillatory movement in the legs, and the pattern of movement changed with different stimulation parameters.[20,21]

Interpretation

Spinal cord circuitry in human beings can be induced to generate cyclic movements of the legs without supraspinal input in response to tonic stimulation of peripheral afferents or direct stimulation of the spinal cord. The importance of these findings have been interpreted as providing evidence for central pattern generation—ie, oscillations induced without input from the brain or from peripheral afferents. The data in this study show 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, emphasising the key role of sensory input in posture and locomotion rather than its independence from sensory input. Second, we show the enabling phenomenon of epidural stimulation, whereby moderate 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. Third, that after months of stimulation and training, voluntary control of leg movement emerged, but only when enabled by modest levels of epidural stimulation. These findings 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.

EMG, respectively, in many patients with clinically motor complete SCI, showing the importance of providing task-specific sensory cues. Our study provides evidence that in patients with SCI, sensory input enabled by epidural stimulation might serve as a spinal circuitry controller during standing and manually facilitated stepping in the absence of clinically detectable supraspinal input (panel).

The patient in this study was eventually able to voluntarily achieve toe extension, ankle dorsiflexion, and leg flexion in the presence of epidural stimulation. In patients with a motor incomplete SCI who have some ability to voluntarily move their legs, a common phenomenon is the loss of specific control of selected muscles.[27] In this study, the activated motor pools were appropriate for the intended movement. 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. Two possible mechanisms are: 1) epidural stimulation provided excitation of lumbosacral interneurons and motorneurons,[28,29] which, combined with the weak excitatory activity of residual descending axons, achieved a level of excitation that was sufficient to activate motorneurons; and 2) axonal regeneration or sprouting might have been induced via activity-dependent mechanisms over a period of 7 months. From a neurobiological and clinical perspective, that this supraspinal control was manifested only in the presence of continuous tonic epidural stimulation is important. Seemingly, conscious control was regained by increasing the level of spinal interneuronal excitability with stimulation to a crucial, but subthreshold level, allowing control via descending pathways.

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

This case study supports the proof of principle that human beings 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 suggest that epidural stimulation has potential as a clinical intervention in combination with task-specific training for the recovery of function after SCI and other neurological disorders.[30] Improvements in array and stimulation technology will be needed for practical application of epidural stimulation, and the addition of pharmacological drugs might further improve functional recovery.

A key limitation of this study is that data were from one research patient and thus generalisability to a population should be cautioned. There were also technical limitations of the stimulator that prevented us from differentially manipulating parameters (voltage and frequency) needed to optimise the completion of different motor tasks. A third limitation was the inability to effectively assess which anatomical connections still existed after the injury and after the stimulation period.

Contributors

SH, YG, JB, CA, and VRE designed the study. JH did the surgical implantation. SH, CA, YC, and CF did the electrophysiological testing during surgery. SH, CA, CF, and AW, collected data and developed the figures. YC designed the data collection system. YG and ER also developed the figures. SH and VRE supervised the study. All authors interpreted the data and wrote the manuscript.

Conflicts of interest

SH, YG, JH, JB, CA, and VRE have a provisional patent pending for an electrode array stimulator system. All other authors declare that they have no conflicts of interest.

Acknowledgments

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