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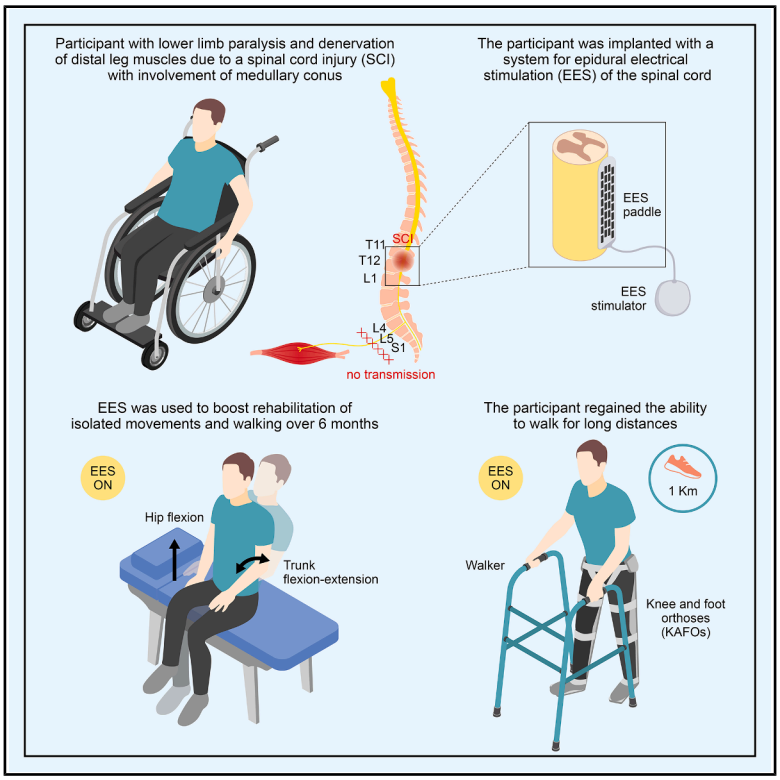
Case report

Epidural electrical stimulation facilitates motor recovery in spinal cord injury involving the conus medullaris: A case study

Graphical abstract



Highlights

- Spinal stimulation plus rehabilitation boosts recovery after conus medullaris injury
- Pre-op exams are key to assess whether the lesion caused peripheral damage
- Tailored treatment may optimize motor function recovery

Authors

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In brief

Albano et al. show how epidural electrical stimulation can be used even in spinal cord injury patient medullary cone involvement to enhance lower limb motor functions. They also demonstrate that motor recovery was combined with a significant improvement in pain, quality of life, cognition, mood, and behavior.

Translation to Patients

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Case report

Epidural electrical stimulation facilitates motor recovery in spinal cord injury involving the conus medullaris: A case study

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CONTEXT AND SIGNIFICANCE Over half of patients with thoracic spinal cord injury (SCI) have T10–T12 vertebral and conus medullaris involvement, often leading to severe paralysis. Recent studies have shown that epidural electrical stimulation (EES), combined with tailored rehabilitation, can restore lower limb motor function after SCI by activating the dorsal spinal roots. However, previous EES trials only included patients with injuries above T10, avoiding potential damage to the roots controlling the legs. Researchers at the MINE Lab (Italy) now provide the first evidence supporting the feasibility and potential efficacy of EES in lower thoracic injuries. In their study, a patient with T11–T12 SCI showed improved motor function, reduced pain, and enhanced quality of life.

SUMMARY

Background: Emerging research increasingly supports that epidural spinal cord electrical stimulation (EES) combined with neurorehabilitation can improve motor recovery in spinal cord injury (SCI) subjects. Patients with lesions involving the medullary cone may be challenging to treat with this approach, probably due to potential peripheral nervous system damage, leaving the open question of whether this large population may benefit from EES.

Methods: A T11–T12 SCI patient, with medullary cone involvement, underwent EES implant in a clinical trial (NCT05926843). During three months of testing, we determined optimal stimulation protocols for improving isolated movements and integrated them to reinstate independent walking with a walker.

Findings: EES substantially boosted hip flexor, spinal erector, and abdominal muscle contraction, improving the patient's performance in isolated movements. Over three months of combining continuous subthreshold EES with personalized rehabilitation, the patient progressed from being unable to walk to overground ambulation using a two-wheeled walker and bilateral knee and foot orthoses. At the time of hospital discharge, the

patient managed to cover 58 m in the 6-min walking test and completed the 10-meter walking test in 40.29 s. Six months after EES implant, the patient was able to walk independently for 1 km with a walker.

Conclusions: These results underscore the potential of neurorehabilitation protocols integrating EES also for patients with medullary cone lesions and pave the way for new rehabilitation prospects.

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INTRODUCTION

Spinal cord injury (SCI) can lead to complete or incomplete loss of sensory, motor, and autonomic functions, thus reducing independence in everyday life activities.[1] According to the SCI level and severity, the extent to which motor control and sensation are affected may vary. Thoracic SCI often results in paraplegia and loss of trunk control, impairing the ability to walk and stand independently.[2,3] The use of epidural electrical stimulation (EES) of the spinal cord can restore or potentiate muscle movements, and when combined with neurorehabilitation, it can lead to unprecedented improvements in motor functions both in complete and incomplete SCI patients.[4–6]

While several studies employing EES for movement restoration have been conducted, all of them focus on SCI patients with lesions higher than T10 (Table S1),[2,4,5,7–10] thus excluding lower thoracic segment (T10–T12) lesions, which account for more than 50% of thoracic SCIs.[11] One possible reason is that these lesions can be associated with injury to the conus medullaris and possibly cause damage to the spinal roots related to the T12-S5 dermatomyotomes targeting the lower limbs. This condition can reduce the efficacy of EES to elicit movements since its mechanisms are based on the recruitment of proprioceptive fibers linked through excitatory synapses to motoneurons at the level of the target root.[12,13] However, EES could provide some benefits in SCI lesions involving the medullary cone if the denervation is not too severe and/or pervasive, as it could restore some limited motor functions that could facilitate the implementation of effective rehabilitation protocols.

To test this hypothesis, we recruited a T11–T12 SCI patient who was unable to walk, stand, or voluntarily move his legs despite two 6-month cycles of intensive rehabilitation in a dedicated spinal recovery unit. He was enrolled in a clinical trial aimed at investigating the effects of EES combined with locomotor training on the recovery of motor function in 10 SCI patients (clinicaltrials.gov: NCT05926843). Here, we provide data from a single patient as this is the only individual with a conus medullaris lesion included in this trial so far. More specifically, we report first information on motor, pain sensation, and quality of life changes over 6 months of treatment, showing the feasibility and potential clinical benefits associated with this procedure in certain SCI cases involving the conus medullaris.

RESULTS

Selective activation of trunk and hip muscles leads to improved isolated movements

The enrolled subject was a 33-year-old male patient with a T11–T12 SCI (Figure 1A) that occurred 4 years before, classified as grade C according to the American Spinal Injury Association impairment scale. At lower limb motor evaluation, only the presence of traces of contraction in the hip flexor and extensor muscles bilaterally was detected, 1/5 according to the Medical Research Council (MRC); no voluntary muscle contractions were observed in the other muscles (MRC 0/5). The preoperative neurophysiological evaluation showed, in addition to the central nervous system damage, signs of denervation from L4 to S1 nerve roots bilaterally (Figure 1A), also indicating a peripheral disorder, hindering the transmission of electrical signals from the dorsal horn of the spinal cord to some muscles (see STAR Methods, experimental model and study participant details).

A commercial EES with a 32-contact paddle, routinely used for chronic pain, was implanted between T11 and L1 (Figure 1B). We then characterized our ability to elicit stimulation responses at the level of trunk muscles (erector spinae and rectus abdominis) and hip flexors and extensor muscles (bilateral iliopsoas, rectus femoris, gluteus medius, and gluteus maximus), identifying contacts principally activating trunk muscles and hip flexors over hip extensors (Figures 1B and S1).

Once optimal stimulation programs were identified (see STAR Methods, EES protocols section for additional description), the neurorehabilitation protocol integrating EES into isolated movements and functional tasks started. Figure 1C shows the rehabilitation timeline, with the main activities highlighted for each time interval (see STAR Methods, neurorehabilitation protocol section and Figure S2 for additional description).

Across the rehabilitation protocol, the combination with EES allowed the patient to train specific isolated movements achieving functional improvements. Specifically, we found increased range of motion (RoM) in bilateral hip flexion (Figure 1D, mixed effects linear model, $p < 0.001$), increased ability to displace his center of mass in the antero-posterior direction without losing balance from a seated position (Figure 1E, mixed effects linear model, $p < 0.001$), and increased RoM in trunk flexion (Figure 1F, mixed effects linear model, $p < 0.001$) when the stimulator was "on" with respect to "off" condition. Notably, in the EES-on condition, the subject always managed to produce a "full" trunk flexion movement (here defined as RoM >60°), while this was often not the case in the off condition. While hip flexion RoMs increased longitudinally in both the on and off conditions (mixed effects linear model, $p < 0.001$), there was no significant longitudinal increase in trunk flexion RoM (mixed effects linear model, $p = 0.28$) and a statistically significant but negligible effect on stability (mixed effects linear model, $p < 0.01$).

Independent overground walking can be reinstated using EES

After the first 3 weeks of isolated movements training, we started a walking rehabilitation protocol using the Moonwalker

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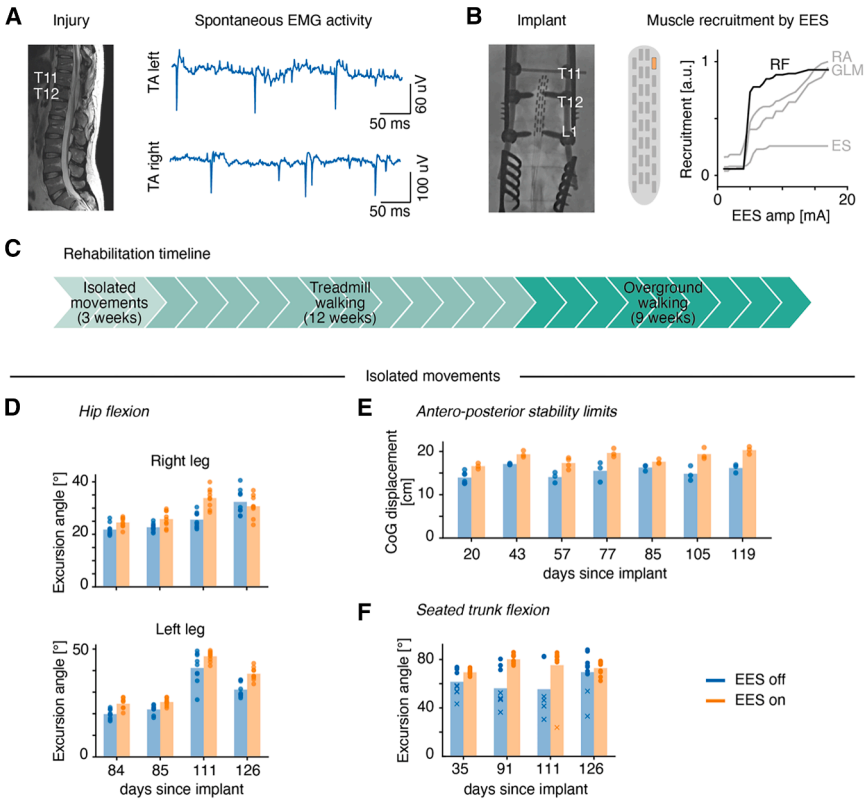

Figure 1. Patient's characteristics and isolated movements with EES

(A) Left: preoperative spine MRI showing T11–T12 myelopathy. Right: needle electromyographic evaluation of right and left tibialis muscle at rest shows positive sharp waves and fibrillation potentials and expression of spontaneous depolarization of muscle fibers due to denervation.

(B) Left: X-ray imaging of electrode paddle after surgical implantation. Right: muscle recruitment following single-pulse EES applied with an example stimulation channel.

(C) Rehabilitation timeline highlighting the duration of the isolated movements, treadmill walking, and overground walking periods.

(D) Excursion angles of the patient's femur from seated position during voluntary hip flexion of right and left legs.

(E) Displacement of the patient's center of gravity in centimeters during seated antero-posterior stability limits assessments.

(F) Seated trunk flexion assessment results in terms of trunk excursion angle.

In (C)–(F), each point represents a repetition of the movement, and bars represent the averages of the points from a single set (same condition, same day). In (F), both points and crosses represent repetitions of the movement, and bars represent the averages across both points and crosses from a single set. Crosses represent repetitions where the excursion angle did not reach 60°. ES, erectus spinae; GLM, gluteus maximus; RA, rectus abdominis; RF, rectus femoris; TA, tibialis anterior.

(https://khymeia.com/en/products/moonwalker/), an omnidirectional treadmill equipped with body weight support (BWS), starting with full BWS and a speed of 0.05 m/s. The subject was equipped with bilateral knee and foot orthoses (KAFOs) to compensate for the lack of knee extension, plantar flexion, and dorsiflexion activation. Figure 2A shows how BWS was progressively decreased while increasing belt speed, reaching a maximum speed of 0.3 m/s and a minimum BWS of 20%. Furthermore, the patient showed a substantial improvement in walking endurance, with the EES condition always guaranteeing higher resistance (Figure 2B). Figure 2C shows that EES resulted in a significantly lower amplitude of trunk oscillation, maintained longitudinally, indicating a pivoting movement on the leg in stance to compensate for the lack of adequate hip flexion in the swing phase. With EES switched on, the additional push on hip flexion allowed the reduction of this compensation strategy.

Three months after EES implant, the patient began walking overground with the aid of a walker and bilateral KAFOs, after a short period of training between the parallel bars. In the 10-m walk test (10-MWT), the improvement of the patient's times was substantially higher for the on condition compared to the off condition (EES: −20.53 ± 3.03 s between one testing day and the following; off: −14.80 ± 2.42 s between one testing day and the following; results reported in the form of [mean slope] ± [standard error]), with significantly lower times for the last two assessments (Figure 2D, mixed effects linear model, $p < 0.01$). In the 6-min walk test (Figure 2E), as well as in endurance test (Figure 2F), he showed a progressive improvement in walking distance with training. Six months after EES implant, the patient was able to complete an endurance test of 1 km. In Video S1, the progression of the subject's walking can be seen across the duration of the trial.

The neurorehabilitation enabled by our EES protocols showed lasting effects in muscle strength (Figure 2G) and pain sensation (Figure 2H). Furthermore, at the last follow-up, the patient showed improvement even in neuropsychological tests, documenting enhancement in daily life activities, cognition, mood, and behavior (Table S2).

DISCUSSION

The present work provides the first evidence that patients who suffered from an SCI with medullary cone involvement can benefit from EES, even when associated peripheral degeneration affects several lower limb muscles. EES can be used to instantaneously increase muscle strength through stimulation of the spared roots and can lead to reinstating independent walking, possibly with the help of assistive orthoses and devices. Moreover, standing and ambulation in paraplegic patients can help prevent long-term secondary medical complications such as delaying scoliosis due to wheelchair use and the associated risk to internal organs, osteoporosis due to reduced weight-bearing activities, poor blood circulation, and an increased risk of blood clots.[14] Preoperative neurophysiological examinations are crucial to define whether peripheral damage has followed

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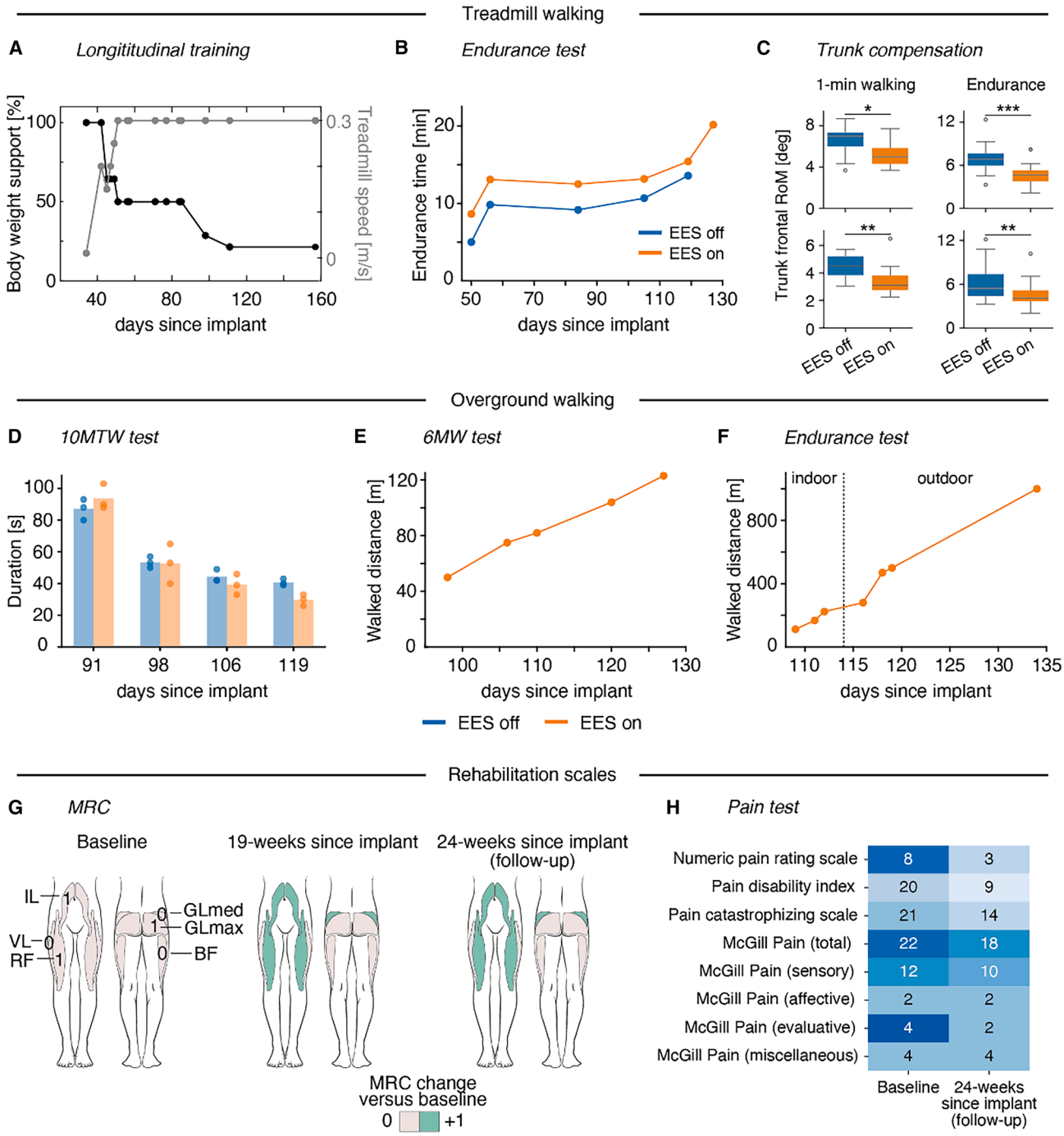

Figure 2. Gait rehabilitation and longitudinal assessment

(A) Percentage of body weight support (black line) and belt speed (gray line) during treadmill walking assessment and rehabilitation across in hospital rehabilitation.

(B) Endurance in minutes during treadmill walking in EES on and off conditions; the body weight support and treadmill belt speed corresponding to each data point are shown in (A).

(C) Trunk compensation during treadmill walking in EES on and off conditions measured as trunk range of motion (RoM) in frontal plane. Results are shown for two repetitions of 1-min walking (performed on the same day, 42 days since implant) and for two repetitions of endurance test performed in two different days (top, 119 days since implant; bottom, 120 days since implant).

(D) Time to complete the 10-MWT in EES on and off conditions. Each point represents a repetition of the assessment, and bars represent the averages of the points from a single set (same condition, same day).

(legend continued on next page)

the lesion and which muscles have been involved or spared, with the aim of precisely defining the potential clinical outcome.

In our case, we knew that it would not be possible to achieve movement of the muscles innervated by nerve roots below L3 (Figure 1A). Thus, we targeted the abdominal and paravertebral muscles to enhance trunk control and activated them concurrently with hip flexors to enable walking with bilateral KAFOs. The motor results achieved were accompanied by a significant improvement in pain, quality of life, cognition, mood, and behavior tests at 6-month follow-up.

EES targeting spared spinal roots provides an instantaneous significant advantage in isolated movements (Figures 1D–1F) and walking kinematics, and thus facilitates rehabilitative training leading to long-term modifications in muscle strength (Figure 2G) and functional abilities (Figures 2D–2F). EES may play a fundamental role in enabling such longitudinal improvements; in fact, following the injury before enrolling in our clinical trial, our patient was involved in intensive rehabilitation programs during two periods of 6 months each, without regaining the ability to independently stand or walk. Rehabilitation without EES was therefore focused on the trunk and upper body in the hope of increasing independence in everyday life. The previous rehabilitation may explain the absence of significant longitudinal effects in trunk stability found in the present study, even though EES produced an instantaneous increase in functionality (Figures 1E and 1F).

EES produced systematic and statistically significant effects on isolated movements (Figures 1D–1F), even though at any given point in time the instantaneous effect was not always large. Nonetheless, the additional neural drive added by EES was sufficient to train the patient to stand and ambulate starting with full BWS, gradually reducing it (Figure 2A) and finally transitioning to independent standing and walking overground in outdoor settings (Figure 2F). As the results of the 10-MTW (Figure 2D) show, there was a process of learning how to exploit the additional drive provided by stimulation, which reduced compensation at the level of the trunk (Figure 2C), and thus led to a more natural gait, leading to a dramatic increase in the patient's endurance (Figures 2B and 2F), allowing more and more intense rehabilitation, which could in turn produce long-term improvement in hip flexor strength (Figure 2G).

Further tests will be necessary to confirm the promising results of this case study and establish the use of EES in cases of conus medullaris lesions as clinical practice.

Limitations of the study

The limitations of this study include its case report design and the need for further research to gain a better understanding of the effect of the EES and rehabilitation. However, this report only presents the results from the first patient with a lesion involving the conus medullaris of the study Neuro-SCS-001; group analyses must be expected to be able to draw more clear and solid conclusions in terms of outcomes like safety, feasibility, and efficacy.

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Silvestro Micera (Silvestro.Micera@santannapisa.it).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- All data reported in this paper will be shared by the lead contact upon request.
- This paper does not report original code.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

ACKNOWLEDGMENTS

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AUTHOR CONTRIBUTIONS

L.A., D.E., F.A., S.R., E.L., S.I., P.M., and S.M. conceived and designed this study. L.A., D.E., F.A., S.R., E.L., C.C., U.D.C., V.F., and L.T. collected the data. S.R., E.L., D.E., F.A., C.C., V.F., L.T., and S.M. performed the analyses. L.A., D.E., and P.M. had unrestricted access to all data. L.A., D.E., F.A., S.R., and E.L. wrote drafts of the manuscript and interpreted the findings. P.M. and S.M. critiqued and revised the manuscript. All the authors read the manuscript, provided feedback, and approved the final version.

DECLARATION OF INTERESTS

L.A. receives or has received research support from Boston Scientific and Fondazione Cariplo. S.M. holds patents on spinal cord stimulation technologies. P.M. receives or has received research support from Boston Scientific. M.F. is editor-in-chief of the *Journal of Neurology*, associate editor of *Human Brain Mapping*, *Neurological Sciences*, and *Radiology*; has received compensation for consulting services from Alexion, Almirall, Biogen, Merck, Novartis, Roche, and Sanofi and for speaking activities from Bayer, Biogen, Celgene, Chiesi Italia SpA, Eli Lilly, Genzyme, Janssen, Merck-Serono, Neopharmed Gentili SpA, Novartis, Novo Nordisk, Roche, Sanofi, Takeda, and TEVA; has participated in advisory boards for Alexion, Biogen, Bristol-Myers Squibb, Merck, Novartis, Roche, Sanofi, Sanofi-Aventis, Sanofi-Genzyme, and Takeda; has participated in scientific direction of educational events for Biogen, Merck, Roche, Celgene, Bristol-Myers Squibb, Lilly, Novartis, and Sanofi-Genzyme; and receives research support from Biogen Idec, Merck-Serono, Novartis, Roche,

(E) Walked distance during the 6-MWT, each point representing an assessment.
(F) Walked distance during overground endurance tests, each point representing an assessment. The dotted line separates tests performed indoors and outdoors.
(G) MRC scores to lower limb muscles not involved in the peripheral denervation process; colors indicate variations with respect to admission values (baseline).
(H) Variation in pain evaluation scores from the preoperative to the 6-month follow-up. The color bar spans each different scale from its minimum (0) to its maximum (different for each scale); the scores are written in the table cells.

the Italian Ministry of Health, the Italian Ministry of University and Research, and Fondazione Italiana Sclerosi Multipla. F.A. is associate editor of *NeuroImage: Clinical*; has received speaker's honoraria from Biogen Idec, Italfarmaco, Roche, Zambon, and Eli Lilly; and receives or has received research support from the Italian Ministry of Health, the Italian Ministry of University and Research, AriSLA (Fondazione Italiana di Ricerca per la SLA), the ERC, the EU Joint Programme—Neurodegenerative Disease Research (JPND), and Foundation Research on Alzheimer Disease (France).

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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  - EES protocols
  - Neurorehabilitation protocol
  - Motor assessment protocol
  - Clinical assessment
  - Neuropsychological evaluation
- ADDITIONAL RESOURCES

SUPPLEMENTAL INFORMATION

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Other		
Epidural electrical stimulation device	Boston Scientific Spa, Marlborough, USA	https://www.bostonscientific.com/
Omnidirectional treadmill	Moonwalker-Khymeia S.R.L., Padova, Italy	https://khymeia.com/
Biofeedback	OAK system-Khymeia S.R.L., Padova, Italy	https://khymeia.com/
Intraoperative electromyography	Inomed Medizintechnik GmbH, Emmendingen, Germany	https://www.inomed.it/

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

All experiments were carried out as part of an ongoing clinical feasibility study which investigates the effects of EES combined with locomotor training on the recovery of motor function in 10 patients with lower limbs paralysis and chronic neuropathic pain after SCI (ID NCT05926843, www.clinicaltrials.gov).

The participants signed a written informed consent before their participation. The study was approved by IRCCS Ospedale San Raffaele ethical committee (protocol approved in October 2022, project ID Neuro-SCS-001) and was conducted in accordance with the Declaration of Helsinki. All surgical and experimental procedures were performed at IRCCS Ospedale San Raffaele and Vita-Salute San Raffaele University, Milan, Italy, in collaboration with the BioRobotics Institute and the Interdisciplinary Health Sciences Research Center, Scuola Superiore Sant'Anna, Pisa, Italy.

Briefly, the study involves clinical, neurophysiological, neuroimaging and neuropsychological evaluations before surgery, the EES surgical procedure, a pre-rehabilitation step for an initial setting of stimulation parameters to induce lower limb motor activation and a subsequent rehabilitation training for at least 8 weeks.

After discharge, the participants are examined at IRCCS Ospedale San Raffaele institute monthly for clinical assessment and one-day locomotor training. At the 6th month, patients undergo a review of clinical history, physiological anamnesis and neurological, neurophysiological, neuro-psychological and neuroimaging assessments.

A 33-year-old male patient with T11-T12 SCI, classified as grade C (motor and sensory incomplete) according to the ASIA impairment scale (AIS), was enrolled in November 2023 in our trial (NCT05926843) upon signing an informed consent. He had a history of SCI occurred 4 years earlier, resulting in a T12 vertebral fracture with T11-T12 myelopathy. Following the injury, he underwent an emergency T10-L2 fusion and decompression of the spinal canal. The surgery was followed by two intensive rehabilitation admissions in a dedicated spinal recovery unit, each lasting 6 months. After completing conventional rehabilitation, the patient was unable to walk, stand or voluntarily move his legs.

At the time of trial enrollment, he was classified as AIS C only due to the presence of traces of contraction in the proximal hip flexor and extensor muscles bilaterally (MRC grade 1); no voluntary muscle contractions (MRC grade 0) were observed in the other muscles of the lower limbs.

At preoperative neurophysiological assessment, cortical somatosensory evoked potentials were absent for lower limb stimulation (tibial nerve) and motor evoked potentials were absent when derived from abductor allucis and tibial muscles bilaterally. On the contrary, a reduced in amplitude but repeatable motor evoked response was recordable from adductor muscle group bilaterally. So, the corticospinal output was partially preserved up to L3 level. The electromyographic evaluation evidenced an almost complete peripheral axonal/neuronal damage of roots/anterior horn from L4 to S1 with persistent mild signs of acute denervation (i.e., fibrillation potentials). Marked but partial axonal chronic damage was observed in the muscles innervated by L2-L3 roots/anterior horn bilaterally. Summing up, the patient had a severe central and peripheral damage almost complete from L4 to S1, and partial at L2-L3 level.

The patient did not have fasciculations, cramps, or involuntary movements in the lower limbs. At sensory examination, both light touch sensation and pin-prick sensation were altered below the level of SCI bilaterally (a score of 1 was recorded). He also complained of lower limbs neuropathic chronic pain (burning dysesthesia and paresthesia in both lower limbs).

The patient was able to independently transfer from a supine to a seated position and from a seated to a supine position, with compensatory movements. He also had neurogenic bladder and bowel function, necessitating self-catheterization and bowel irrigation procedures.

METHOD DETAILS

Neurosurgical procedure

The patient underwent surgical procedure of lumbar laminectomy, paddle lead insertion and internal pulse generator (IPG) implant under general anesthesia in November 2023. In detail, after placing the patient in a prone position, an intraoperative X-ray fluoroscopy (Artis Pheno Robotic C-arm Angiography system, Siemens Healthineers GmbH, Erlangen, Germany) was performed to map the spine anatomy of the patient and to guide the incision.

An approximately 6-cm midline skin incision was performed, the muscle fascia was opened, and then the paraspinal muscles were retracted bilaterally. Excision of the midline ligamentous structures and laminectomy between L2 and L3 was performed, and the dura mater was exposed to enable the insertion of the paddle in the epidural space. A 67 mm long, 32-contact paddle with contact spacing of 3 mm was used (CoverEdge X 32 lead, Boston Scientific Spa, Marlborough, USA). It was placed over the midline and advanced rostrally to the target location (intervertebral disc between T11 and T12 with the aim of recruiting the abdominal and erector spinae muscles through the more rostral paddle contacts). Electromyography of lower limb muscles was intraoperatively conducted using the Neuroexplorer 2019 monitoring (Inomed Medizintechnik GmbH, Emmendingen, Germany) while EES was applied through the stimulation system (Boston Scientific Spa, Marlborough, USA) connected to the implanted paddle. Single EES pulses (2 Hz) were delivered at increasing amplitude to elicit muscle responses that were recorded from subdermal or intramuscular needle electrodes. After the neurophysiological evaluations, the paddle was secured using anchors sutured to the ligaments, and a final X-ray fluoroscopy was then acquired to register the final position of the paddle. Thereafter, an IPG (Wavewriter alpha 32, Boston Scientific Spa, Marlborough, USA) was inserted into a subcutaneous pocket in the participant's abdomen. The paddle array cables were then tunneled between both openings and connected to the IPG.

EES protocols

First, we applied single stimulation pulses from each paddle contact in turn, with a frequency of one pulse every 0.5 s, thus allowing muscle evoked potentials recorded through superficial EMG to remain separated. We set 300 μs of pulse-width, and increased amplitude every 5 s, from no current injected to the point where most muscles seemed to have reached a saturation of the evoked motor and electrical responses. We computed the average peak-to-peak amplitude of the recorded evoked muscle responses for each amplitude and muscle and normalized using the maximum peak-to-peak for each given muscle. To deal with noise in the recordings, we assumed the curves to be monotonic and corrected accordingly. The resulting recruitment curves are shown in Figure S1.

These recruitment curves were employed to guide the formulation of the stimulation protocols for isolated movements (hip flexion, abdominal contraction, trunk stability) and walking. For bilateral hip flexion we looked at maximally selective recruitment of RF, obtained with cathodes in electrodes 2 (for the left side) and 25 (for the right side). For RA activation, cathodes in electrodes 2 (for the left side) and 26–27 (for the right side) produced maximally selective activation, and for trunk stability the electrodes eliciting RA contraction were activated concurrently with the ones producing maximal ES contraction, namely 25 for the left side and 27 for the right side. Walking was then obtained by activating concurrently the electrodes for trunk stability and hip flexion.

Starting with these contacts we progressively improved the stimulation protocols following indications from the clinical team and feedback from the patient until we got to the final stimulation configurations. While isolated movements were generally better when the stimulation frequency was set at 30 Hz, walking was improved when a frequency of 40 Hz was employed. In all cases, 300 μs pulse-width was employed. Amplitudes were adjusted on a day-to-day basis with left side muscles requiring in general lower stimulation amplitudes than right side muscles to be activated.

Stimulation protocols were kept continuously on during the tasks at intensity levels that were modulated according to the posture of the patient below motor threshold so that the patient could modulate muscle activation through voluntary contraction when desired.

Neurorehabilitation protocol

The patient performed physical training for 3 h per day for 5-day a week for 4 months.

The main objectives were to recover activation of residual musculature of the lower limbs, to improve the control of the trunk, to reach and maintain the standing position with the assistance of orthotic devices, to regain the ability to walk. After identifying EES programs for right and left hip flexor muscles, the patient was trained to activate his left and right hip flexors against gravity from a supine position, with the hip extended and the EES turned on. Initially, training began with only visible contractions of the hip flexors and gradually progressed to performing the movement against gravity. The exercises were conducted from an advantageous position for the hip flexors, where they were stretched in a supine position with the hip extended and the knee flexed.

The trunk training involved several motor control exercises with a biofeedback using Virtual Reality and Inertial Measurement Units (IMUs) with a combined EES program on rectus abdominis, erector spinae muscles, rectus femoris and gluteus maximus. The patient, while sitting, had to perform monodirectional movements (trunk flexion/extension, left/right rotation, left/right lateral bending) and omnidirectional movements (coupled/combined movements).

At the beginning of the rehabilitation program, the patient was unable to independently achieve and maintain an upright stance. Therefore, two Knee-Ankle-Foot Orthosis (KAFO) were customized for the patient by a team of orthopedic technicians. KAFOs allowed locking the knee flexion and extension, permitting the subject to maintain the standing position. The patient began thus to train

the body weight shifting in a standing position with upper limbs supported using a biofeedback (OAK system-Khymeia S.R.L., Padova, Italy) with a EES program acted on abdominis and trunk muscles.

Walking rehabilitation started on an omnidirectional treadmill (Moonwalker-Khymeia S.R.L., Padova, Italy) with body-weight support (BWS) and KAFO braces and progressively trained up to overground with walker.

At discharge, the patient was provided with a kit containing a dedicated tablet and wearable sensors (VRRS Home-Kit, Khymeia, Padova, Italy) to perform exercises based on Virtual Reality and augmented feedback at home.

The patient was assessed at baseline, at discharge and at 6-month from admission. The evaluations were conducted using clinical scales, inertial sensors and surface EMG with and without stimulation. The recordings of walking were made on the treadmill (consisting in 1 min of walking and endurance) and overground (10-Meter Walking Test, 6-Minute Walking Test, endurance test) with and without the stimulation.

Motor assessment protocol

To evaluate the effectiveness of stimulation protocols on isolated movements, we performed assessments of hip flexion, trunk flexion, and evaluated antero-posterior stability limits.

We evaluated treadmill walking through endurance tests, leaving the patient walking at a preset constant speed until he indicated to us the reaching of his maximal exertion level, walking time was employed as a performance metric. When the patient was still in the first phases of gait rehabilitation, we performed training sessions consisting of 1-min walking, that have been used in the present study to measure trunk oscillation in the frontal plane in EES on and off conditions.

Overground walking was assessed through the 10-MWT, measuring the time to walk 10 m in a straight line, and the 6-MWT, measuring the distance covered by the patient in 6 min. During the 6-MWT, the patient was required to perform a full 180° turn every 18 m. Finally, we performed indoor and outdoor overground walking endurance tests, measuring the distance covered by the patient.

Clinical assessment

At study entry, at discharge and at 6-month from admission, an experienced neurosurgeon and physiotherapist performed clinical assessment. The medical research council (MRC) scale[1] was used for assessing muscle strength from grade 5 (normal) to grade 0 (no visible contraction). The lower extremity functional scale (LEFS)[2] was used as a measure of lower extremity function. Spasticity was evaluated by the modified Ashworth scale.[3] Pain sensation was assessed through several questionnaire: the numerical rating scale (NRS),[4] pain disability index (PDI),[5] pain catastrophizing scale (PCS),[6] McGill pain questionnaire (MPQ).[7]

Neuropsychological evaluation

Expert neuropsychologist performed neuropsychological and behavioral evaluations at study entry and at 6-month. The following tests were administered: the mood and cognition were evaluated with the Beck depression inventory scale,[8] State trait anxiety scale,[9] Italian dimensional apathy scale[10] and Montreal cognitive assessment[11]; the 36-Item Short Form Health Survey questionnaire (SF-36)[12] was used for evaluating Health-Related Quality of Life; attention and executive functions were evaluated with the symbol digit modality test,[13] trail making test,[14] and Stroop test; the Rey Auditory Verbal Learning Test and digit span test were used to evaluate memory; the Rey figure copy and Benton test were used to assess visual-spatial ability.

ADDITIONAL RESOURCES

Clinicaltrials.gov registration number: NCT05926843.