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# Spinal cord imaging markers and recovery of standing with epidural stimulation in individuals with clinically motor complete spinal cord injury

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## Abstract

Spinal cord epidural stimulation (scES) is an intervention to restore motor function in those with severe spinal cord injury (SCI). Spinal cord lesion characteristics assessed via magnetic resonance imaging (MRI) may contribute to understand motor recovery. This study assessed relationships



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Author contributions

ER and ACS contributed to the study conception. ER, ACS, SJH, and CAA contributed to the study design. RJB, MN and SM contributed to spinal cord MRI collection. MB performed epidural stimulation implantation. CAA, SJH, and ER contributed to standing data collection and analysis. ACS, KAW, RJB, and SM contributed to spinal cord MRI analysis. BU contributed to the statistical analysis. ER, ACS and KAW created the figures. ER and ACS wrote the first draft of the manuscript. All the authors contributed to the interpretation of results, revised the manuscript and approved its final version.

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**Conflict of interest** The authors declare no competing interests.

**Ethics approval, consent to participate and consent for publication** Each participant signed informed consent for spinal cord epidural stimulator implantation, stimulation, activity-based training, and physiological monitoring studies, conducted according to Declaration of Helsinki standards and University of Louisville Institutional Review Board approval (ClinicalTrials.gov identifiers NCT02037620, NCT02339233, and NCT03364660). Each participant also consented to publish their data collected during this research study.

between standing ability with scES and spared spinal cord tissue characteristics at the lesion site. We hypothesized that the amount of lateral spared cord tissue would be related to independent extension in the ipsilateral lower limb. Eleven individuals with chronic, clinically motor complete SCI underwent spinal cord MRI, and were subsequently implanted with scES. Standing ability and lower limb activation patterns were assessed during an overground standing experiment with scES. This assessment occurred prior to any activity-based intervention with scES. Lesion hyperintensity was segmented from T2 axial images, and template-based analysis was used to estimate spared tissue in anterior, posterior, right, and left spinal cord regions. Regression analysis was used to assess relationships between imaging and standing outcomes. Total volume of spared tissue was related to left ($p = 0.007$), right ($p = 0.005$), and bilateral ($p = 0.011$) lower limb extension. Spared tissue in the left cord region was related to left lower limb extension ($p = 0.019$). A positive trend ($p = 0.138$) was also observed between right spared cord tissue and right lower limb extension. In this study, MRI measures of spared spinal cord tissue were significantly related to standing outcomes with scES. These preliminary results warrant future investigation of roles of supraspinal input and MRI-detected spared spinal cord tissue on lower limb motor responsiveness to scES.

### Keywords

Spinal cord injury; Epidural stimulation; Standing; Spinal cord MRI; Spinal cord lesion

## Introduction

Motor complete spinal cord injury (SCI) results in devastating consequences that include the inability to stand and walk. The loss of nonspecific supraspinal tonic drive to the lumbosacral spinal circuitry controlling posture and locomotion disrupts its sustainable excitability (Harkema 2008), leading to motor dysfunction. It appears that the excitability of the human lumbosacral spinal circuitry is particularly altered after severe SCI compared to other mammals (Cote et al. 2017), and this may explain why some animal models (i.e., cats) can recover standing and stepping after complete SCI (De Leon et al. 1998a, b). In contrast, humans do not demonstrate similar recovery capabilities. Hence, the application of spinal cord epidural stimulation (scES) for motor function recovery in humans was initially designed to mimic the tonic supraspinal drive lost after SCI, so that sensory information from lower limbs could serve as a source of control to generate appropriate motor patterns during standing and stepping (Edgerton et al. 2004; Harkema et al. 2011; Rejc and Angeli 2019).

However, unexpected recovery of volitional lower limb movement with scES in supine position was also observed in individuals with clinically motor complete SCI (Harkema et al. 2011; Angeli et al. 2014). Our research group and others subsequently showed that supraspinal inputs can also be integrated by the spinal circuitry together with peripheral sensory information during weight-bearing standing and stepping, modulating the motor pattern promoted by scES (Angeli et al. 2014; Grahn et al. 2017; Rejc and Angeli 2019; Gill et al. 2020). Volitional intent to contribute to motor pattern generation was a key component in the recovery of walking in individuals with motor complete SCI (Angeli et al. 2018; Gill et al. 2018). Clinically motor complete SCI is often not anatomically complete (Kakulas

2004), and it is hypothesized that the limited spared and dormant fibers that cross or bypass the lesion site can carry the descending signals to the lumbosacral circuitry, resulting in activation pattern generation and modulation when scES appropriately alters the spinal circuitry excitability (Angeli et al. 2014; Mishra et al. 2017).

We have recently investigated whether the characteristics of spared spinal cord at the lesion site may play a role in the recovery of volitional lower limb movement from supine position promoted by scES (Rejc et al. 2020). In particular, we applied quantitative, template-based approaches (Smith et al. 2018, 2020, 2021) to assess spinal cord magnetic resonance images (MRIs) collected before scES implantation. We found that, prior to any training with scES, the ability to perform ankle or lower limb flexion was not related to the amount and region of the spared spinal cord. However, some aspects of motor control, such as coordination features between antagonist muscles, were importantly and significantly associated with the spared cord characteristics. This follow-up study aimed to assess the relationship between standing ability with scES and spared spinal cord tissue characteristics at the lesion site prior to any scES-based intervention. We hypothesized that the amount of lateral spared cord tissue would be related to the ability to maintain independent extension in the ipsilateral lower limb.

# Methods

## Participants

Eleven individuals ($n$ = 8 males and $n$ = 3 females) with chronic, clinically motor complete SCI are included in this study (Table 1). Each participant signed informed consent for scES implantation, stimulation, activity-based training, and physiological monitoring studies, conducted according to Declaration of Helsinki standards and University of Louisville Institutional Review Board approval (Clinical-Trials.gov identifiers NCT02339233, NCT02037620 and NCT03364660). International Standards for Neurological Classification of Spinal Cord Injury (Burns et al. 2012) was used for classifying the injury using the ASIA (American Spinal Injury Association) Impairment Scale (AIS). Data presented in this study were collected before the beginning of any intervention with scES.

## Spinal cord MRI collection

Details on MRI collection have been previously reported (Rejc et al. 2020) and the cervical-thoracic images were used in this present study. Briefly, prior to epidural stimulator implantation, 2D magnetic resonance images of the spinal cord were collected using a 3T system (Siemens Magnetom Skyra, Siemens Medical Solutions, Malvern, PA USA) with Turbo Spin Echo T2-weighted pulse sequences. Typical sagittal parameters were: repetition time (TR) = 3000 ms, echo time (TE) = 74 ms, flip angle = 160°, echo train length = 17, acquisition matrix = 320 × 240, reconstruction matrix = 320 × 320, phase field of view (FOV) = 100%, partial Fourier = 75%, bandwidth = 600 Hz/pixel, in-plane resolution = 1.125 mm × 1.125 mm, slice thickness = 3 mm, and averages = 2.

Sequential axial images were acquired from the foramen magnum to the T3–4 level, obtained either with a 10% gap (standard) or no gap. Example axial parameters were: TR =

5190 ms, TE = 74 ms, flip angle = 160°, echo train length = 26, acquisition matrix = 256 × 179, reconstruction matrix = 512 × 512, phase FOV = 100, partial Fourier = 70%, bandwidth = 610 Hz/pixel, in-plane resolution = 0.35 mm × 0.35 mm, thickness = 3 mm, and averages = 2.

## Spinal cord MRI analysis

Imaging analysis details have been previously described (Rejc et al. 2020). Briefly, the open-source Spinal Cord Toolbox (Version 4.3.0) (De Leener et al. 2017) was used to calculate the amount of spared white matter using the PAM50 template (Fonov et al. 2014; De Leener et al. 2017; Dupont et al. 2017). White matter tracts within the anterior, posterior, right lateral, and left lateral spinal cord were combined to quantify the amount of spared tissue within these four regions (Cloney et al. 2018; Rejc et al. 2020). An experimenter blinded to the clinical history and experimental measures manually segmented the images to generate binary spinal cord and spinal cord lesion masks (Rejc et al. 2020). The lesion masks were projected to the axial plane, and the percentage of spared region volume (non-lesion) was calculated for each of the four white matter regions (Rejc et al. 2020).

In this study, we additionally considered two other variables characterizing the position of the scES paddle electrode with respect to the lumbosacral spinal cord, which significantly correlated with the ability to generate volitional lower limb movement after motor complete SCI (Mesbah et al. 2021). These two imaging parameters are: (1) the estimated percent coverage of the lumbosacral enlargement volume by the scES paddle (LS enlargement coverage), and (2) the sum of distances from the top of the scES paddle to the maximal enlargement, and from the caudal end of the paddle to the conus tip (relative paddle position).

## Standing experimental procedures and analysis

Research participants began the experimental sessions in the laboratory approximately 2–3 weeks after the surgical implantation of the spinal cord epidural stimulation unit. Spatiotemporal mapping of the spinal cord motor-evoked responses was performed with the individuals relaxed in supine position (Sayenko et al. 2014; Mesbah et al. 2017), and was particularly important to determine the individualized map of motor pools activation. Stimulation parameters for standing (Stand-scES) were determined following dedicated guidelines (Rejc et al. 2015) over 2 experimental standing sessions.

Standing ability, lower limb activation pattern and ground reaction force were assessed during a subsequent overground standing assessment performed prior to the beginning of any scES-based intervention. Standing was performed in a customized standing apparatus comprised of horizontal bars anterior and lateral to the individual. Stand-scES was applied in sitting; the participant began the sit-to-stand transition using the horizontal bars of the standing apparatus for assistance and support; trainers positioned at the trunk, pelvis, and knees manually assisted as needed during this transition. If during standing, the knees, hips, or trunk flexed beyond the normal posture, assistance at the knees distal to the patella, at the hips below the iliac crest, and at the upper trunk was provided manually by trainers to promote extension.

The goal for the participant was to stand for 30 min (Study 2 and 3, Table 1) or 10 min (Study 1, Table 1) with the least amount of external assistance provided manually by trainers (i.e., attempting to achieve independent extension of the lower limbs and independent control of hips and trunk). Seated resting periods occurred when requested by the individuals. Standing ability was quantified by the duration of independent extension of different body segments (left knee, right knee, both knees simultaneously, hips) expressed as a percentage of total standing time. Electromyography (EMG) and force plates (Kistler, Holding AG, Winterthur, Switzerland) data were collected at 2000 Hz using a hard-wired AD board and a custom-written acquisition software (LabView, National Instruments, Austin, TX). EMG data were band-pass filtered (10–500 Hz) and force data low-pass filtered (10 Hz). EMG was collected bilaterally from gluteus maximus, rectus femoris, vastus lateralis, medial hamstrings, tibialis anterior, medial gastrocnemius, and soleus. Time- and frequency-domain EMG features that we previously found related to standing ability were calculated and expressed as an average across the investigated muscles within each participant (Mesbah et al. 2019). In particular, EMG pattern variability was quantified by assessing the coefficient of variation of the EMG linear envelope (Rejc et al. 2017b). Continuous Wavelet Transform was applied to calculate EMG median frequency and its standard deviation (Mesbah et al. 2019). Finally, the coefficient of variation of the vertical ground reaction forces was also considered for analysis.

### Statistical analysis

Seven MRI outcomes (spared tissue of total, anterior, posterior, right, and left spinal cord; lumbosacral enlargement coverage by scES paddle, relative paddle position) and 8 motor outcomes (duration of independent extension of different body segments, EMG and force plate variables; Supplementary Table 1) were initially considered for each research participant. For the analysis, we only considered variables that had non-zero variability. All the outcomes were regressed on all the imaging markers variables one by one using linear models. Estimates were presented as the least square mean change in outcome associated with a 1-unit increase in imaging markers measures and associated standard error. Data analysis was performed in SAS 9.4 (SAS Inc, Cary, NC).

## Results

The four spinal cord white matter regions of interest assessed in this study are exemplified in Fig. 1. Briefly, the left and right cord spared tissue were on average 14.8 ± 16.4% (range 0–55.9%) and 19.5 ± 15.7% (range 0–47.1%), respectively. The anterior cord spared tissue was 49.2 ± 33.6% (range 0–87.0%), the posterior cord spared tissue was 14.8 ± 17.0% (range 0–53.2%), and the total cord spared tissue was on average 15.4 ± 12.7% (range 0–42.3%). The amount of spared tissue in these regions of interest varied substantially across individuals. Figure 1 exemplifies the spared and lesioned spinal cord tissue for two representative individuals. Participant A110 (Fig. 1A), who demonstrated more spared cord in all regions, also achieved the longest bilateral lower limb independent extension (83% of session duration). On the other hand, A41 (Fig. 1B) showed no spared cord in the four regions of interest, and no ability to achieve independent extension of either lower limb.

The statistical analyses performed in this study revealed that standing ability outcomes (i.e., duration of independent lower limb(s) extension) were significantly and directly related with the total amount of spared cord tissue, as well as with the amount of spared tissue of different cord regions (Table 2). For example, spared tissue on the left spinal cord region was significantly related to left lower limb extension ($p = 0.019$). We also found a non-significant trend for spared tissue on the right spinal cord versus right lower limb extension ($p = 0.138$). Figure 2 depicts individual data points of the relationships between representative standing ability outcomes and amount of spared cord tissue. It can be noted that these data points are not consistently clustered in relation to the clinical detection of residual sensation (i.e., AIS B vs AIS A). On the other hand, standing ability was not found to be related with the two features characterizing the scES paddle electrode position with respect to the lumbosacral spinal cord (i.e., Table 2; $p$ values ranging from 0.242 (duration of independent hips extension vs LS enlargement coverage) to 0.762 (duration of bilateral knees independence vs LS enlargement coverage)). Finally, EMG and force plate variables assessed during standing were not significantly related with spared cord tissue characteristics.

Interestingly, some individuals demonstrated the ability to volitionally modulate standing motor output promoted by scES. For example, starting from a condition of standing with bilateral knees extended, participant A96 was able to volitionally flex the right knee while maintaining left knee extension, and subsequently generate an extension pattern that led to regain extension of the right lower limb (Fig. 3A). The same individual was also able to volitionally promote bilateral knees flexion (interrupted by the manual ‘hard stop’ of the trainer) and the subsequent extension generated from a squatted position (Fig. 3B). Interestingly, the activation pattern resulting in bilateral flexion included EMG bursts of flexor muscles (iliopsoas and tibialis anterior, bilaterally), which was different than the general reduction in EMG activity observed in the right lower limb during unilateral flexion (Fig. 3A).

## Discussion

In this preliminary study, we found that measures of spared spinal cord tissue across the lesion site were significantly related to the ability to stand with scES in 11 subjects with chronic, clinically motor complete SCI. The total volume of spared tissue was correlated to left lower limb extension, right lower limb extension, and bilateral lower limb extension during standing with scES on. In line with the current understanding of spinal cord neuroanatomy (i.e., location of lateral corticospinal tracts), we also found that spared left cord tissue was related to left lower limb extension, and a positive trend for spared right cord tissue versus right lower limb extension.

Decades of work on animal models with complete SCI transection demonstrate that peripheral sensory information can serve as a source of control for generating effective standing and stepping motor patterns when scES is applied to appropriately modulate the excitability of spinal circuitry controlling posture and locomotion (Edgerton et al. 2004). More recently, we reported similar findings in individuals diagnosed with chronic, clinical and neurophysiological motor complete SCI (Harkema et al. 2011; Rejc et al. 2015). For example, lower limb loading and extension related to sit-to-stand transition promoted the generation of lower limb activation patterns effective to maintain independent extension during standing overground when appropriate scES parameters, which elicited no leg movement and negligible EMG in sitting, were applied (Rejc et al. 2015). Conversely, without scES, little or no EMG activity is generally recorded from the lower limb muscles of these research participants, who require constant trainers' manual assistance at the hips and knees to maintain upright posture (Rejc et al. 2015, 2017b; Mesbah et al. 2019). In addition, robust locomotor-like EMG activity was facilitated by the combination of sensory information related to assisted stepping on a treadmill and scES (Harkema et al. 2011).

However, contrary to the complete SCI transaction in animal models, the spinal cord lesion is often not anatomically complete in humans, even after the most severe injuries leading to chronic complete paralysis (Kakulas 2004). This spared and dormant connectivity across the lesion conceivably carries residual descending information that becomes sufficient to generate volitional leg movements under non-weight-bearing conditions (Angeli et al. 2014; Darrow et al. 2019), to modulate the motor pattern during assisted stepping and standing with independent knees extension (Angeli et al. 2014; Rejc and Angeli 2019) (Fig. 3), and to initiate and control walking and stepping overground (Grahn et al. 2017; Angeli et al. 2018; Gill et al. 2018) when appropriate tonic scES parameters are applied. It is worth noting that scES re-enabled volitional leg muscle activation and movements even in those clinically motor complete SCI individuals who did not demonstrate any functional motor connectivity between the supraspinal and spinal centers below the level of injury as evaluated by neurophysiological assessments (transcranial magnetic stimulation and/or residual motor output with EMG) performed without spinal stimulation (Angeli et al. 2014, 2018).

Taken together, these findings suggest that residual supraspinal inputs play an important role in the recovery of walking and standing with scES in individuals with clinically motor complete SCI, and thus support the need for additional mechanistic studies focused on this area. In this preliminary work, we uniquely demonstrated that spared spinal cord tissue surrounding the lesion was directly related to standing ability with scES prior to any activity-based training with spinal neuromodulation (Table 2; Fig. 2). Our preliminary results provide evidence to support the hypothesis that the limited spared and dormant fibers that bypass the lesion site can carry descending signals to the lumbosacral circuitry, contributing to standing pattern effectiveness (Table 2) and modulation (Fig. 3) when scES appropriately regulates the spinal circuitry excitability. While the mechanisms involved in the direct relationships between spared spinal cord tissue at the lesion site and standing ability with scES are not yet known, it can be hypothesized that the residual supraspinal input can be integrated by the spinal circuitry controlling posture to contribute to the enhancement of lower limb extension pattern primarily promoted by scES and peripheral sensory information. Volitional initiation and modulation of lower limb extension patterns were reported for clinically motor complete SCI individuals in non-weight-bearing settings with scES on (Peña Pino et al. 2020), and even with scES off after long-term spinal cord stimulation (Rejc et al. 2017a; Peña Pino et al. 2020). Volitional initiation and modulation of lower limb extension with scES was also exemplified while SCI individuals were in upright position with body weight partially supported (Grahn et al. 2017) or standing overground

(Fig. 3). However, some individuals also showed the ability to volitionally engage residual inhibitory pathways to reduce activation amplitude and modulate lower limb motor output during standing (Fig. 3; (Rejc and Angeli 2019)). In rats with severe SCI and complete motor paralysis implanted with scES, greater training-induced regenerative sprouting into corticospinal tracts at the lesion site were associated with restored voluntary control of locomotion (van den Brand et al. 2012). In individuals with incomplete injuries, spared spinal cord tissue in the lateral corticospinal tract regions is related to the better voluntary motor output of the ipsilateral lower extremities (Smith et al. 2018, 2020). In alignment with these findings, our results demonstrate a significant relationship with left sided spared cord tissue and the ability to generate left lower limb extension, and we also found a positive trend with right spared cord tissue and right lower limb extension. We hypothesize that with our future planned research expanding the number of participants and using higher resolution imaging, a significant relationship will be demonstrated on both the right and left sides.

We also found that spared tissue in the posterior cord was significantly related to standing ability. While we are unsure of the underlying mechanisms behind this finding, we theorize that proprioceptive information ascending in the posterior column and surpassing the lesion site may be important for our participants' postural control with scES on. Human studies have confirmed the importance of proprioceptive information for brainstem-mediated subconscious, automatic upright postural control (Inglis et al. 1994; Bloem et al. 2000, 2002). This is further supported by cat studies that demonstrated postural extension with brainstem stimulation (Mori et al. 1989) and reduced automatic postural responses after inducing pharmacological disruption to the somatosensory system (Stapley et al. 2002). In addition, there is evidence that proprioceptive information can activate particularly the lumbosacral enlargement lower extremity extensor networks in humans with complete SCI, which is likely contributing to the standing abilities of our participants (Dietz and Muller 2004; Dietz et al. 2009).

On the other hand, we did not find significant relationships between the scES paddle electrode position and our standing motor outcomes. This contrasts with our recent study showing that increased scES paddle coverage of the lumbosacral enlargement was related to improved performance in volitional lower limb movement tasks performed in supine (Mesbah et al. 2021). Given this lack of finding, we now postulate that discrete independent joint movements of the lower limbs may require a more specific electrode placement to access particular locations of the spinal circuit, while the standing task may require a more generalized modulation of the lumbosacral circuitry controlling posture. In fact, stimulation site and electrode configuration have important implications for topographical organization of the activation pattern facilitated by scES. For example, largest spinal cord-evoked potentials detected from a given muscle are elicited by scES with the cathode (i.e., active electrode) site positioned over the segmental location of the related motoneuron pools (Hofstoetter et al. 2021). Similarly, localized stimulation of rostral or caudal areas of lumbar spinal cord results in selective topographical recruitment of proximal or distal lower extremity muscles, respectively, while wide-field electrode configurations can promote more global responses in both proximal and distant leg muscles (Sayenko et al. 2014).

We recently found that measures of spared tissue in spinal cord regions across the lesion site were significantly and meaningfully correlated with aspects of volitional lower limb motor control under non-weight-bearing conditions, prior to any training with scES, all while the stimulator was on (Rejc et al. 2020). The anterior spinal cord region was significantly associated with less antagonist electromyographical (EMG) activation during volitional ankle dorsiflexion attempts. The right spinal cord region was significantly correlated with EMG activation of the right hamstrings during volitional right knee flexion attempts. Total spinal cord spared tissue was also significantly associated with less co-contraction of the hamstrings and iliopsoas during knee flexion attempts. Our present study's findings align with our previous work, except we did not find a significant relationship between the anterior cord region and standing outcomes ($p$ = 0.06–0.10).

### Limitations

This study implemented routine clinical MRIs of modest resolution, which allowed us to provide estimations of spinal cord damage to specific regions, while did not allow us to estimate reliably spinal cord damage to specific white matter tracts. Future research is warranted and underway to expand the number of participants and collect high-resolution MRI across the lesion site to validate these findings and also estimate damage to specific white matter pathways. Another limitation is the manual nature of lesion and spinal cord segmentation, which is time-consuming and rater dependent, although good inter-rater reliability has been demonstrated (Smith et al. 2018). Future work will also employ machine-learning approaches, such as convolutional neural networks, for the automated measurement of spinal cord damage (Gros et al. 2019).

In conclusion, in this pilot study involving participants with chronic clinically motor complete SCI, MRI measures of total spared spinal cord tissue across the lesion site were significantly related to standing ability outcomes with scES on. Spared tissue in distinct spinal cord regions were also associated with standing ability outcomes. These preliminary results warrant future investigation on the role of supraspinal input and MRI-detected spared spinal cord tissue and its effect on lower limb motor responsiveness to lumbosacral scES.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Data availability

Data that support the will be made available through material transfer agreement upon reasonable request.

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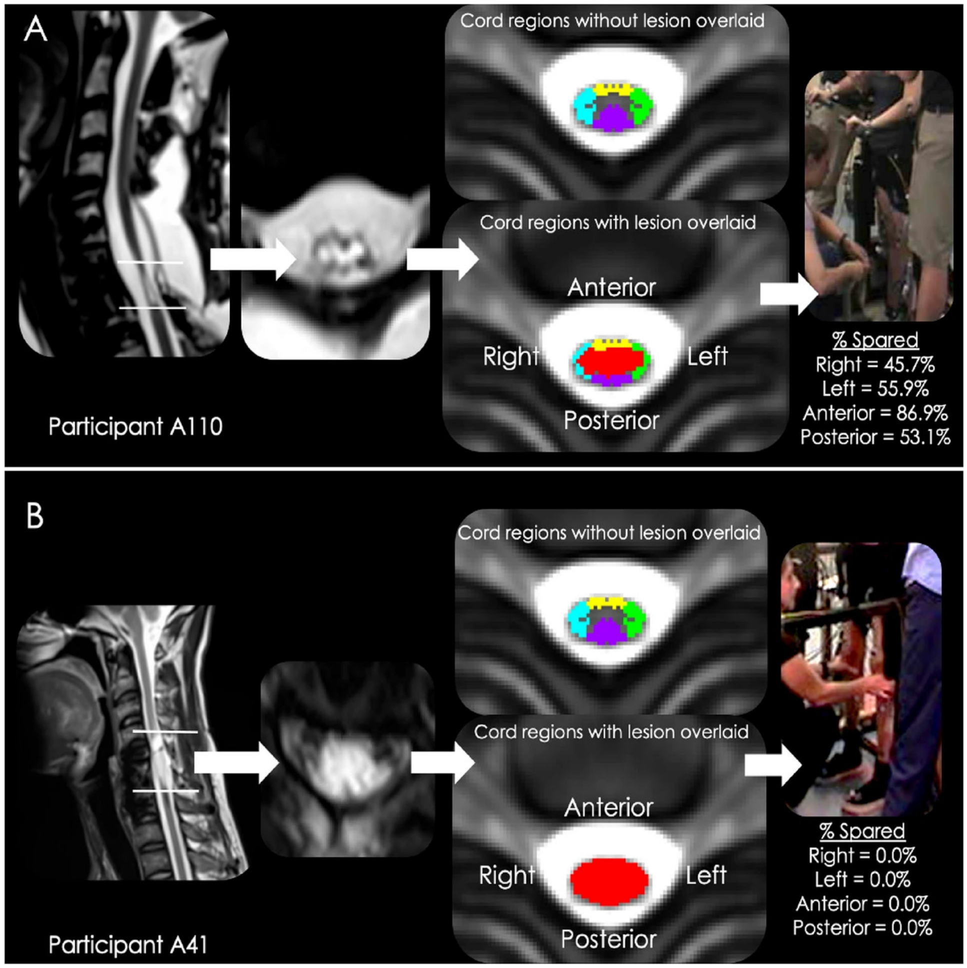


**Fig. 1.**

Imaging results from two representative research participants. **A** depicts an individual (A110) who demonstrated more spared cord in all regions and also better scES-promoted standing ability. **B** represents an individual (A41) who did not show spared cord tissue in the four regions of interest or any ability to achieve independent extension of either lower limb. From left to right: a mid-sagittal T2-weighted image with lesion hyperintensity visible, an axial T2-weighted image with lesion hyperintensity visible, the axial template showing each participant's aggregated damage with the four regions depicted, and the percentages of spared tissue in these regions corresponding to standing ability with scES on.

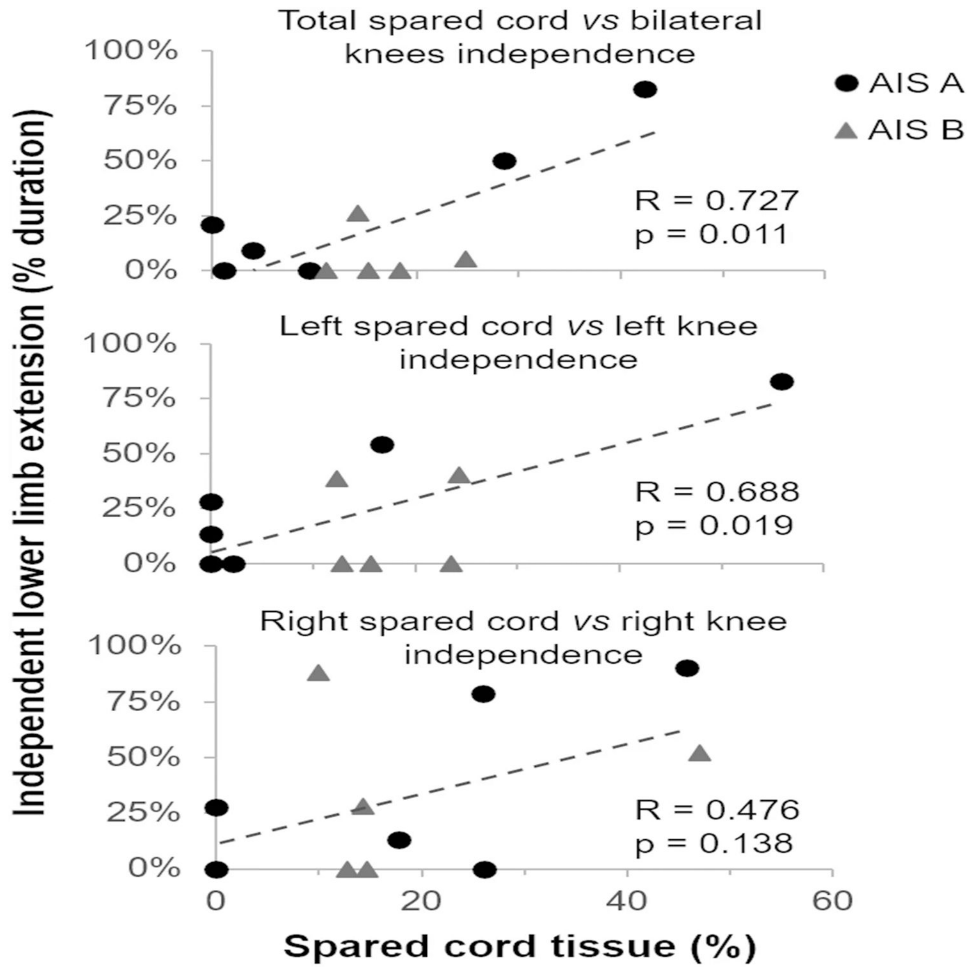


**Fig. 2.**

Duration of standing with independent bilateral, left and right lower limb extension is plotted against the amount of spared tissue of representative cord regions. Spinal cord injured individuals graded sensory and motor complete (AIS A) are identified by black circles, and those graded motor complete and sensory incomplete (AIS B) by grey triangles

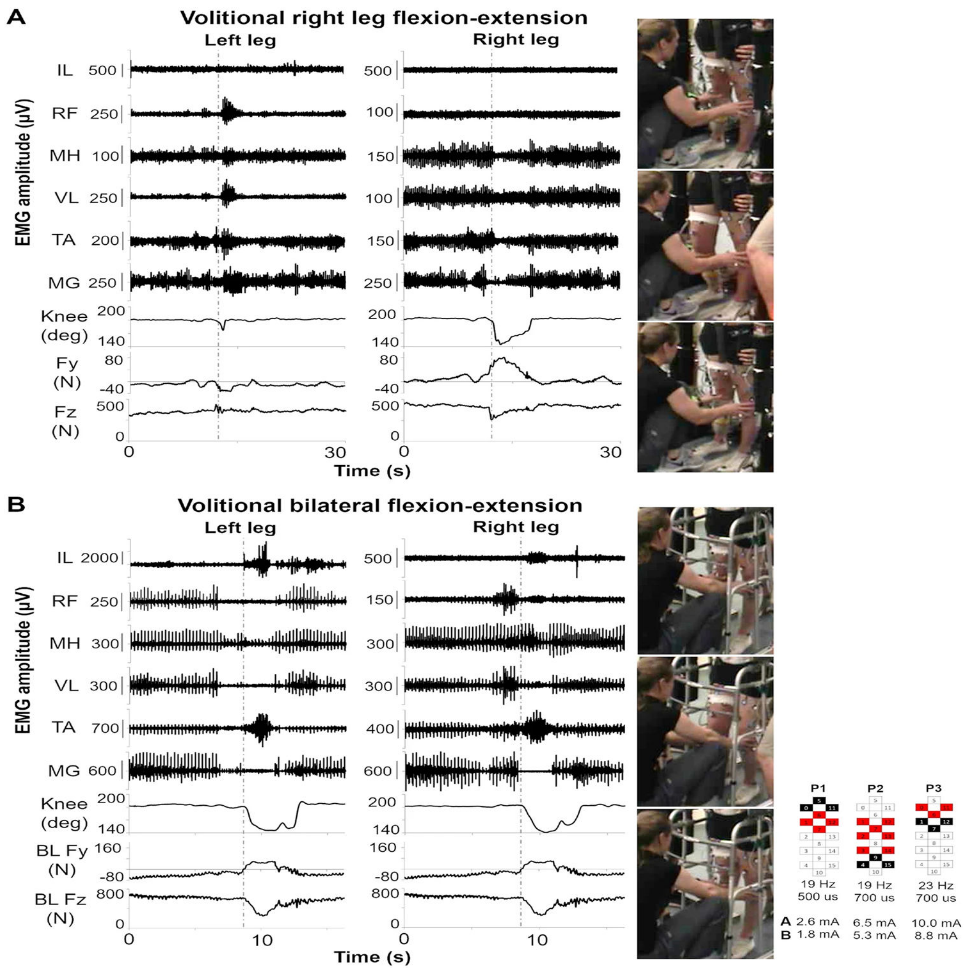


**Fig. 3.**

Time course of electro-myographic (EMG), kinematic and kinetic data collected from participant A96 during standing overground with epidural stimulation. From bilateral lower limb independent extension, the participant volitionally attempted to perform: **A** right knee flexion and subsequent extension, while maintaining left lower limb extension: **B** bilateral lower limb flexion (interrupted by the manual assistance at the knees by the trainer) and subsequent extension. *IL* iliopsoas; *RF* rectus femoris; *MH* medial hamstrings; *VL* vastus lateralis; *TA* tibialis anterior; *MG* medial gastrocnemius. Antero-posterior (Fy) and vertical (Fz) ground reaction force traces are also reported. Electrode configuration (cathodes in black, anodes in red, inactive in white), frequency, pulse width, and intensities applied in Panels A and B are reported for each of the three epidural stimulation programs concurrently applied (P1 to P3). This dataset was collected after 80 sessions (2 h/day; 5 days/week) of stand training with epidural stimulation

**Table 1**

Characteristics of the research participants

| Pub ID | Age range (yrs) | Sex | Time between injury and surgery (yrs) | Injury level | AIS | Approx. lesion center | Study |
|---|---|---|---|---|---|---|---|
| B30 | 21–25 | F | 3.2 | T1 | B | C6–C7 | 1 |
| B23 | 26–30 | M | 4.2 | C7 | B | C5 | 1 |
| B21 | 31–35 | M | 6.9 | C4 | B | C5 | 2 |
| A41 | 21–25 | M | 7.2 | C4 | A | C5 | 2 |
| A68 | 31–35 | M | 3.8 | C5 | A | C6 | 2 |
| A99 | 16–20 | M | 2.8 | C4 | A | C4–C5 | 3 |
| A101 | 31–35 | M | 2.4 | C2 | A | C3–C4 | 3 |
| A96 | 26–30 | F | 3.1 | C4 | A | C5 | 3 |
| A110 | 21–25 | F | 5.8 | C5 | A | C7 | 3 |
| B41 | 26–30 | M | 8.6 | C8 | B | C7 | 3 |
| B47 | 41–45 | M | 8.2 | C4 | B | C4–C5 | 3 |

*F* female; *M* male. Injury level: neurological level of the lesion by AIS (American Spinal Injury Association (ASIA) Impairment Scale). Approx. lesion center: vertebral level used for Spinal Cord Toolbox template registration based on the approximate lesion center. Each individual was enrolled in an interventional study focused on either the facilitation of standing and stepping (Study 1), the recovery of cardiovascular function (Study 2), or the recovery of cardiovascular function, volitional leg movements, and standing (Study 3)

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## Table 2

Associations between standing motor outcomes and imaging outcomes

| Standing motor outcomes | MRI outcomes | Estimate (SE) | *p* value |
|---|---|---|---|
| L leg independent (% duration) | L cord (% spared) | 1.2 (0.4) | **0.019** |
| | R cord (% spared) | 1.2 (0.5) | **0.030** |
| | Post cord (% spared) | 1.3 (0.3) | **0.004** |
| | Tot cord (% spared) | 1.7 (0.5) | **0.007** |
| R leg independent (% duration) | L cord (% spared) | 1.4 (0.6) | **0.042** |
| | Post cord (% spared) | 1.8 (0.4) | **0.001** |
| | Tot cord (% spared) | 2.2 (0.6) | **0.005** |
| BL independence (% duration) | L cord (% spared) | 1.1 (0.4) | **0.019** |
| | Post cord (% spared) | 1.3 (0.3) | **0.002** |
| | Tot cord (% spared) | 1.5 (0.5) | **0.011** |
| BL independence (% duration) | LS enlargement coverage (%) | 0.2 (0.6) | 0.762 |
| | Relative paddle position (mm) | 0.5 (0.5) | 0.345 |
| EMG pattern variability (a.u.) | Tot cord (% spared) | 0.01 (0.01) | 0.757 |
| EMG MdF (Hz) | | − 0.47 (0.94) | 0.627 |
| EMG MdF SD (Hz) | | − 0.18 (0.48) | 0.714 |
| Fz CV (a.u.) | | − 0.01 (0.01) | 0.586 |

*L* left; *R* right; *BL* bilateral; *a.u.* arbitrary unit; *MdF* median frequency; *MdF SD* median frequency standard deviation; *Fz CV* coefficient of variation of the vertical ground reaction forces; *MRI* magnetic resonance imaging; *Post* posterior; *Tot* total; *LS* enlargement coverage estimated percent coverage of the lumbosacral enlargement volume by the epidural stimulator paddle; relative paddle position sum of distances from the top of the epidural stimulator paddle to the maximal enlargement, and from the caudal end of the paddle to the conus tip. Only statistically significant associations (p values in bold) between standing ability and spinal cord lesion imaging outcomes are reported