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Restoring locomotion in motor-complete spinal cord injury via trunk-mediated control using a commercial epidural spinal cord stimulator

Graphical abstract

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In brief

Agnesi et al. show that trunk movements can modulate epidural spinal cord stimulation in people with motor-complete spinal cord injury. Trunk extension switches stimulation-induced lower-limb activity from extension to triple flexion, enabling participants to control stepping through their residual trunk movements.

Highlights

- Trunk flexion-extension modulates the effects of spinal cord stimulation
- Trunk extension switches stimulation from extension to triple flexion
- Trunk-mediated control enables walking after motor-complete spinal cord injury
- Trunk-controlled locomotion is associated with improved clinical scores

Translation to Patients

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Restoring locomotion in motor-complete spinal cord injury via trunk-mediated control using a commercial epidural spinal cord stimulator

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CONTEXT AND SIGNIFICANCE People with motor-complete spinal cord injury generally cannot voluntarily control their lower limbs, and stimulation-assisted walking commonly depends on externally programmed stimulation sequences. Here, we show that residual trunk movements can be used to modulate the effects of epidural spinal cord stimulation and directly control lower-limb movements. By extending the trunk, participants switched stimulation-induced activity from weight-supporting extension to triple lower-limb flexion, allowing them to initiate and regulate stepping with a walker. This trunk-mediated control strategy enabled functional walking and was accompanied by improvements in clinical mobility and independence scores. These findings introduce a reliable interface between residual body movements and spinal cord stimulation that may reduce dependence on external controllers and facilitate more autonomous locomotion after severe spinal cord injury.

SUMMARY

Background: Spinal cord stimulation is emerging as a novel approach to restore movement in patients affected by spinal cord injury. Recent advances have shown restoration of locomotion in patients with complete motor lesions using sophisticated new systems including a brain machine interface. Despite the great potential, this approach is hindered by the inherent complexity and absence of approvals for clinical use.
Methods: Here, we tested a novel strategy to restore locomotion in patients with motor-complete spinal cord injury using voluntary trunk movements to modulate the motor output produced by a commercially available epidural spinal cord stimulator.
Findings: Four participants with thoracic AIS A–B injuries gained volitional modulation of stimulation-enabled movement without external interfaces or brain decoding, achieving standing and walking over

four months of rehabilitation. The approach transformed passive stimulation into self-initiated movement, enabling functional mobility.

Conclusions: This simple and potentially scalable method successfully leverages clinically available spinal cord stimulators to allow locomotion even in patients unable to produce voluntary contractions below the lesion, advancing accessible neuromodulation for motor-complete spinal cord injury.

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INTRODUCTION

Epidural spinal cord stimulation (eSCS) has shown the potential to become a cornerstone in neurorehabilitation, offering innovative solutions for restoring motor functions in individuals with spinal cord injury (SCI). In people with motor-incomplete SCI, corresponding to American Spinal Injury Association Impairment Scale (AIS) grades C and D, residual descending pathways may preserve some voluntary motor control, and activity-based rehabilitation alone can lead to improvements in motor function.[1] Studies combining eSCS with intensive rehabilitation have reported additional gains in muscle strength and walking performance, in some cases over relatively short training periods.[2–4] In individuals with motor-complete SCI (AIS grades A–B), voluntary motor output is absent or too limited for recovery to be expected from rehabilitation alone. In the studies by Gill et al.[5] and Angeli et al.,[6] eSCS was therefore combined with intensive activity-based rehabilitation, enabling substantial recovery of standing and stepping functions and, in selected participants, overground walking. However, the individuals who achieved these outcomes exhibited, at least during training, residual voluntary muscle activation detectable by electromyography. These observations have contributed to the concept of ''discomplete'' SCI: individuals classified as motor-complete according to the AIS examination who nevertheless retain spared descending neural connections that may provide the physiological substrate for rehabilitation and eSCS to act synergistically.

One possibility to produce functional improvement in patients with motor-complete SCIs who do not exhibit any signs of ''discompleteness'' is proposed in Rowald et al.[7], where spatiotemporally modulated patterns of eSCS enabled such patients to ambulate and perform several everyday life activities. While in that case activity-based protocols were activated through interfaces including clickers in the assistive device (walker) used by the patients, Lorach et al.[8] further showed that an ECoG-based brain-machine interface can decode cortical intentions in real time and relay them to a spinal stimulator, enabling real-time control of stimulation patterns. Together, these studies mark major milestones in neuroprosthetics, demonstrating robust functional recovery even in cases once deemed irreversible.

However, these highly engineered interventions also present important challenges. They require specialized teams to manage the longitudinal adaptation of both neural decoding algorithms and stimulation protocols, involve invasive brain surgery, and depend on substantial resources for the development and regulatory approval of dedicated devices. These factors may limit their accessibility and scalability, highlighting a fundamental trade-off between providing voluntary control over stimulation and reducing technological and clinical complexity sufficiently to support broader adoption of eSCS.

To address this challenge, we present a novel strategy, which we call trunk-mediated control (TMC), enabling eSCS-assisted independent locomotion in individuals with motor-complete SCI lacking any evidence of residual corticospinal connectivity using a commercially available stimulation system in a clinical setting and after a relatively short period of task-specific training. Participants were trained to use trunk movements to modulate the motor effects of individually tailored stimulation programs, switching between lower-limb extension for standing and triple flexion for stepping. This approach provides real-time control over flexion and extension during gait while offering a less complex and less invasive alternative to brain-spine interfaces.

RESULTS

Clinical information

This study reports data from four consecutive participants, including one woman, enrolled in the clinical trial NCT05926843, which investigates the effects of eSCS combined with locomotor training in individuals with chronic traumatic SCI. These were the first participants enrolled in the trial who were classified as functionally motor-complete (AIS grade A or B). Participants were identified according to their order of recruitment as P05, P06, P07, and P08. Neurological lesion levels were T7, T4, T7, and T6, respectively. All participants had undergone spinal fixation at the time of injury, followed by conventional inpatient rehabilitation. At the time of implantation, all participants had an MRC score of 0 in every tested lower-limb muscle, indicating the absence of visible voluntary muscle contraction. Additional demographic and clinical characteristics are reported in Table S1.

All participants were implanted with a CoverEdge X32 Surgical Lead connected to a Spectra WaveWriter implantable pulse generator (Boston Scientific, Marlborough, MA, USA). The electrode paddle was positioned between T11 and L1 (Figure S1) and optimized individually using intraoperative neurophysiological monitoring (Methods – Patient enrollment and surgery). Following implantation, all participants were hospitalized for 4 months of eSCS-based training.

Spinal cord stimulation can produce lower limb extension and flexion

In all four participants, tonic eSCS elicited sustained knee extension. Knee extension protocols were performed unilaterally, with each lower limb characterized separately (frequency: 10 Hz for

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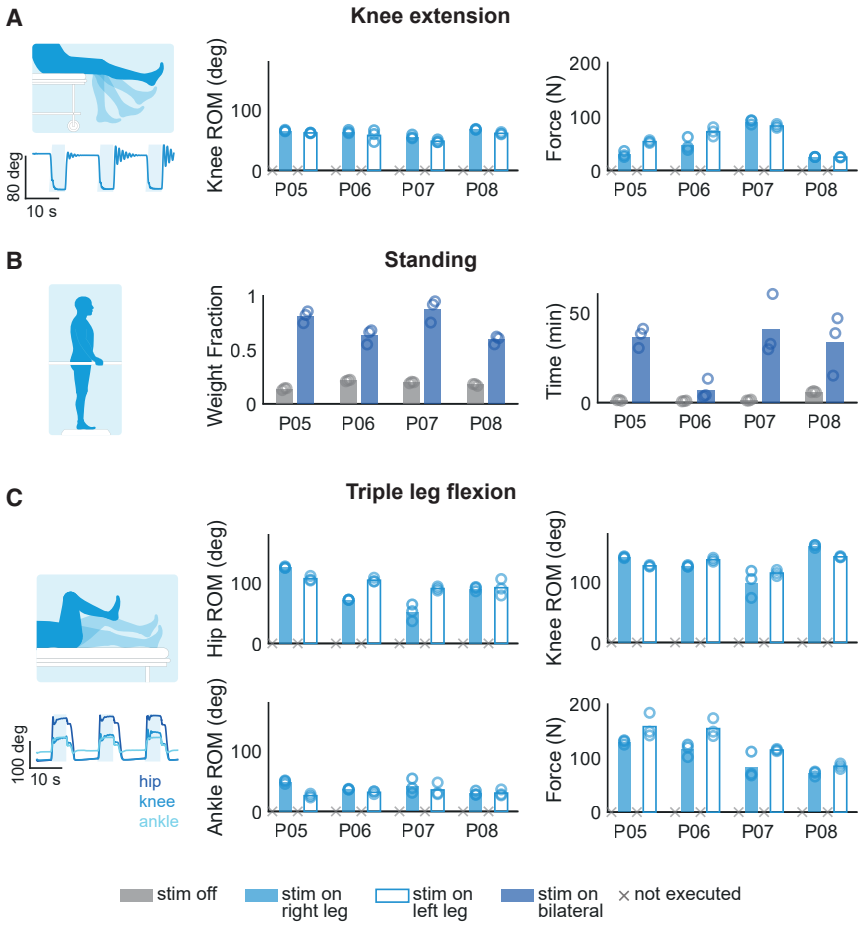

Figure 1. Isolated movements and standing endurance

(A) Stimulation-induced unilateral leg extension against gravity with the patient sitting. Example trace on the left from P08 (left leg). Range of motion (ROM) and force calculated for unilateral left and right knee extension.

(B) Bilateral knee extension can be used to achieve prolonged standing with substantial weight supported through the lower limbs The three circles in each participant represents the last three recording of standing performed.

(C) eSCS at higher stimulation frequencies can be used to induce ipsilateral lower limb flexion resembling triple flexion in the supine position. Example trace on the left from P08 (left leg). ROM and force calculated for unilateral left and right lower limb flexion. For each test, three repetitions are displayed. X: test could not be performed.

P05 [right lower limb], P07, and P08; 20 Hz for P05 [left lower limb] and P06 ; pulse width: 300 μs; electrode configuration and stimulation amplitude as in Table S2). Across participants and tested lower limbs, eSCS produced a knee extension range of 63° ± 6° (mean ± standard deviation across all participants) and a mean knee-extension force of 53 ± 25 N (mean ± standard deviation across all participants; Figure 1A and Video S1).

With eSCS ON, all participants were able to maintain standing for prolonged periods. At the last assessment, standing endurance was 41 min for P05, 13 min for P06, 60 min for P07, and 46 min for P08, significantly longer than in the OFF condition (linear mixed-effects model; fixed effect = 27 min, 95% confidence interval [CI] = [19, 35] min, $p < 0.001$; three ON and three OFF condition tests per participant, four participants, corresponding to a total $n = 24$ data samples). During eSCS-assisted standing, participants supported 73% ± 14% (mean ± standard deviation across all participants) of their body weight through the lower limbs, compared with 18% ± 3% in the OFF condition (linear mixed-effects model; fixed effect = 54%, 95% CI = [48%, 61%], $p < 0.001$; three ON and three OFF condition tests per participant, four participants, corresponding to a total $n = 24$ data samples; Figure 1B).

Higher stimulation frequencies elicited triple flexion of the stimulated lower limb, comprising hip and knee flexion together with ankle dorsiflexion. Stimulation was delivered at 50 Hz in P05, 60 Hz in P06 and P07, and 80 Hz on the left and 60 Hz on the right in P08, using a pulse width of 300 μs. Electrode configurations and stimulation amplitudes are reported in Table 2. Across participants and tested lower limbs, eSCS produced ranges of 94° ± 23° for hip flexion, 136° ± 21° for knee flexion, and 44° ± 28° for ankle dorsiflexion (mean ± standard deviation across all participants). The force generated during hip flexion varied considerably across participants, with a mean value of 114 ± 33 N (mean ± standard deviation across all participants); Figure 1C and Video S2). Triple flexion could be elicited using several ipsilateral electrode contacts, providing flexibility in the selection of stimulation configurations for subsequent functional tasks (Figure S2).

Increased stimulation intensity modifies eSCS-induced movement

We found that triple lower-limb flexion could generally be elicited by increasing the stimulation amplitude, pulse width, or frequency of a protocol that, at lower values of these parameters, produced knee extension (Figures 2A and S3; Table S4). This transition was accompanied by increased recruitment of muscles contributing to lower-limb flexion, including the rectus femoris, biceps femoris, and tibialis anterior, together with reduced recruitment of the vastus lateralis, the principal knee extensor (Figure 2B).

To assess the reproducibility of this transition, stimulation amplitude was repeatedly alternated between a lower and a higher value. Low-amplitude stimulation consistently produced strong vastus lateralis recruitment and weak rectus femoris recruitment, whereas high-amplitude stimulation produced the opposite pattern. The two conditions formed clearly separated and readily clustered (Methods – Stimulation-enabled tasks) recruitment regimes, demonstrating a reproducible

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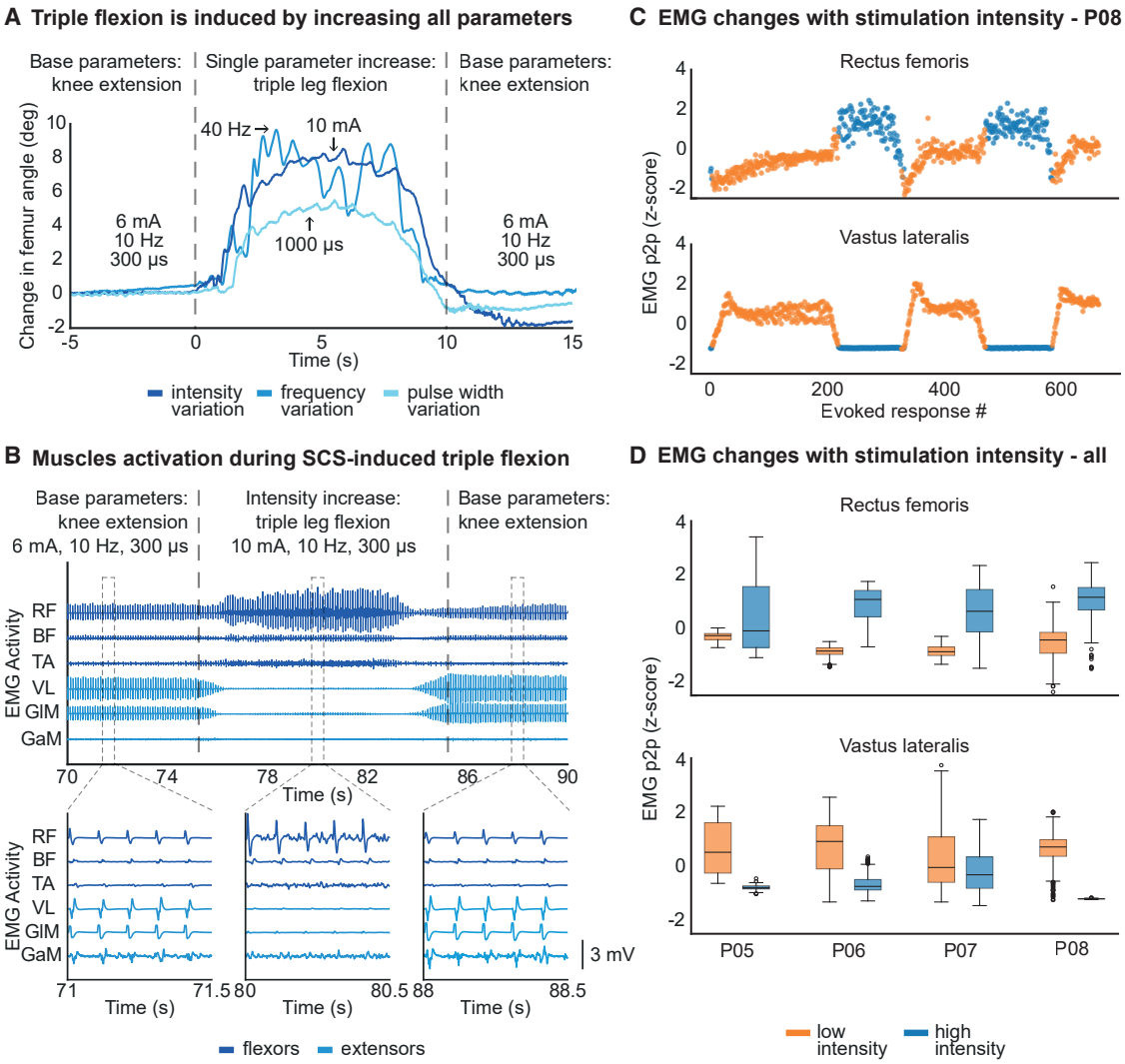

Figure 2. Effect of the modification of stimulation parameters

(A) Change in femur angle produced by increasing each stimulation parameter individually. Example traces from P08 (left leg) showing change in hip angle during stimulation delivered with higher parameters.

(B) Example of EMG activity during triple lower limb flexion in P08 (left leg), obtained during 10 Hz stimulation by increasing stimulation intensity (RF, rectus femoralis; BF, biceps femoris; TA, tibialis anterior; VL, vastus lateralis; GlM, gluteus medius; GaM, gastrocnemius medialis). Stimulation artifacts have been previously blanked from the raw signal.

(C) Examples of EMG compound muscle action potential (CMAP) peak-to-peak values over time from P08 (left leg).

(D) Boxplots of EMG CMAP peak-to-peak amplitudes for the rectus femoris and the vastus lateralis, grouped by low- or high-intensity stimulation. All data were collected using the left leg in all patients.

intensity-dependent switch between extensor- and flexor-dominated motor responses (Figures 2C and 2D). The decrease in vastus lateralis recruitment and the concomitant increase in rectus femoris recruitment were both highly significant (Mann-Whitney U test with Bonferroni correction; $p_{adj} < 0.001$, except for vastus lateralis transitions in P07 where $p_{adj} = 0.2$; rank-biserial correlations [r_{rb}] were 0.995, 0.994, 0.961, and 0.885 for rectus femoris and −0.663, −0.183, −0.246, and −0.986 for vastus lateralis patients P05, P06, P07, and P08 respectively; all available peak-to-peak values have been employed; $n > 100$ for each class).

Trunk-mediated switching between extensor and flexor recruitment regimes enables locomotion

We observed that postural changes can alter stimulation thresholds in eSCS and that such changes in perceived intensity can produce changes in the motor outcome of stimulation. Based on this observation, we then characterized whether small trunk extension movements may trigger a controlled lower limb extension-to-flexion transition. In Figure 3A, we show that from a reclined position with a stimulation program producing leg extension, when participants performed a trunk extension movement, this was followed by an increase of the rectus femoris

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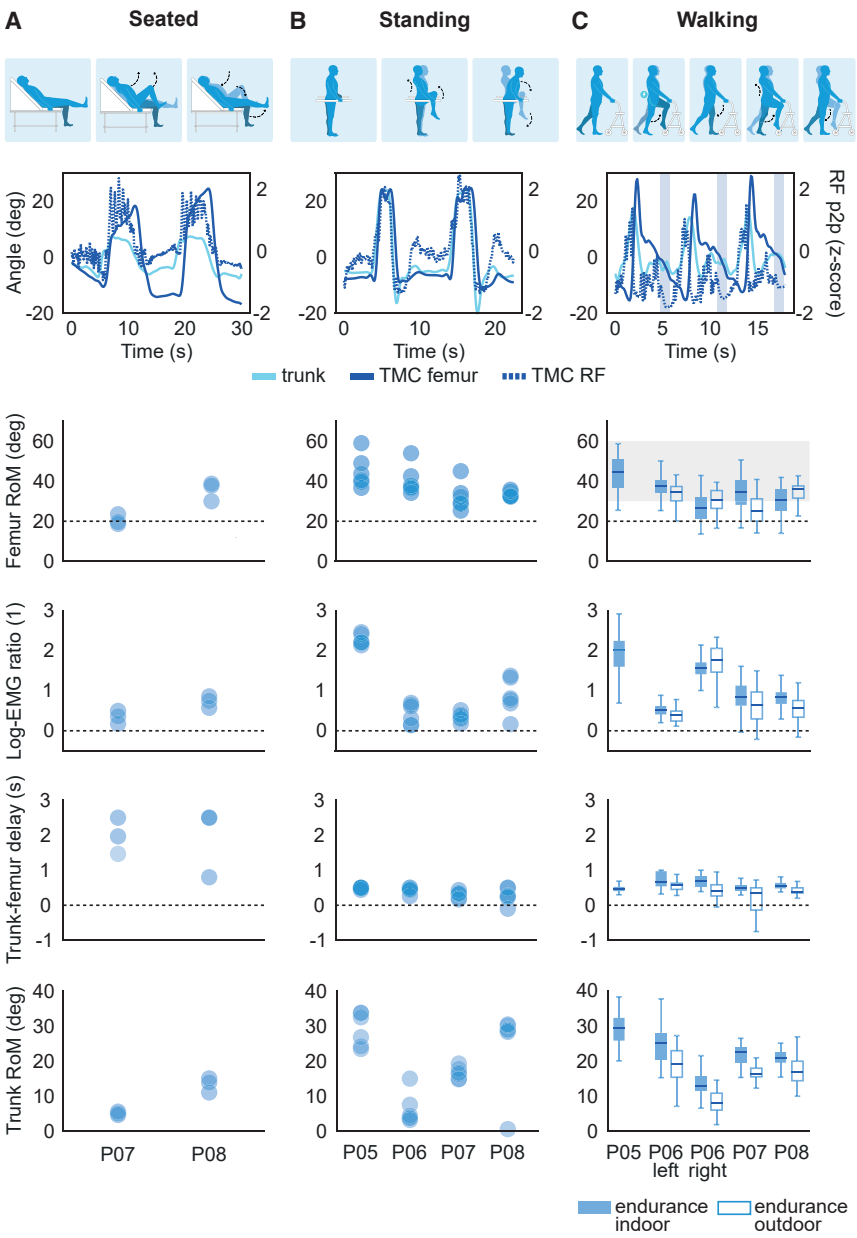

Figure 3. Characterization of trunk-mediated control

Examples of trunk-mediated control (TMC) with the patient in a semi-reclined position (A), standing (B), and walking (C). Graphs at the top are representative data from patient P08 (left leg). From top to bottom the graphs represent the following: the ROM of the femur during TMC lower limb triple flexion; the change in EMG CMAP peak-to-peak values, estimated through the logarithm of the ratio of the EMG peak-to-peak amplitudes at trunk movement onset and peak; the delay between the movement of the trunk peak extension and the TMC hip peak flexion; and the ROM of the trunk during TMC. P05 and P07 used TMC on the right side, P06 bilaterally, and P08 on the left side.

EMG activity and thus by a hip flexion movement (see Table S5 for the employed stimulation protocols). When the trunk was returned to the initial rest position, the lower limb returned extended. We report that the hip flexion caused a femur angular movement of 28° ± 8° (mean ± standard deviation across all participants); its peak was systematically preceded by the peak of trunk extension (1.96 ± 0.64 s), which in turn corresponded to an increase in rectus femoris-evoked response with respect to the rest position. The trunk extension required to evoke hip flexion was 9° ± 4°.

Then, with the participant standing at the parallel bars thanks to the bilateral knee extension generated by eSCS, we determined whether this lower limb extension-to-flexion transition could be elicited on one lower limb (TMC side) without destabilizing the participant. The stimulation intensity on the TMC side was set just below the threshold at which the motor outcome changed from extension to flexion, while the intensity on the contralateral side was set at the lowest value providing functional support during standing (see Table S6 for the employed stimulation protocols). The participant was then instructed to perform trunk extension movements to control the knee-extension-to-triple-flexion transition in the TMC side while standing (Figure 3B). Again, we measured the femur angular movement (37° ± 8°; mean ± standard deviation across all participants) and found that the trunk movement preceded the femur movement (mixed-effects linear model, intercept = 0.38 s, 95% CI = [0.29, 0.46] s; z-test with the alternative hypothesis of delay greater than zero, $p < 0.001$; six samples for each one of the four patients) and was associated to an increase of rectus-femoris-evoked EMG (mixed-effects linear model, intercept = 0.98, 95% CI = [0.22, 1.73], $p = 0.006$; six samples for each one of the four patients). Interestingly, participant P06 was able to identify specific trunk movements to induce selective left or right triple flexion during knee extension stimulation (Video S3).

To enable locomotion, bilateral alternated hip flexion is needed. Therefore, for all participants except P06, a cyclic stimulation program to induce triple flexion in the lower limb not controlled via TMC (contralateral cyclic stimulation [CCS]) was added to provide the possibility for alternated hip flexions enabling gait. This additional program was set at a frequency between 40 and 100 Hz (optimal frequencies were empirically determined to be 40 Hz in P05, 60 Hz in P07, 100 Hz in P08) and was activated cyclically (e.g., 1 s ON and 4 s OFF, based on

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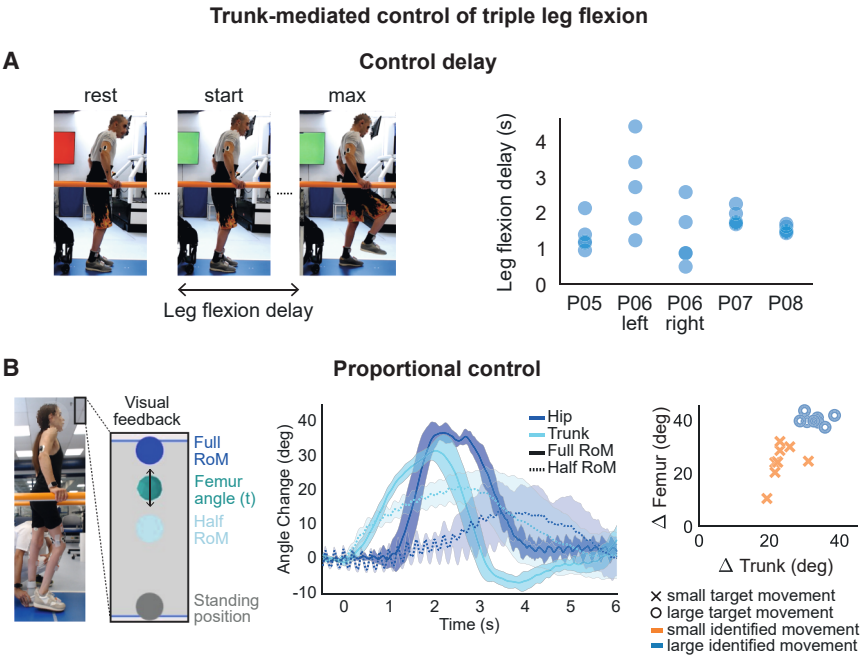

Figure 4. Estimation of controllability and reliability of TMC

(A) Delay between visual cue and TMC hip flexion peak.

(B) Proportional control of TMC-mediated hip flexion; (*Left*) Representation of the task. Standing position and full- and half-range-of-motion (RoM) circles are the targets for the real-time representation, (green circle). (Middle) Average of movement repetitions for the half- and full-ROM movements. (*Right*) Clustering of the movements based on the change in trunk and femur angle. All data are from P08.

(C) Habituation during walking; (*Left*) Example of femur ROM for both TMC (left leg) and CCS (right leg) in P08. (*Right*) Estimation of habituation in all patients during endurance walking. P05 and P07 used TMC on the right side and CCS on the left. P06 used TMC bilaterally. P08 used TMC on the left side and CCS on the right side.

participant preferences), using contacts and stimulation intensities selected to produce a reliable, controlled triple flexion without interfering with the TMC side triple flexion (see Table S7 for the employed stimulation protocols). This allowed all participants to walk with eSCS programs ON, using a walker and foot-ankle orthoses if necessary (Methods – Patient management and training) but without the need of any manual assistance nor body-weight support. In Figure S4, we show the sequence of events enabling locomotion. In Figure 3C, we show hip flexion ranges (first quartile above 20° in all endurance tests and median above 30° in seven out of nine endurance tests), trunk extension-hip flexion peak delays (Wilcoxon test with Bonferroni correction, $p_{adj} < 0.001$ for all endurance tests except for P07 outdoor endurance, where $p_{adj} = 0.01$; $r_{rb} = 0.9$ except for P07 outdoor endurance, where $r_{rb} = 0.5$; 50 samples for each of 9 endurance tests), and rectus femoris EMG increase contextual to trunk extension (Wilcoxon test with Bonferroni correction; $p_{adj} < 0.001$ for all endurance tests; $r_{rb} > 0.97$; 50 samples for each of 9 endurance tests). Across all endurance tests performed by all patients, trunk flexion-extension ranges had a median lower than 30°.

Trunk-mediated control is reliable and controllable

We next evaluated whether TMC could generate hip flexion that was both controllable and reliable. Controllability was defined as the ability to elicit flexion at the intended time and achieve distinct hip-flexion responses, whereas reliability referred to the consistency of the achieved flexion angle across repeated movements and over time. We first asked all participants to perform TMC-mediated hip flexion in response to a visual cue while maintaining an eSCS-enabled standing position at the parallel bars and quantified the delay between cue presentation and peak hip flexion (Figure 4A and Video S3). Except for P06, who was additionally required to selectively control left- and right-sided hip flexion through TMC, all participants successfully produced a visible hip-flexion movement in every trial before the subsequent visual cue. Across participants, peak hip flexion was reached on average 1.8 ± 0.8 s (mean ± standard deviation) after cue presentation. We then assessed whether TMC enabled achieving different magnitudes of evoked hip flexion. During a non-immersive virtual-reality task while maintaining an eSCS-enabled standing position at the parallel bars, participant P08 produced two distinct hip-flexion profiles by performing trunk-extension movements of different amplitudes (Figure 4B and Video S4). These two movement conditions resulted in clearly separated hip-flexion responses, with the corresponding profiles occupying distinct regions of the joint space defined by peak trunk extension and peak hip flexion. Gaussian-process clustering distinguished the two response profiles with a homogeneity score of 1.

Finally, to characterize reliability, we evaluated the decrease in hip-angle range for the TMC and CCS sides across the first 50

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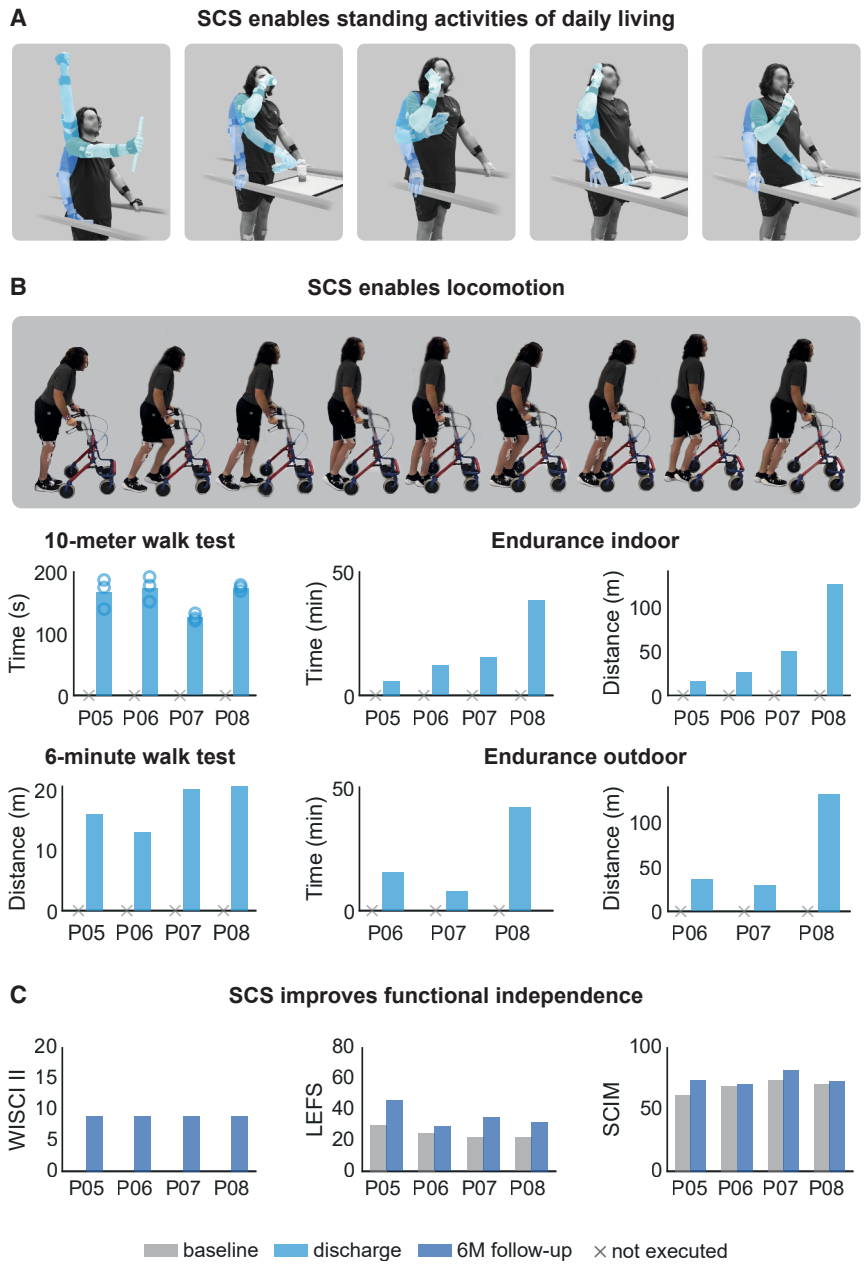

Figure 5. Functional outcomes at hospital discharge and follow-up

(A) Activities of daily living performed while standing with unimanual support (P07).

(B) (*Top*) Examples of gait patterns obtained with TMC of triple flexion and contralateral cyclic stimulation in P07. (*Bottom*) Gait outcomes include the results of 10 meters walking test, 6-min walking test, as well as the indoor and outdoor endurance. P05 did not perform any outdoor endurance.

(C) Clinical scales at baseline and at the end of the study. At baseline, all patients had a WISCI II score of 0.

steps of indoor endurance walking in all participants (Figure 4C). Comparing the median range of the last to first 10 steps, we obtained values always higher than 0.79. Both endurance tests in P08 and indoor endurance in P07 were long enough to also compute the same habituation ratio across the first 100 steps, which displayed similar values, with a minimum value of 0.77 (Figure S5).

Longitudinal functional outcomes

Even though throughout the duration of this study none of our participants recovered any degree of voluntary direct control of lower limb muscle contraction (maintaining 0 MRC score on every lower limb muscle), all four participants were able to independently stand and walk with eSCS ON. Even though participants required their arms to keep balance at the parallel bars, by the end of the study, participants P05, P07, and P08 managed to maintain standing even with unimanual support, so that they could use one hand to perform daily activities. Figure 5A and Video S5 show participants performing a variety of functional tasks while standing, such as removing a jacket, a task requiring considerable coordination and mid-task transfer of support from one hand to the other. Participants P07 and P08 also demonstrated the ability to perform fine-manipulation tasks that required precise handling of small objects while standing (e.g., playing Jenga; Video S6).

Likewise, all four participants were able to ambulate independently (without manual assistance nor body-weight support) using TMC-/CCS-based eSCS (Figure 5B). All participants were able to perform the 10-meter walking test (161 ± 25 s; mean ± std across all participants) and the 6-min walking test (17 ± 4 m; mean ± std across all participants), showing the ability to cover short indoor distances. When tasked with endurance tests, P06, P07, and P08, all could walk more than 10 min without any pause, with P08 notably covering more than 132 meters over 42 min. Participants were also able to walk over inclines, perform turns, and walk outdoor over uneven, rugged concrete surfaces (Video S7).

Before implantation and at 6 months, corresponding to the end of the study period for each participant, we assessed the WISCI II, LEFS, and SCIM scores (Figure 5C). The most pronounced change was observed in the WISCI II, with all participants improving from a score of 0 (unable to stand or walk) to a score of 9 (walking 10 m with a walker and orthoses). For the LEFS, P05, P07, and P08 showed improvements exceeding

the minimal clinically important difference (MCID) of nine points. For the SCIM, improvements exceeding the MCID of four points were observed only in P05 and P07.

Throughout active eSCS sessions, participants were continuously monitored clinically and were systematically questioned regarding any symptoms suggestive of autonomic dysfunction. No one reported symptoms compatible with hypotension (e.g., lightheadedness, blurred vision, and nausea), nor symptoms suggestive of excessive sympathetic activation, such as severe headaches, palpitations, or epistaxis. In P07 and P08, blood pressure and heart rate were monitored during active stimulation sessions in the standing positions with CCS active (Table 8). No clinically relevant abnormalities were observed, and the modest increase in heart rate recorded was considered a physiological response to exercise rather than a stimulation-related adverse effect.

DISCUSSION

In this study, we have shown that a commercial spinal cord stimulator can be used to allow independent standing and walking in motor-complete (AIS A-B) participants with no evidence of a discomplete lesion, exploiting our newly introduced TMC without requiring adaptive spatiotemporal patterns of eSCS.

After establishing that parameter changes associated with increased charge delivery to the targeted neural structures could induce a switch from extensor to flexor activation (Figure 2), we investigated whether this phenomenon could be harnessed through changes in trunk posture. Previous studies have demonstrated that posture can substantially modulate sensory thresholds during eSCS,[9–12] a known challenge when dealing with neuropathic chronic pain. Instead, we sought to exploit it by determining whether small trunk flexion-extension movements could alter the effective stimulation intensity enough to trigger a controlled transition from lower-limb extension to flexion.

We termed this strategy TMC. During locomotion, TMC enabled a participant-initiated transition from an extensor-dominated stance phase, which provided weight support, to a flexor-dominated swing phase, which advanced the lower limb. Based on these encouraging initial observations, we developed a training pipeline to incorporate TMC into an eSCS-assisted walking strategy. Participants first practiced TMC while seated under bilateral extensor stimulation, using trunk movements to induce unilateral lower-limb triple flexion. They then practiced the same strategy while standing with tonic bilateral extensor stimulation. During the initial training sessions, P06 identified distinct trunk movements that could induce either left or right triple flexion under the same knee-extension stimulation. The other participants, however, were initially unable to control this transition independently on both sides. Because our primary objective was to enable locomotion in this severely impaired population within the limited duration of allowed hospitalization for our trial, and because bilateral TMC control could not be assumed to be achievable in all participants even with intensive training, we adopted a hybrid strategy. TMC was trained on the side in which triple flexion could be elicited most reliably, whereas CCS periodically evoked triple flexion in the opposite limb. Participants learned to alternate TMC-induced flexion on one side with CCS-induced flexion on the other, thereby reproducing the basic bilateral coordination required for stepping. They subsequently refined the timing of their trunk movements to interleave TMC-induced steps with CCS-induced contralateral steps, ultimately enabling walker-assisted locomotion (Figures 2D and S5). Training progressed relatively rapidly: participants generally achieved standing within the first month, began walking practice during the second or third month, and were discharged after approximately 4 months.

At no point during the study did any participant recover the ability to voluntarily elicit visible muscle contractions in body regions affected by the SCI. All lower-limb contractions and movements, including those required for locomotion, were generated through tailored eSCS programs. Accordingly, baseline or stimulation-OFF assessments of lower-limb motor performance were not informative, except for standing at the parallel bars. In the OFF condition, participants lacked sufficient lower-limb rigidity to support a substantial proportion of their body weight and therefore relied predominantly on their upper limbs to maintain an upright posture. This comparison was included to demonstrate that the prolonged standing endurance observed during stimulation could not be explained by arm support alone but depended on eSCS-induced lower-limb extension. In this first report, we did not specifically assess whether repeated eSCS produced long-term therapeutic changes in the strength of stimulation-evoked contractions, nor did we quantify the longitudinal effects of the motor training itself.

In line with past studies,[7,13] we found that tonic eSCS can support robust and sustained standing by generating stable knee extensor activity and reliable lower limb weight bearing for periods approaching or exceeding 1 h, without muscle fatigue becoming functionally limiting, as often occurs in functional electrical stimulation (FES) paradigms for prolonged standing and locomotion.[14,15] Classical FES studies have reported marked muscle fatigue only after a few minutes of continuous stimulation,[16,17] resulting in limited standing endurance (e.g., a median standing time of 3 min reported in Mushawar et al.[18]), and, in some cases, knee collapse during walking.[19] Although isolated reports have documented substantially longer standing times, including several hours in Krajl et al.,[16] the broader FES literature indicates that patients have rarely sustained standing for more than 30 min.[20] Moreover, quadriceps stimulation alone has often been insufficient to support walking, as illustrated by Marsolais and Kobetic,[21] in which only one of three participants completed a walking endurance test, and by Kobetic et al.,[19] in which knee bracing was required.

The precise physiological basis of TMC remains to be clarified and will require future investigations combining animal experiments with biomechanical[22–24] and neuro-electric modeling.[7,24–27] Nevertheless, several observations emerge from this initial clinical report. The ability to elicit triple flexion by increasing stimulation amplitude, pulse width, or frequency for a given electrode configuration (Figure 1A), together with the concurrent suppression of activity in other muscles (Figure 1D) and the consistent emergence of triple flexion across the tested paddle contacts (Figure S2), suggests that this coordinated lower-limb response reflects recruitment of a spinal circuit or reflex whose output becomes dominant over the more segmentally organized afferent-to-efferent

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responses typically observed during low-frequency eSCS. Such segmental responses have been supported by computational,[7,26,28,29] animal,[26] and human[30] studies. Conventional eSCS protocols generally recruit muscles according to the segmental organization of the spinal cord, with hip flexors and knee extensors typically represented more rostrally than knee flexors, ankle dorsiflexors, and plantar flexors.[31] Muscles innervated by the same spinal segment are therefore often recruited concurrently and may co-contract during eSCS.[2,3]

Taken together, these observations support the interpretation that triple flexion may result from activation of a withdrawal-like spinal response, a phenomenon initially described by Sherrington in 1910 and previously explored as an FES strategy during the 1980s and 1990s.[32–36] This interpretation is also consistent with the higher stimulation intensities required to elicit triple flexion compared with lower-limb extension (Table S2). Low-threshold extensor responses during eSCS are generally attributed to the recruitment of large-diameter proprioceptive afferents,[26] whereas the human withdrawal reflex is conventionally associated predominantly with high-threshold, thinly myelinated Aδ cutaneous afferents,[37,38] which exhibit higher electrical stimulation thresholds.[39,40] Although a withdrawal-like reflex provides a plausible interpretation, the precise mechanisms and neuronal populations through which eSCS produces lower-limb triple flexion remain beyond the scope of this study. Future modeling and electrophysiological investigations will be required to clarify the underlying physiology.

One of the principal limitations of withdrawal-reflex-mediated triple flexion described in the FES literature is habituation, which progressively reduces flexion amplitude across repeated stimuli.[41,42] Here, at the gait-cycle durations used by our participants, approximately 5–6 s, only modest habituation was observed (Figure 3C), and it did not prevent continuous endurance walking for periods of up to 40 min. This finding is consistent with von Dincklage et al.,[43] who reported that interstimulus intervals of several seconds substantially reduce habituation, even at moderate stimulus intensities. No participant reported stimulation-related discomfort during these sessions. Moreover, the absence of separate fine control over hip, knee, and ankle flexion did not prevent effective limb advancement. On the contrary, the coordinated activation of hip and knee flexors together with ankle dorsiflexors may help address the well-known difficulty of managing foot drop through eSCS alone.[44]

The triple-flexion response observed during TMC resembled that elicited by increasing stimulation amplitude, pulse width, or frequency for a fixed electrode configuration, suggesting that trunk movements may increase the effective stimulation intensity experienced by the targeted neural structures. This interpretation is consistent with previous reports proposing that postural changes can alter sensory thresholds by modifying the geometry between stimulating electrodes and target neural structures,[45] as well as experimental evidence that neck extension reduces the dorsal subarachnoid space.[46] We therefore hypothesize that trunk movements transiently alter the geometry of the spinal canal or the position or tension of the spinal roots, thereby modifying their responsiveness to a fixed stimulation program. Through this mechanism, participants may have been able to switch between lower-limb extension and triple flexion without changing the programmed stimulation parameters.

In conclusion, we show that individuals with motor-complete SCI can use small, deliberate trunk movements to modulate the effects of eSCS and initiate a transition from an extensor-dominated configuration, supporting upright posture and weight bearing, to a coordinated triple-flexion pattern suitable for limb advancement. After training, participants were able to use TMC to elicit repeatable and graded flexion responses with predictable timing. When combined with CCS, this strategy enabled walker-assisted overground locomotion despite the absence of visible voluntary lower-limb contractions without stimulation. Participants also reported that trunk movements could modulate the response of the cyclically stimulated limb, although this observation was not formally quantified. Rather than reproducing a physiological gait pattern, the present approach provides a pragmatic means of restoring patient-initiated locomotion in a profoundly impaired population. Importantly, it was implemented using a commercially available eSCS system, without continuous kinematic sensing, adaptive stimulation algorithms, or invasive decoding of supraspinal signals. These findings therefore identify TMC as a simple and potentially clinically accessible strategy that allows patients' volitional modulation of stimulation-enabled movement.

Limitations of the study

A major limitation of this study is the small sample size. Nevertheless, the fact that four consecutive participants were able to learn and use this strategy for walker-assisted locomotion supports its potential reproducibility in similarly impaired individuals. The relatively short duration of the protocol represents an additional limitation. Larger studies with longer follow-up will be required to determine the durability of the observed functional gains and their generalizability across different neurological levels, injury etiologies, and clinical profiles.

Because eSCS and training were delivered together and not experimentally dissociated, the longitudinal functional gains observed over the 4-month protocol should be attributed to the combined stimulation-enabled training intervention rather than to TMC or eSCS specifically. Indeed, specific training is necessary for the patient to be able to perform TMC eSCS-assisted locomotion.

The locomotor strategy introduced here also resulted in gait kinematics that were not fully physiological. A more comprehensive characterization of lower-limb kinematics and motor control was beyond the capabilities of the inertial measurement system used in this trial. Future studies should therefore incorporate more accurate motion-capture technologies, such as stereophotogrammetry, to quantify joint trajectories, intersegmental coordination, compensatory trunk movements, and gait symmetry with greater precision.

Future work should also directly investigate whether bilateral TMC can be achieved more consistently in this population. P06 was able to use trunk movements to control triple flexion in both lower limbs, demonstrating that bilateral TMC is feasible in at least some individuals. However, it remains unclear whether all patients could acquire independent bilateral control with more extensive training. Should this not be the case, computational

modeling and neuroimaging could help determine whether inter-individual differences in spinal anatomy, electrode position, or residual neural connectivity influence the feasibility of each control strategy. Such approaches may ultimately support the prospective identification of the stimulation and training paradigm best suited to each patient.

Even though the reinstated locomotion allowed patients who are chronically completely paralyzed to cover short distances at limited speed, our protocol offers important clinical, social, and personal benefits. Locomotion provides a task-specific cardiovascular and musculoskeletal workout that supports the maintenance of bone density, muscle trophism, and aerobic fitness.[47–50] Socially, even short episodes of upright standing promote face-to-face communication, facilitate engagement in family and community life, and enhance independence.[51] On a personal level, it re-establishes a basic motor function, fostering a sense of agency, motivation, and psychological well-being. Further studies with longer observation periods will be required to confirm these benefits and establish appropriate benchmarks for assessing functional performance in this emerging population of patients who regain the ability to walk despite being unable to ambulate without assistance. Existing normative values and MCID were developed for ambulatory populations and may therefore not adequately capture meaningful changes in these individuals. Notably, even though stair climbing was not an explicit goal of rehabilitation, some participants were able to ascend several steps, suggesting that the results presented in this report may be a first step toward the use of commercially available spinal cord stimulators to promote increased independence and quality of life for motor-complete SCI patients.

RESOURCE AVAILABILITY

Lead contact

Requests for further information and 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 according to data sharing agreements between the institutions involved.
- The code employed to perform data analysis has been deposited at https://doi.org/10.5281/zenodo.21771970 and is publicly available as of the date of publication.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

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AUTHOR CONTRIBUTIONS

Conceptualization: F.A., D.E., L.A., S.R., S.I., P.M., S.M.; Data curation: F.A., D.E., S.R.; Formal analysis: F.A., S.R.; Funding acquisition: L.A., S.I., P.M., S.M.; Investigation: F.A., D.E., L.A., S.R., F.G., F.C., E.P., M.S., V.F., C.C., L.T., F.A., L.B., P.C., J.D.P., L.R.B., C. Mandeli, C. Mura, H.C., C.B., U.D.C., A.C.; Methodology: F.A., D.E., S.R., E.L.; Project administration: L.A., A.T., J.C., S.I., P.M., S.M.; Resources: L.A., A.T., A.F., M.F., S.I., P.M., S.M.; Software: F.A., S.R.; Supervision: P.I., P.M., S.M.; Validation: F.A., S.R., E.L.; Visualization: F.A., D.E., S.R., E.L.; Writing – original draft: F.A., D.E., L.A., S.R., S.M.; Writing – review & editing: all authors. F.A., D.E., L.A., S.R. had unrestricted access to all data. All authors read and approved the final article and take responsibility for its content.

DECLARATION OF INTERESTS

L.A. and P.M. receive or have received research support from Boston Scientific. L.A. receives or has received research support from Fondazione Cariplo. S.M. holds patents on spinal cord stimulation technologies (US20170354819a1, "System for selective spatiotemporal stimulation of the spinal cord"; US10279167B2, "System to deliver adaptive epidural and/or subdural electrical spinal cord stimulation to facilitate and restore locomotion after a neuromotor impairment"; US10265525B2, "System to deliver adaptive epidural and/or subdural electrical spinal cord stimulation to facilitate and restore locomotion after a neuromotor impairment"; CA2874101C, "Apparatus and method for restoring voluntary control of locomotion in neuromotor impairments"; US11420062B2, "Neurostimulation system for central nervous stimulation (CNS) and peripheral nervous stimulation (PNS)"; US10981004B2, "System for selective spatiotemporal stimulation of the spinal cord"; and WO2018114906A1, "A sensory information compliant spinal cord stimulation system for the rehabilitation of motor functions").

STAR★METHODS

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

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SUPPLEMENTAL INFORMATION

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
Analysis of experimental data	This paper	https://doi.org/10.5281/zenodo.21771970
Matlab	Mathworks Inc., Natick, Massachusetts, United States	https://www.mathworks.com
Python	Python Software Foundation	https://www.python.org/
Other		
Epidural electrical stimulation device	Boston Scientific Spa, Marlborough, USA	https://www.bostonscientific.com/
Inertial Measurements Units acquisition system	MTw Awinda, Xsens, Netherlands	https://www.xsens.com/
Surface electromyography system	Wave X, Cometa srl, Milan, Italy	https://www.cometasystems.com/
Handheld dynamometer for force measurement	NOD, OT Bioelettronica, Turin, Italy	https://otbioelettronica.it/
Stabilometric platform and Biofeedback system	VRRS EVO, Khymeia, Padova, Italy	https://khymeia.com/
Intraoperative electromyography	Inomed Medizintechnik GmbH, Emmendingen, Germany	https://www.inomed.it/

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Patient enrollment and surgery

All experiments were carried out as part of an ongoing clinical feasibility study which investigates the effects of eSCS 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 eSCS 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 eight weeks. After discharge, the participants are examined at IRCCS Ospedale San Raffaele institute at the sixth month, and undergo a review of clinical history, physiological anamnesis and neurological, neurophysiological, neuro-psychological and neuroimaging assessments. At enrollment, all participants presented MRC grade 0 in all lower limb muscles.

The participants underwent surgical procedure of lumbar laminectomy, paddle lead insertion and internal pulse generator (IPG) implant under general anesthesia. In detail, after placing the participant 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 participant 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 eSCS 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.

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Participants information on sex, age, gender and race was physician-reported. Information on socioeconomic status was not collected.

METHOD DETAILS

Patient management and training

General management of patients

The participants underwent daily in-patient rehabilitation/training program during the postoperative hospitalization. Physiotherapy was administered five days per week through therapist-guided sessions led by specialized physiotherapists at IRCCS Ospedale San Raffaele.

Each rehabilitation session was preceded by a 20-min bout of passive, static stretching of the lower limbs, conducted twice daily. The sequence was standardized and applied in the same order at every session focusing on muscle groups that are particularly susceptible to hypertonia and shortening after complete spinal cord injury. This was intended to lower resting muscular activity and limiting the emergence of contractures, thereby facilitating subsequent task-specific training. A dedicated program to preserve and augment upper-limb strength was implemented throughout the hospital stay. Sessions combined calisthenic exercises, free-weight routines, and machine-based resistance work, with the intensity and modality adjusted to each participant's capabilities. The rest of the time, participants underwent either passive eSCS lower limb stimulation or performed functional tasks enabled by eSCS such as standing and locomotion. The division of participant rehabilitation and eSCS-enabled training is illustrated in Figure S6.

Design of stimulation protocols

Stimulation protocols comprised one to four stimulation areas, each defined by an electrode configuration and specific stimulation intensity, frequency, and pulse width. Pulse width was maintained at 300 μs in all protocols. Each electrode configuration consisted of a set of anodes and cathodes selected from the 32 contacts of the epidural paddle or the implantable pulse generator (IPG) case. Each active electrode was assigned a percentage indicating the proportion of the total current delivered through a cathode or collected through an anode. All stimulation protocols used in this study are reported in Tables S2–S7.

To identify the optimal electrode configurations for knee extension, mapping was performed separately for each lower limb while the participant was in a semi-seated position, with the feet unsupported. Stimulation was delivered at 10 Hz, and the current amplitude was progressively increased until the maximal achievable knee extension was obtained. During this procedure, care was taken to minimize the co-activation of the hamstring, adductor, and gastrocnemius muscles. Electrode configurations for eliciting triple flexion were subsequently mapped bilaterally, resulting in one stimulation program for each side. These evaluations were performed with the participant in the supine position to ensure safety and allow unrestricted joint excursion.

The stimulation program used for standing was generally obtained by concurrently activating the two stimulation areas selected to induce unilateral knee extension. When necessary, additional stimulation areas were included to recruit the gluteal, abdominal, and/or paraspinal muscles. All tuning was performed empirically through palpation.

The locomotion program was generally derived from the standing program and subsequently adjusted according to the side selected for trunk-mediated triple flexion. On this side, the amplitude of the knee-extension stimulation was set immediately below the threshold at which trunk movement triggered triple flexion. On the contralateral side, the stimulation amplitude was set to the lowest value that still provided reliable knee extension. Cyclic stimulation of the contralateral limb was generally based on the electrode configuration previously identified for eliciting isolated triple flexion, with stimulation parameters adjusted to account for interactions with the concurrently active stimulation areas. Each contralateral stimulation cycle lasted 1 s (or 2 s with 1 s of ramp, based on participant preference). The interval between successive cycles was progressively shortened during training, with all participants ultimately using inter-cycle intervals of 4–6 s.

eSCS-enabled training program

The eSCS-enabled training program combined passive stimulation-assisted exercise with active functional training. Passive exercise was used to repeatedly mobilize the lower limbs through knee extension and triple flexion, whereas active training followed a progressive pathway from isolated trunk-mediated control to standing and overground locomotion.

Participants completed daily passive eSCS-assisted exercise targeting knee extension and lower-limb triple flexion. Knee extension was trained in a semi-seated position using a program that produced bilateral leg extension. Stimulation was delivered in cycles of 5 s on and 5 s off, and participants were instructed to complete at least 20 min of exercise per lower limb each day.

Triple flexion was trained separately for each lower limb using cycles of 3 s of stimulation followed by 8 s without stimulation. Participants were instructed to complete approximately 10 min of triple-flexion exercise per lower limb each day. These exercises were performed independently after the stimulation programs had been configured and their safe execution had been verified by the clinical team.

Active training followed a stepwise progression from isolated trunk-mediated control in a semi-seated position to standing and overground locomotion. During the initial phase, participants were positioned with the feet unsupported and received unilateral stimulation producing sustained knee extension. The stimulation amplitude was adjusted to immediately below the threshold at which triple flexion occurred without an intentional trunk movement. Participants were then instructed to extend the trunk to trigger the transition from knee extension to lower-limb triple flexion.

Both lower limbs were initially evaluated. Except when reliable control could be achieved bilaterally, the side on which triple flexion was elicited most consistently and with the least effort was selected for trunk-mediated control (TMC) training. Participants subsequently practised this task independently for approximately 30 min per day to improve the reliability and timing of the transition.

Standing was trained in parallel using a stimulation program that produced bilateral lower-limb extension. Participants initially stood between parallel bars with upper-limb support and physiotherapist assistance. Assistance was progressively reduced and daily training continued until they could maintain an upright posture with extended knees while applying only light hand support to the bars. Daily standing practice was then expanded to include unidirectional and multidirectional weight shifting, standing with unilateral hand support, and task-specific functional activities. When required, additional stimulation areas targeting the gluteal, abdominal, or paraspinal muscles were incorporated to address participant-specific postural and biomechanical requirements.

Once TMC could be performed reliably in the semi-seated position, participants reproduced and refined the same strategy during standing at the parallel bars. They practised using trunk extension to induce triple flexion of the TMC-controlled limb while maintaining extension and weight support through the contralateral limb. Training focused on coordinating trunk movement with the stimulation-induced transition, unloading the flexing limb, and preserving postural stability during limb advancement.

Locomotor training was initially performed between parallel bars under close physiotherapist supervision. The walking program combined TMC on the selected side with cyclic contralateral stimulation (CCS), which periodically elicited triple flexion of the opposite limb. Training subsequently progressed to indoor overground walking using either a two-point or four-wheeled walker, selected according to the participant's balance and support requirements.

Walking distance and session duration were progressively increased, and endurance exercises were adapted to individual tolerance. Therapist assistance was gradually reduced as participants became more capable of initiating steps, transferring weight, and maintaining balance. The interval between successive CCS cycles was also progressively shortened to increase stepping frequency as coordination between TMC and cyclic stimulation improved.

Turning was practised using the TMC-controlled limb as the pivot, while repeated CCS-driven steps of the contralateral limb traced a progressive arc. Step amplitude, trunk orientation, and walker positioning were adjusted until the participant could complete an approximately 180° turn while maintaining balance.

Orthotic management

- P05. The participant achieved independent standing and walking without the need for lower-limb orthoses.
- P06. Because of bilateral gastrocnemius muscular retractions, custom-made AFOs were fabricated from plaster casts. The orthoses incorporated a heel lift to accommodate the plantarflexed ankle position while providing stable ankle alignment during standing and gait training. These orthoses were used throughout both standing and walking activities.
- P07. Bilateral SaeboStep dorsiflexion assist orthoses were prescribed to maintain ankle dorsiflexion during the swing phase of gait and reduce foot drop. In addition, custom-made foot orthoses were fabricated to control excessive subtalar pronation during both standing and walking.
- P08. A left SaeboStep dorsiflexion assist orthosis was used during gait training to maintain ankle dorsiflexion during the swing phase and reduce foot drop. A right Peromed ankle orthosis was prescribed to control ankle inversion/eversion, providing mediolateral ankle stability during standing and gait.

Data acquisition and processing

Surface electromyographic signals

EMG data were collected at 2000 Hz using a 16 channels wireless system (WaveX, Cometa Systems, Italy) with bipolar superficial electrodes positioned on the selected muscles according to the guidelines presented in.[52] Recordings were obtained bilaterally from gluteus maximus, gluteus medius, rectus femoris, vastus lateralis, biceps femoris, tibialis anterior, gastrocnemius. Rectus femoris muscle activation was employed to monitor hip flexions due to its ease of access compared to the iliopsoas, that is instead the main hip flexor but is deep and is routinely recorded through needle EMG. After visually inspecting the raw signals, we removed stimulation artifacts through blanking. The length of blanked sections depended on the number of stimulation areas concurrently activated but it never affected the shape of the evoked CMAPs. We extracted from each CMAP its peak-to-peak amplitude and employed that as a proxy for local muscle activation in time.

Inertial kinematic measurements

Kinematic measurement were acquired at 100 Hz using seven IMU sensors (MTw Awinda, Xsens, Netherlands) positioned on the participant's sternum, femurs, tibias, and feet. Knee and ankle angles were computed from the two sensors placed on femur and tibia, and tibia and foot respectively. To obtain good estimates of hip angles, an IMU placed on the sacrum would be required. We could not place this sensor because applying pressure in an area where the participants had reduced sensation could cause skin injury without their awareness. If the trunk does not undergo much flexion-extension, the sensor on the sternum has been at times been used as a replacement for the sacrum sensor. Since in this work trunk movements were the only way our participants had to modulate the effects of stimulation on their lower limbs, they were carried to continuously perform trunk flexion-extensions, making the estimate of hip angles using femur and sternum/trunk sensors unreliable. Thus, we decided to estimate hip angles using the pose of the femurs alone.

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Muscle-exerted force measurements

Force values reported for knee extension and hip flexion were collected using a dynamometer (NOD hand-held dynamometer OT Bioelettronica). With participants sitting or supine, the device was positioned close to the limb slightly above the ankle for knee extension, slightly above the knee for hip flexion and was held in position by a physiotherapist while stimulation was delivered. Peak force values were recorded.

Weight discharged through lower limbs while standing

During standing tests, participants stood upon a force platform (stabilometric balance, Khymeia, Italy) sampling at 120 Hz. Fraction of weight was obtained by averaging over time the force discharged through the platform and dividing it by the participants' weight.

Blood pressure and heart rate measurements

In P07 and P08 we measured blood pressure and heart rate using a blood pressure monitor (IntelliVue MX450, Philips, Netherlands) with the patient sitting at rest, immediately after verticalization and after 10 min. During these tests eSCS for standing was active together with CCS.

Stimulation-enabled tasks

Participants were evaluated on several tests, ranging from isolated movements to standing and walking.

Passive eSCS-elicited movements

The range of motion and force generated during stimulation-evoked knee extension and lower-limb triple flexion were assessed separately for each limb. All measurements were repeated three times.

For knee-extension testing, participants were positioned semiseated with the knee aligned with the edge of the examination table and the lower leg hanging freely, such that the tibia was approximately perpendicular to the floor at rest. Stimulation was then activated to elicit knee extension and subsequently deactivated, allowing the lower leg to return passively to its initial position. Knee-extension range of motion was quantified as the angular excursion of the tibia from the resting position to the maximal extension reached during stimulation.

Knee-extension force was assessed in the same position using a handheld dynamometer placed against the distal anterior tibia, close to its resting position. The physiotherapist resisted the stimulation-evoked movement to obtain an approximately isometric contraction, and the peak force across the three trials was retained for analysis.

For triple-flexion testing, participants were positioned supine with both lower limbs fully supported on the examination table. Stimulation was activated to elicit simultaneous hip and knee flexion together with ankle dorsiflexion. After stimulation was discontinued, the physiotherapist gently returned the limb to the starting position. The maximal angular excursions of the hip, knee, and ankle from the resting position were quantified during each trial.

Triple-flexion force was subsequently assessed using a handheld dynamometer positioned against the anterior aspect of the distal thigh, immediately proximal to the knee. The physiotherapist resisted the stimulation-evoked hip flexion to obtain an approximately isometric contraction, and the peak force across the three trials was retained.

Because none of the participants exhibited visible voluntary contractions of the lower-limb muscles at any time during hospitalization, isolated movements could not be elicited in the absence of stimulation. Accordingly, no baseline or stimulation-OFF measurements were performed for these assessments.

We showed the transition between extensor- and flexor-dominated motor responses produced by changes in stimulation parameters. Participants were positioned as described for the isolated knee-extension assessment, with the lower leg hanging freely from the examination table. Two stimulation programs were applied that differed only in one parameter (i.e., only one between current amplitude frequency, or pulse width), while electrode configuration, and the other parameters remained unchanged. The lower parameters values elicited an extensor-dominated response, whereas the higher values elicited lower-limb triple flexion.

For each participant, stimulation was alternated between the two values to assess transitions in both directions, from the low-to the high-amplitude condition and from the high-to the low-amplitude condition. Three transitions in each direction were recorded, except in P05, for whom technical problems with the acquisition system prevented completion of the full recording protocol.

Further EMG analysis was performed for the change in stimulation intensity, the most relevant parameter with regard to TMC. Surface electromyography was recorded throughout the assessment. Because the commercial stimulation system did not provide synchronization triggers indicating the exact time at which the stimulation amplitude was changed, the transition between stimulation conditions was identified from the evoked electromyographic responses. Specifically, compound muscle action potentials recorded from the vastus lateralis and rectus femoris were grouped using a clustering analysis to distinguish the extensor- and flexor-dominated stimulation regimes. Details of the clustering procedure are provided in the Statistical analysis section of the Methods.

Standing endurance

If necessary (as in the stimulation-OFF condition), participants were assisted from the wheelchair into an upright position between the parallel bars, with both feet placed on a balance platform that continuously recorded the load transmitted through the lower limbs. In the stimulation-ON condition, stimulation was activated while the participant was still seated in the wheelchair and remained active throughout the transfer, standing phase, and endurance assessment.

Standing endurance was timed from the moment the participant reached the upright position and continued until the participant reported exhaustion or requested termination of the test. No body-weight-support system was used, although participants were

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permitted to use their hands on the parallel bars for balance and upper-limb support. For each trial, we recorded standing duration and the weight transmitted through the feet.

On each assessment day, participants completed one trial with stimulation ON and one trial with stimulation OFF, with the OFF being performed aways first and 5 min of rest between the two. Although participants exhibited no visible voluntary contractions of the lower-limb muscles, the stimulation-OFF condition was included to determine whether standing endurance in the ON condition could be explained solely by upper-limb strength and support on the parallel bars, rather than by stimulation-enabled lower-limb extension and weight bearing.

Assessments were repeated longitudinally until the participant achieved a standing duration of at least 40 min. To obtain a stable within-participant estimate and support the statistical comparison between stimulation conditions, the analyses included the final three assessment days available for each participant.

Static trunk-mediated control from seated and standing position

TMC was characterized first in a semi-seated position and then during eSCS-enabled standing. Participants received unilateral stimulation producing knee extension, with amplitude set immediately below the threshold for spontaneous triple flexion. They were instructed to extend the trunk to trigger triple flexion and then return to the initial posture to restore knee extension.

The same task was subsequently performed while standing between parallel bars. Participants shifted weight to the contralateral limb, used trunk extension to flex the TMC-controlled limb, and returned the trunk toward neutral to re-establish knee extension. No body-weight-support system or manual assistance for limb flexion was used.

Trunk and femur kinematics were filtered using a fourth-order low-pass Butterworth filter with a cutoff frequency of 1 Hz. Peak trunk extension and peak femur flexion were detected with a minimum prominence equal to 50% of the robust range of the corresponding signal, defined as the difference between its 95th and 5th percentiles. Each femur-flexion peak was associated with the corresponding trunk-extension peak. Femur and trunk excursions were calculated from the local minimum angle preceding each peak to the peak value, and the trunk-to-hip delay was defined as the time between peak trunk extension and peak femur flexion.

Rectus femoris CMAP peak-to-peak amplitudes were quantified around the basis of the trunk movement (last local minimum before peak) and after peak trunk extension. The extension-associated response was defined as the maximum CMAP amplitude within 0.5 s after peak trunk extension. EMG modulation was expressed as the logarithm of the ratio between the extension- and rest-associated responses, with positive values indicating greater rectus femoris recruitment around trunk extension.

Overground walking

Participants completed the 10-m walk test and the 6-min walk test with eSCS active. For the 10-m walk test, participants walked along a straight 10-m path, and the time required to complete the distance was recorded. For the 6-min walk test, participants walked back and forth along an 18-m indoor walkway, turning at each end. The primary outcome was the total distance covered within 6 min.

When a participant remained able to walk after completing the 6-min test, the assessment continued under the same conditions to characterize indoor walking endurance. Participants continued walking along the 18-m walkway, including repeated 180° turns at each end, until they requested termination or could no longer continue safely. Total walking duration and distance were recorded.

Participants who were able to walk for more than 6 min indoors were also evaluated during an outdoor endurance test. This assessment was performed along a straight, level path to minimize the influence of repeated turning. Walking continued for as long as tolerated, and the total duration and distance traveled were recorded. All participants except P05 completed the outdoor endurance assessment.

No body-weight-support system was used during any walking assessment, and physiotherapists did not provide manual assistance for weight transfer, balance, or lower-limb advancement. Participants used the walker selected during training according to their individual support requirements.

All walking assessments were performed with stimulation ON. In P05, P07, and P08, participants controlled the swing of one lower limb through trunk-mediated control (TMC), whereas swing of the contralateral limb was elicited through cyclic contralateral stimulation (CCS). P06 controlled the swing of both lower limbs using TMC. Because none of the participants exhibited visible voluntary contractions of the lower-limb muscles at any point during hospitalization, walking could not be performed in the stimulation-OFF condition.

Analysis of walking kinematics and evoked muscle responses

Walking dynamics were characterized from trunk and lower-limb kinematic signals and stimulation-evoked electromyographic responses. Kinematic signals were low-pass filtered using a fourth-order Butterworth filter with a cutoff frequency of 1 Hz. Peak trunk extension and peak hip flexion were identified from the corresponding filtered signals. Peaks were required to have a minimum prominence equal to 50% of the robust range of the corresponding signal, defined as the difference between its 95th and 5th percentiles.

Hip and trunk excursions were quantified for each step as the angular range between the minimum hip/trunk angle between a peak in hip flexion and the subsequent peak. The resulting hip range values were compared with reference ranges reported for healthy walking, approximately 30°–60°, and with the threshold of 20° used as a reference for pathological populations walking at very low speeds.[53–56]

To characterize the temporal relationship between trunk movement and lower-limb advancement during TMC, we calculated the delay between each peak in trunk extension and the associated subsequent peak in hip flexion. The consistency of this delay across steps was used to assess whether trunk extension reliably preceded stimulation-mediated lower-limb flexion.

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Within each CCS cycle, we also identified the peak in trunk flexion. Rectus femoris compound muscle action potential amplitudes were quantified peak-to-peak around peak trunk flexion and after peak trunk extension. The extension-associated response was defined as the maximum rectus femoris peak-to-peak amplitude occurring within 0.5 s after the trunk-extension peak. Modulation of the evoked response was expressed as the logarithm of the ratio between the extension-associated and flexion-associated amplitudes. Positive values therefore indicated greater rectus femoris activation around peak trunk extension than around peak trunk flexion, whereas negative values indicated the opposite pattern.

The angular excursion of the trunk during each movement cycle was also quantified to estimate the magnitude of trunk movement required to perform TMC.

Finally, we investigated whether stimulation-evoked lower-limb movements decreased during prolonged walking. For each lower limb, hip excursion during the last 10 steps was divided by that measured during the first 10 steps. This analysis was performed over the first 50 or 100 available steps of each endurance assessment, depending on the number of valid steps completed by the participant. Ratios were calculated separately for the TMC-controlled and CCS-controlled limbs, with values below 1 indicating a reduction in movement amplitude over time.

Timed trunk-mediated control of hip flexion

The ability to elicit TMC-mediated flexion at a desired time was assessed while participants maintained an eSCS-enabled standing position between the parallel bars. Participants were instructed to remain in the resting standing configuration until presentation of a visual cue and then to perform the trunk movement used during training to elicit triple flexion of the TMC-controlled limb. P05, P07, and P08 performed the task with the limb selected for unilateral TMC, whereas P06 was instructed to selectively elicit left- or right-sided flexion according to the cue. We determined the time between the presentation of the visual cue and the maximum hip flexion from the videos of the tasks.

Graded control of TMC hip flexion

The capacity to modulate the magnitude of TMC-mediated hip flexion was evaluated in P08 using a non-immersive virtual-reality task while the participant maintained an eSCS-enabled standing position at the parallel bars. Femur inclination, measured using an inertial sensor, controlled the displacement of a virtual object along a one-dimensional trajectory. Two target positions were displayed, requiring the participant to produce two distinct magnitudes of hip flexion through trunk-mediated control.

At the beginning of each trial, the participant maintained the resting standing position. After presentation of the target, the participant performed a trunk-extension movement of the amplitude considered necessary to move the virtual object toward the indicated position. Trunk and femur kinematics were recorded throughout the task. For each trial, peak trunk extension and peak femur flexion were extracted relative to the initial resting position.

The separability of the two movement profiles was evaluated in the two-dimensional feature space defined by peak trunk extension and peak femur flexion. The observations were clustered using a Gaussian mixture model, and the correspondence with the known target (large or small required hip flexion) was quantified using the homogeneity score.

QUANTIFICATION AND STATISTICAL ANALYSIS

Continuous variables are reported as mean ± standard deviation. Individual participant values are shown whenever possible.

Standing duration and lower-limb weight bearing were compared between stimulation-ON and stimulation-OFF conditions using linear mixed-effects models with stimulation condition as a fixed effect and participant as a random intercept.

For the amplitude-switching experiment, vastus lateralis and rectus femoris CMAP peak-to-peak amplitudes were classified into two regimes using Gaussian mixture clustering. CMAP amplitudes were compared between regimes using two-sided Mann–Whitney U tests, with rank-biserial correlation as effect size.

During testing of TMC while standing, trunk-to-hip delays and rectus femoris log-ratios were analyzed using linear mixed-effects models with participant as a random intercept. The model intercept was tested against zero using a one-sided Wald test, corresponding to the hypotheses that trunk extension preceded hip flexion and that rectus femoris recruitment was greater around trunk extension than trunk flexion. During endurance walking, the same quantities were compared with zero separately for each recording using one-sided Wilcoxon signed-rank tests with rank-biserial correlation as effect size.

Multiple comparison p-values were corrected using Bonferroni correction.

For all mixed-effect linear models, the fixed effect was reported in terms of its mean value and 95% confidence interval (CI).

Statistical significance was set at $p < 0.05$. Analyses were performed in Python using SciPy, scikit-learn, and statsmodels.