Journal of Neurotrauma
XX: 1–13 (XXXX 00, 2023)

DOI: 10.1089/neu.2023.0403

Journal of Neurotrauma

ORIGINAL ARTICLE

Standing Reactive Postural Responses of Lower Limbs With and Without Self-Balance Assistance in Individuals With Spinal Cord Injury Receiving Epidural Stimulation

Collin D. Bowersock,[1–3] Tanvi Pisolkar,[1] Xupeng Ai,[4] Chenfei Zhu,[4] Claudia A Angeli,[1,5,6] Susan J Harkema,[1,2,5] Gail Forrest,[7,8] Sunil Agrawal,[4,9] and Enrico Rejc[1,2,7,10,*]

Abstract

Spinal cord epidural stimulation can promote the recovery of motor function in individuals with severe spinal cord injury (SCI) by enabling the spinal circuitry to interpret sensory information and generate related neuromuscular responses. This approach enables the spinal cord to generate lower limb extension patterns during weight bearing, allowing individuals with SCI to achieve upright standing. We have shown that the human spinal cord can generate some standing postural responses during self-initiated body weight shifting. In this study, we investigated the ability of individuals with motor complete SCI receiving epidural stimulation to generate standing reactive postural responses after external perturbations were applied at the trunk. A cable-driven robotic device was used to provide constant assistance for pelvic control and to deliver precise trunk perturbations while participants used their hands to grasp onto handlebars for self-balance support (hands-on) as well as when participants were without support (free-hands). Five individuals with motor complete SCI receiving lumbosacral spinal cord epidural stimulation parameters specific for standing (Stand-scES) participated in this study. Trunk perturbations (average magnitude: $17 \pm 3\%$ body weight) were delivered randomly in the four cardinal directions. Participants attempted to control each perturbation such that upright standing was maintained and no additional external assistance was needed. Lower limb postural responses were generally more frequent, larger in magnitude, and appropriately modulated during the free-hands condition. This was associated with trunk displacement and lower limb loading modulation that were larger in the free-hands condition. Further, we observed discernible lower limb muscle synergies that were similar between the two perturbed standing conditions. These findings suggest that the human spinal circuitry involved in postural control retains the ability to generate meaningful lower limb postural responses after SCI when its excitability is properly modulated. Moreover, lower limb postural responses appear enhanced by a standing environment without upper limb stabilization that promotes afferent inputs associated with a larger modulation of ground reaction forces and trunk kinematics. These findings should be considered when developing future experimental frameworks aimed at studying upright

[1]Kentucky Spinal Cord Injury Research Center, Departments of [2]Neurological Surgery, [6]Bioengineering, University of Louisville, Louisville, Kentucky, USA.
[3]Department of Mechanical Engineering, Northern Arizona University, Flagstaff, Arizona, USA.
Departments of [4]Mechanical Engineering, [9]Rehabilitation and Regenerative Medicine, Columbia University, New York, New York, USA.
[5]Frazier Rehabilitation Institute, University of Louisville Health, Louisville, Kentucky, USA.
[7]Kessler Foundation, West Orange, New Jersey, USA.
[8]Department of Physical Medicine and Rehabilitation, Rutgers New Jersey Medical School, Newark, New Jersey, USA.
[10]Department of Medicine, University of Udine, Udine, Italy.

*Address correspondence to: *Enrico Rejc, PhD, Kessler Foundation, 1199 Pleasant Valley Way, West Orange, NJ, 07052, USA E-mail:* erejc@kesslerfoundation.org; enrico.rejc@uniud.it

postural control and activity-based recovery training protocols aimed at promoting neural plasticity and sensory-motor recovery.

Keywords: epidural stimulation; postural control; spinal cord injury; standing

Introduction

Clinically motor complete spinal cord injury (SCI) disrupts the communication between the supraspinal and spinal cord centers, leading to paralysis and the inability to stand, walk, or control posture. A promising avenue used to restore neuromuscular function below the level of injury during standing is tonic lumbosacral spinal cord epidural stimulation (scES). In the last decade, proof of principle studies involving individuals with chronic, clinically motor complete SCI reported that activity-based training with scES has the potential to restore motor function for standing and walking.[1–5]

To date, much of the research implementing scES to facilitate the recovery of standing in individuals with motor complete SCI has focused on investigating and enhancing the primary contributors for independent lower limb extension effective to bear body weight. We showed that individual-specific scES parameters appropriate to facilitate standing (Stand-scES) promote negligible electromyography (EMG) activity and no leg movement in sitting, and enable the spinal circuitry to interpret the sensory information related to the sit-to-stand transition (i.e., leg loading and extension) to result in the generation of effective lower limb extensor patterns.[5–7] We have also characterized effective lower limb extensor patterns using EMG time- and frequency-domain features. EMG patterns with higher power, lower median frequency, and lower variability were associated with independent lower limb extension as compared with activation patterns requiring external (manual) assistance to maintain extension and weight bearing.[7] Task specific activity-based training with Stand-scES plays an important role in standing motor function recovery. We observed that standing ability improved after a period of stand training but declined after a subsequent block of step training.[4] Conversely, the concurrent practice of standing and stepping can lead to the improvement of both motor tasks.[2,3] More recently, we also observed that some individuals can volitionally modulate the lower limb activation pattern while standing with Stand-scES,[6] and that the ability to achieve independent lower limb extension prior to any training with Stand-scES may be associated with the amount of spared spinal cord tissue at the lesion site.[8]

At this stage, to further pursue the goal of motor recovery and functional mobility in this population, it appears of paramount importance to expand the research focus from the ability to achieve independent lower limb extension to the overall recovery of upright postural control. This is a key facet of rehabilitation, as postural control is a foundational ability for performing upright motor tasks important in the home and community.[9–12] The ability of mammals to control posture relies on the interaction between supraspinal and spinal postural control systems,[13–15] although the relative contribution of each system is still not well understood. The spinal control system receives inputs from the limb sensory receptors and creates corrective motor responses by activating limb flexors and extensor muscles.[16] After SCI, it is thought that postural control is disrupted because of the loss of the supraspinal postural control system inputs, and because of the loss of supraspinal tonic drive to the spinal postural networks.[15,17] However, evidence from animal models with complete spinal transection suggests that a reduced postural control may still reside within the spinal networks and that the excitability modulation promoted by scES may facilitate some level of postural control beyond upright standing.[18–24]

Upright postural control is affected by the involvement of upper limbs for self-stabilization. In the able-bodied population, the placement of upper limbs on a fixed surface results in a change in postural control strategy and overall increased stability.[25] Weight-bearing-related sensory information, which plays a critical role in standing motor control in SCI individuals receiving Stand-scES, is also altered when postural perturbations are controlled with hands-on fixed handlebars as compared with self-unassisted (hands-off) standing.[26] This is important because individuals with motor complete SCI regularly practice standing and stepping with scES placing their upper limbs on supportive devices (e.g. walker or standing frame) for self-balance assistance. However, to date, it is unknown whether and how this self-balance assistance strategy influences lower limb postural responses and motor re-learning.

The purpose of this work was to investigate the lower limb responses to postural perturbations delivered by a robotic upright stand trainer[27] during self-assisted and self-unassisted standing in individuals with motor complete SCI receiving Stand-scES. We hypothesized that standing with hands off handlebars (i.e., unassisted) will result in larger, and overall, more appropriate lower limb postural responses. The findings of this work can provide important insights into the human spinal cord's ability to generate postural responses after a motor complete SCI, which can have a direct impact on the future development of experimental frameworks

Table 1. Characteristics of the Research Participants

Pub ID	*Age(Years)*	*Sex*	*Time since injury (Years)*	*Level of injury*	*AIS*
A96	29	F	5.3	C4	A
A82	37	M	8.8	C4	A
B45	36	M	9.3	C7	B
B07	35	M	14.4	T2	B
B23	38	M	9.4	C4	B

Pub ID, publication identifier; level of injury, neurological level of the lesion by AIS (American Spinal Injury Association [ASIA] Impairment Scale); C, cervical; T, thoracic.

focused on postural control as well as activity-based rehabilitation protocols aimed at promoting neural plasticity and motor recovery in individuals with SCI receiving spinal cord neuromodulation.

Methods

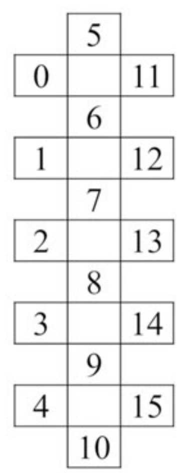
Participants

Five individuals with cervical ($n=4$) or high-thoracic ($n=1$) motor complete SCI, who had been previously implanted with a spinal cord epidural stimulation unit[28] and were ≥5 years from injury, participated in this study (Table 1). These individuals had previously practiced standing with Stand-scES as part of other interventional studies and had demonstrated the ability to stand with bilateral independent knees extension. The experimental protocol was approved by the Institutional Review Board at the University of Louisville (IRB #17.1024) and was in accordance with the declaration of Helsinki. All participants provided written informed consent before participating in this study.

Spinal cord epidural stimulation implant and parameters

During the surgical implantation procedure, a midline bilateral laminotomy was performed typically at the L1-L2 disk space. An electrode array with 16 contacts (Medtronic Specify 5–6-5 lead) was placed into the epidural space at the midline. Electrophysiological mapping was performed after initial placement to optimize the location of the paddle electrode based on evoked responses recorded from bilateral surface EMG electrodes (Motion Lab Systems, Baton Rouge, LA) placed over representative lower limb muscles. After the final placement of the electrode array, the electrode lead was tunneled subcutaneously and connected to the neurostimulator (Medtronics, Intellis in participants A96, A82, B45, and B07; Restore ADVANCED in participant B23).

Table 2. Spinal Cord Epidural Stimulation Parameters

Pub ID	*Stimulation parameters*	*Electrode array*
A96	**P1.** 0- 5- 11- // 1+ 6+ 7+ 12+ ; 3.2 mA; 500 µs; 19 Hz **P2.** 4- 9- 15- // 1+ 2+ 3+ 7+ 12+ 13+ 14+ ; 6.8 mA; 700 µs; 19 Hz **P3.** 1- 7- 12- // 0+ 6+ 11+ ; 11.2 mA; 700 µs; 23 Hz	
A82	**P1.** 2- 3- 13- 14- // 0+ 5+ 6+ 11+ ; 3.1 mA; 700 µs; 30 Hz **P2.** 7- 8- // 0+ 4+ 5+ 6+ 9+ 10+ 11+ 15+ ; 2.0 mA; 700 µs; 30 Hz	
B45	**P1.** 2- 7- 13- // 0+ 1+ 6+ 12+ ; 3.5 mA; 890 µs; 35 Hz **P2.** 10- 15- // 1+ 2+ 3+ 4+ 7+ 8+ 9+ 12+ 13+ 14+ 4.4 mA; 500 µs; 35 Hz	
B07	**P1.** 0- 1- 8- 11- 12- // 4+ 5+ 6+ 9+ 10+ 15+ ; 4.5 mA; 1000 µs; 22 Hz **P2.** 3- 8- 14- // 1+ 4+ 7+ 9+ 12+ 15+ ; 2.0 mA; 1000 µs; 22 Hz **P3.** 2- 8- 13- // 0+ 4+ 5+ 6+ 9+ 11+ 15+ ; 2.1 mA; 1000 µs; 22 Hz **P4.** 2- 3- 8- 13- 14- // 0+ 1+ 4+ 5+ 6+ 7+ 9+ 10+ 11+ 12+ 15+ 4.5 mA; 1000 µs; 22 Hz	
B23	**P1.** 5- 6- 11- // 1+ 2+ 7+ 8+ 12+ 13+ ; 2.1 V; 450 µs; 40 Hz **P2.** 0- // 2+ 3+ 5+ 6+ 7+ 11+ 12+ ; 2.5 V; 450 µs; 40 Hz **P3.** 1- 2- 6- 7- // 0+ 5+ ; 1.0 V; 450 µs; 40 Hz	

Multiple stimulation programs (P1 to P4) were applied to the research participants in an interleaved fashion (B23), or with independent frequencies (A96, A82, B45, B07) to facilitate standing, depending on the stimulator unit characteristics. Active contacts of the 16-electrode array are listed as cathodes (-) or anodes (+). Stimulation pulse width, frequency, and representative amplitude are also reported for each stimulation program; stimulation amplitude was adjusted throughout each session if needed.

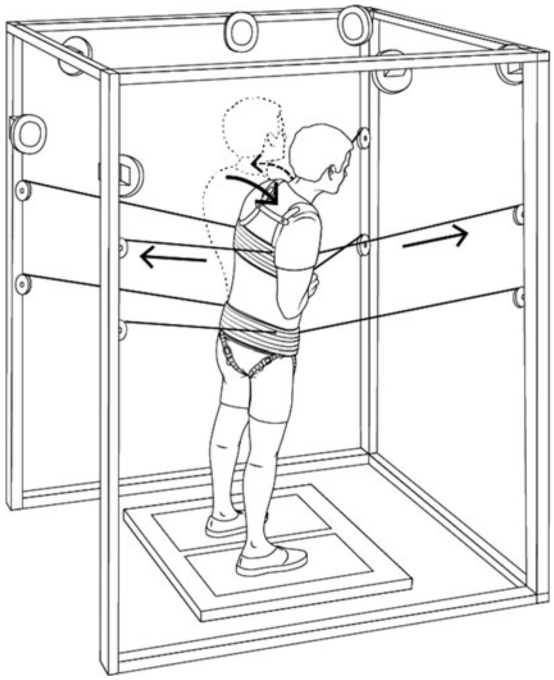


FIG. 1. Schematic of the Robotic Upright Stand Trainer (RobUST) during a right-side perturbation. Trunk perturbations are powered by mounted motors and delivered by the cables attached to the trunk harness while pelvis motors and cables apply a constant force to assist pelvic control. Trunk kinematic data are collected through motion capture cameras and kinetic data are collected through embedded force plates and instrumented handlebars (not shown).

In this study, tonic task-specific Stand-scES was applied to promote standing. The individual-specific Stand-scES parameters applied are reported in Table 2. All research participants had undergone the process of selection of Stand-scES parameters for standing prior to the beginning of the present study because they had been enrolled in previous interventional studies that included standing. The approach implemented for the selection of Stand-scES parameters to promote standing is reported in previous publications by our group.[5,29,30]

Robotic Upright Stand Trainer (RobUST)

The specifics of the RobUST design and functionality have been previously described in detail,[27] and the feasibility of its implementation in a population of SCI individuals unable to stand independently has been also reported.[31] Briefly, the device consists of an aluminum frame (80/20 Inc, Indiana) with 12 mounted motors (Maxon Motor, Switzerland) for force generation (Fig. 1). Cables are routed from the motors through pulleys and connected to a dedicated harness at the trunk and pelvis. Dedicated sensors (LSB302 Futek, CA) measure the tension applied at each cable. The RobUST is equipped with eight infrared cameras (Vicon Bonita 10; Denver, CO) to capture the instantaneous position of reflective markers placed at the back of the trunk and pelvic harnesses, which is needed for the proper functioning of the device and is also collected for kinematic analysis. Additionally, two embedded force plates (Bertec, Columbus, OH) are implemented to measure ground reaction forces.

Experimental protocol

Standing postural control was assessed by delivering trunk perturbations in four cardinal directions (front, back, left, right) through the RobUST, while the research participants were standing in either of the two standing conditions: (1) using their hands to grasp fixed handlebars for self-balance assistance (hands-on), or (2) with their hands off fixed handlebars (free-hands). For this protocol, the pelvis was assisted by RobUST using a constant force of 80 N to facilitate appropriate hip extension and pelvic tilt, with additional manual trainer assistance provided as needed. This constant force was found to be optimal for pelvis stability while allowing the pelvis to safely move when excessive forces were generated, such as unexpected muscle spasms. No perturbations considered for analysis in this study exhibited displacement of the cables connected to the pelvis harness.

The four RobUST trunk motors exerted a low-level constant force (30 N) that provided appropriate cable tension to remove any slack in the cables before perturbations without hindering or promoting trunk movement. Perturbations were characterized by a trapezoidal force with 0.15 sec rise time, 0.8 sec constant time, and 0.15 sec fall time. Perturbation magnitude was selected during an acclimation session and was relative to the participant's body weight (BW). Perturbation magnitudes equal to 10, 15, and 20% BW were attempted, and the magnitude ensuring a safe and challenging environment was selected. Specifically, the goal was to induce meaningful trunk movement while allowing the participant to control, at least partially, the displacement. Perturbation magnitude was on average $17 \pm 3\%$ BW, and was held constant within each participant across perturbation directions and standing condition (hands-on or free-hands). Retro-reflective markers were placed at the back of the trunk to capture its relative position from the starting position during each perturbation.

Four perturbations per direction were delivered randomly to each participant under the two standing conditions so that a total of 16 hands-on and 16 free-hand perturbations were attempted. Perturbation onset was preceded by a 3 sec countdown, and its direction was not disclosed to the participant. The perturbation was deemed successful if the participant was able to regain and/or maintain the standing posture for at least 3 sec after the end of a perturbation without the need of any additional trainer's assistance. Also, during the free-hands condition, the perturbation was considered unsuccessful if participants used their upper limbs to grasp the handlebars for support. If needed, manual assistance was provided between 4 and 10 sec after the perturbation by a trainer to bring the trunk back to the center position before the next perturbation. Only successful perturbations were considered for further analysis.

Data acquisition and analysis

Successful perturbation control, motor force, trunk kinematic data, force plate data, and EMG of the lower limb muscles were collected during each perturbation. Lower limb muscles included bilateral adductor magnus (AD), vastus lateralis (VL), medial hamstring (MH), tibialis anterior (TA), and medial gastrocnemius (MG). A LabVIEW PXI system (National Instruments, Austin, TX) was used to record the forces generated by the DC motors (Maxon Motor, Switzerland) at 200 Hz. Trunk kinematic data was captured at 100 Hz, and ground reaction forces were captured at 1000 Hz. EMG activity was recorded by bipolar surface electrodes with a fixed inter-electrode distance (17 mm) at 2000 Hz. A low-pass digital filter was applied to motor and force plate data with a cutoff frequency of 25 Hz.[32,33] Kinematic data of the trunk were low-pass filtered at 6 Hz. EMG data was band-pass digital filter (20–500 Hz), rectified, and then lowpass filtered (25 Hz).

Each outcome variable was assessed in a 3-sec time window, from perturbation onset to 3 sec after perturbation onset. Perturbation onset was defined by the time point at which the perturbation force was larger than the average baseline force plus three standard deviations. Left and right perturbations were grouped into lateral perturbations with kinematic, kinetic, and EMG variables expressed as ipsilateral or contralateral to the direction of the perturbation. Front and back perturbations were independently analyzed. Primary outcomes included trunk excursion, percent change from baseline in peak vertical ground reaction forces (Vgrf) and peak resultant horizontal ground reaction forces (Hgrf), percent change from baseline in EMG amplitude, and the rate of each EMG response types (i.e., increased activation, no change, or inhibition compared with baseline). Baseline data were assessed over a 1.5 sec time window from 2.2 to 0.7 sec prior to perturbation onset. Trunk excursion was calculated as the maximum distance traveled by the trunk geometrical center.[27] The percent change in Vgrf and Hgrf from baseline was calculated as follows. For lateral perturbations, ipsilateral and contralateral Vgrf and Hgrf were calculated by use of the left and right force plates, to determine the amount of perturbation-induced loading and unloading as well as Hgrf modulation. For front and back perturbations, the total force recorded from the two force plates was used to determine Vgrf and Hgrf modulation. The percent change from baseline in EMG amplitude for each muscle and perturbation was calculated using a 1.5-sec sliding window over the 3-sec time period after the perturbation onset, with a 0.025-sec overlapping window. The 1.5 sec window with the maximum EMG integral detected over the 3-sec time period was considered for analysis. Finally, this maximum EMG integral was used to define the type of EMG response. EMG responses that were larger than the baseline EMG integral plus three standard deviations were considered as ''increased activation.'' Responses that were less than the baseline EMG integral minus three standard deviations were considered as ''inhibition.'' All other responses were considered as ''no change'' from the baseline.

Muscle synergies were extracted as follows. For each of the 10 lower limb muscles considered in this study, mean muscle activity during each time bin was calculated for each trial. These mean values were assembled to form an EMG data matrix (M) for each participant:

$$\begin{aligned}&\text{EMG matrix (M): 4 bins(BK \& PR1, 2, 3)}\\&\times 4\text{ directions}\times\text{successful trials per direction}\end{aligned} \tag{1}$$

Where BK is background bin, which was set as 450–150 ms before the perturbation onset to represent the resting activity of each muscle. PR1-3 are the postural response bins. Each PR bin lasts for 500 ms with PR1 beginning at the onset of the 1.5 sec window that had the maximum EMG integral following the perturbation (see previous description of EMG integral calculation). Subsequent PR bins begin at the end of the previous PR bin.

Matrix for each participant was then normalized by the corresponding maximum value in each muscle row. Muscle synergies were extracted by using the non-negative matrix factorization (NNMF) method.[34–36] Based on the NNMF method, the EMG matrix (M) is composed of a linear combination of several muscle synergy vectors (Wi), which are recruited by the synergy activation coefficients (ci). Therefore, we have

$$M = c1W1 + c2W2 + \cdots + cnWn \tag{2}$$

Muscle synergy vector Wi provides information about which muscles are involved in the *i*th synergy and their relative contributions (range 0–1). Muscle synergies are time invariant and stable across perturbation directions. Synergy activation coefficient ci reflects the activation level changes of the synergy Wi over time bins and perturbation directions.[37]

Muscle synergy number can be changed to adequately reconstruct the group EMG matrices. Specifically, in Equation 2, we can increase the muscle synergy number n to reduce the error between the left and the right side; that is, the original and reconstructed matrix. The reconstruction level is quantified by the variability accounted for (VAF):

$$\mathrm{VAF} = \left(1 - \frac{\left(M - \sum_{i=1}^{n} c_i W_i\right)^2}{M^2}\right) \times 100\% \tag{3}$$

We increased the muscle synergy number until it could account for at least 90% of the overall VAF.[38]

Statistical analysis

All five participants of this study achieved successful attempts with hands-on and free-hands during lateral and back perturbations, contributing to the related results and statistical comparisons. Conversely, two participants (A96 and B23) demonstrated successful front perturbations with free-hands; therefore, only descriptive statistics (mean and standard error) have been reported for this perturbation direction. The effect of hands placement for self-balance assistance (hands-on vs. free-hands) on the continuous variables of this study (trunk displacement, ground reaction forces, and EMG amplitude) was analyzed within lateral and back perturbations with linear mixed models that included a random intercept for individual variability. The model assumptions of normality, linearity, homoskedasticity, and independence were checked. If these assumptions were violated, log-transformation was applied to trunk excursion and ground reaction force data, or outliers (i.e., data points that were >2.5 standard deviations far from the mean distribution) were removed for EMG amplitude variables, as they presented both negative and positive values and could not be reliably transformed. A 2×3 χ^2 Goodness of Fit Test was used to determine whether the distribution of EMG response types (increased activation, no change, inhibition) was equal between the hands-on and free-hands conditions for each muscle analyzed. Multiple 2×1 χ^2 post-hoc tests using Bonferroni corrections were used to determine which frequency of EMG response types differed between the free-hands and hands-on conditions. All tests used an α level of 0.05 to denote a statistical difference.

Muscle synergies generated with hands-on and free-hands were compared by the coefficient of determination, which is a matrix of size $M \times 4n$ (number of synergies $\times$ 4 time bins each trial). We first calculated the mean value of the EMG signals in time bin APR1, 2, 3 for each trial (this leads to a matrix of size $M \times n$, with n representing the number of all trials, covering all directions). We then calculated the coefficient of each synergy in each direction by averaging this matrix by direction to obtain a matrix of size $M \times 4$.

Results

In line with the research hypothesis, the kinematic, kinetic, and EMG postural responses to standing trunk perturbations were generally more robust with free-hands than with hands-on. For example, Figure 2 shows a relevant EMG burst generated in response to a lateral perturbation by four of the five lower limb muscles ipsilateral to the perturbation direction when it was controlled with free-hands. Conversely, negligible EMG modulation was observed in the same muscles during the hands-on condition. Loading (i.e., Fz) of the lower limb ipsilateral to the perturbation and unloading of the contralateral lower limb, as well as horizontal (Fx, medial-lateral, and Fy, anterior-posterior) ground reaction force modulation, were also more pronounced with free-hands (Fig. 2).

On average, trunk excursion was 30% and 90% greater during free-hands perturbations in the lateral ($p < 0.001$) and back ($p < 0.001$) directions, respectively (Figs. 3A and 4A). Lateral perturbations with free-hands resulted in greater percent change from baseline in ipsilateral loading (9%; $p < 0.001$) and contralateral unloading (22%; $p < 0.001$) compared with hands-on (Fig. 3A). Similarly, with free-hands, Hgrf percent change from baseline tended to be greater for back perturbations (7%; $p = 0.102$; Fig. 4A).

During lateral perturbations, the distribution of EMG response types was significantly different for multiple muscles between the two standing conditions (Fig. 3B). The proportion of ipsilateral VL and MG responses differed between hands-on and free-hands conditions (VL, $\chi^2(2,61) = 7.34$, $p = 0.025$; MG, $\chi^2(2,61) = 6.64$, $p = 0.036$). Post-hoc analysis revealed significantly more responses showing an increased EMG activation for these two ipsilateral muscles (VL, $\chi^2 = 8.02$, $p = 0.005$; MG, $\chi^2 = 6.59$, $p = 0.010$) during the free-hands condition. Further, the lack of baseline EMG modulation (i.e., no change) was significantly more frequent ($\chi^2 = 5.48$, $p = 0.019$) with hands-on for ipsilateral MG. The proportion of contralateral MH and MG responses also differed between hands-on and free-hands conditions (MH, $\chi^2(2,61) = 10.59$, $p = 0.005$; MG, $\chi^2(2,61) = 10.50$, $p = 0.005$). During free-hands perturbations, contralateral MH demonstrated a lower rate of increased EMG activation responses ($\chi^2 = 9.27$, $p = 0.002$), whereas the rate of responses resulting in decreased EMG activation (i.e., inhibition) was higher ($\chi^2 = 5.86$, $p = 0.015$; Fig. 3B). Further, the contralateral MG also showed a greater rate of inhibition responses ($\chi^2 = 7.04$, $p = 0.008$). The EMG amplitude modulation during lateral perturbations also showed marked differences depending on the upper limbs condition (Fig. 3C). EMG amplitude of ipsilateral AD, VL, and MG was 19%, 34%, and 25% higher during the free-hands than during the hands-on condition (AD, $p = 0.031$; VL, $p = 0.003$; MG, $p = 0.007$). Similarly, EMG amplitude of contralateral VL and MH was 27% ($p = 0.044$) and 19% ($p = 0.002$) lower during the free-hands condition.

During back perturbations, the rate of MG and AD EMG response types were significantly different between the hands-on and free-hands conditions (MG, $\chi^2(2,76) = 9.42$,

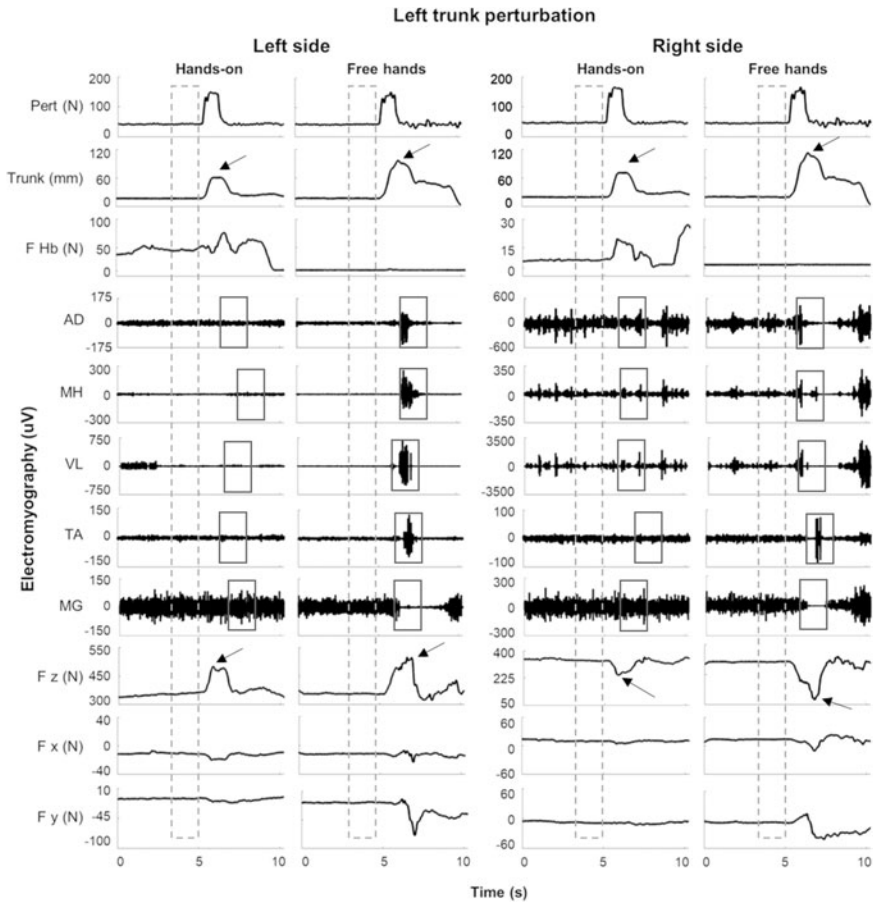


FIG. 2. Left and right side representative electromyography (EMG), and kinetic and kinematic responses from a left perturbation (magnitude: 15% body weight) with hands-on handlebars and with free-hands, collected from participant B23. Perturbation force (Pert) and resultant trunk excursion (Trunk) are not side specific, and the same trace was plotted in both the left and the right side panels to better interpret the time course of the other variables. Baseline data are calculated from the 1.5-sec window depicted by the dashed boxes. Peak trunk excursion and vertical ground reaction force (F z) change from baseline are augmented during the free-hands condition (see arrows). EMG activity during the 1.5-sec window with the largest EMG integral (solid boxes) over the time window of interest is compared with the baseline EMG activity. Generally, with free-hands, there is an increase in EMG activity on the left side and a decreased activation on the right side. Conversely, there is an overall lack of response in the hands-on condition. AD, adductor magnus; MH, medial hamstring; VL, vastus lateralis; TA, tibialis anterior; MG, medial gastrocnemius; F x, medial-lateral ground reaction force; F y, anterior-posterior ground reaction force.

$p=0.009$; AD, $\chi^2(2,76)=7.79$, $p=0.020$) (Figure 4B). Post-hoc analysis indicated that free-hands promoted significantly fewer responses resulting in increased EMG activation of MG ($\chi^2=14.11$, $p<0.001$) and significantly more responses resulting in decreased EMG activation of MG ($\chi^2=8.09$, $p=0.004$) compared with the hands-on condition. Also, a greater rate of responses resulting in increased AD EMG activation ($\chi^2=20.74$, $p<0.001$) was observed with free-hands. Finally, hands-on again favored a trend of a greater rate of responses with no change from baseline (AD: $\chi^2=6.78$, $p=0.009$; MG: $\chi^2=3.41$; $p=0.065$). During back perturbations, the two upper limb conditions promoted muscle-specific EMG amplitude modulation trends (Fig. 4C). EMG amplitude generated by AD and VL were higher with free-hands (16%, $p=0.023$ and 16%, $p=0.086$, respectively) than with hands-on. Conversely, lower MG amplitude (-12%, $p=0.013$) and MH amplitude (-11%, $p=0.102$) was noted with free-hands (Fig. 4C).

Front perturbation data assessed for the two participants that achieved successful attempts in both upper limb conditions also showed trends of larger trunk

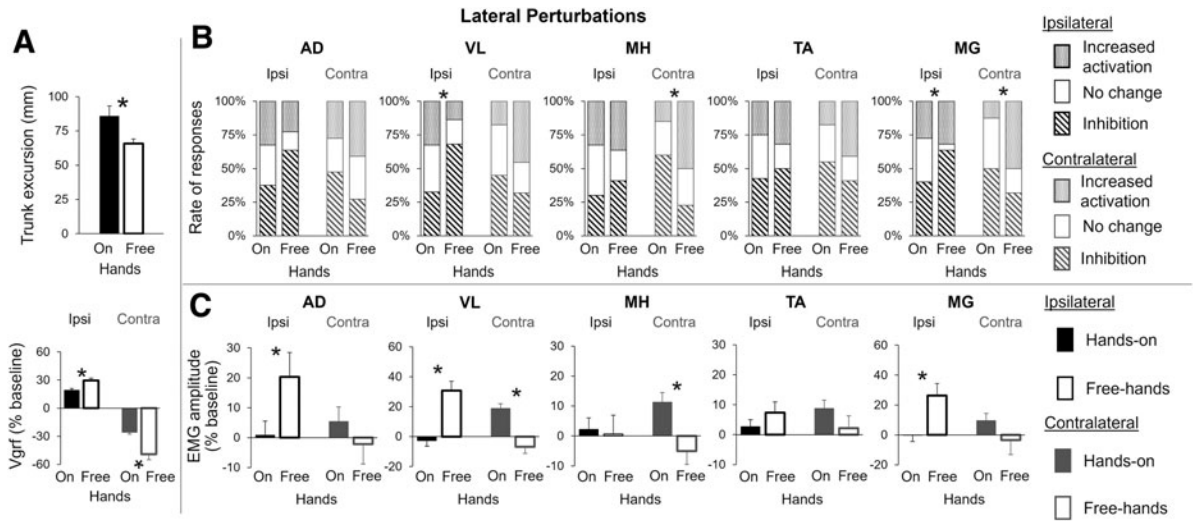


FIG. 3. Group averages ($n = 5$ participants) during hands-on (On) and free-hands (Free) lateral perturbations for (**A**) trunk excursion and vertical ground reaction force (Vgrf) perturbation response, (**B**) rate of electromyography (EMG) response types, and (**C**) EMG amplitude. Free-hands perturbations lead to larger trunk excursion and larger change in loading and unloading on the ipsilateral and contralateral sides, respectively (**A**). Free-hands perturbations also resulted in greater rate of increased activation response in the ipsilateral vastus lateralis (VL) and medial gastrocnemius (MG), and greater rate of contralateral inhibition in the medial hamstring (MH) and medial gastrocnemius (**B**). These responses were also generally greater in amplitude (**C**). AD, adductor magnus; TA, tibialis anterior. Error bars represent the standard error. Successful attempts considered for analysis were 40 for hands-on and 22 for free-hands. *Significant difference between hands-on and free-hands.

excursion (+57%) and larger Hgrf (+10%) with free-hands than with hands-on (Fig. 5A). Additionally, it is worth noting the trends of larger EMG amplitude of VL (+34%) and MH (+21%) while controlling front perturbations with free-hands compared with hands-on (Fig. 5B).

Four muscle synergies were sufficient to reproduce >90% variability of the lower limb EMG patterns in both upper limb conditions for all participants of this study. Each muscle synergy (W) demonstrated a subset of one to four muscles characterized by relatively high weights (e.g., >0.5) whereas the other muscles showed low or no weights (Fig. 6). Generally, each muscle presented with high weight only in one of the four synergies identified. Further, with one exception (L MG), the muscle synergies appeared to be side specific, with W1 and W4 highlighting high weights of right-side muscles, and W2 and W3 highlighting high weights of left-side muscles. Interestingly, the synergies identified in the hands-on condition were very similar to those generated with hands-off, as quantified by coefficients of determination (r^2) ranging between 0.87 (W2) and 0.95 (W1).

Discussion

The findings of this study provide evidence that, after a motor complete SCI, the human spinal cord receiving Stand-scES can generate robust lower limb postural responses to trunk perturbations during standing facilitated by external assistance for pelvis stabilization, and that these responses are markedly affected by the involvement of upper limbs for self-stabilization.

Lower limb postural responses to trunk perturbations were generally augmented with free-hands (Fig. 2). For example, during lateral perturbations, extensor muscles (VL and MG) of the ipsilateral side to the perturbation showed a $\sim$27% average increase in baseline EMG activity with free-hands, and these increased activation responses were significantly more frequent (Fig. 3B) and greater in magnitude (Fig. 3C) than in the hands-on condition. Also, lower limb muscles contralateral to the perturbation tended to reduce their baseline activation with free-hands, showing EMG amplitudes that were lower than with hands-on (Fig. 3C). In other words, EMG activity was greater on the side ipsilateral to the perturbation and lesser on the contralateral side in the free-hands condition. These lower limb postural responses were associated with the loading of the ipsilateral side to the perturbation and the unloading of the contralateral side for both upper limb conditions, and these changes in loading and unloading were significantly larger in magnitude in the free-hands condition (Fig. 3A). These findings are

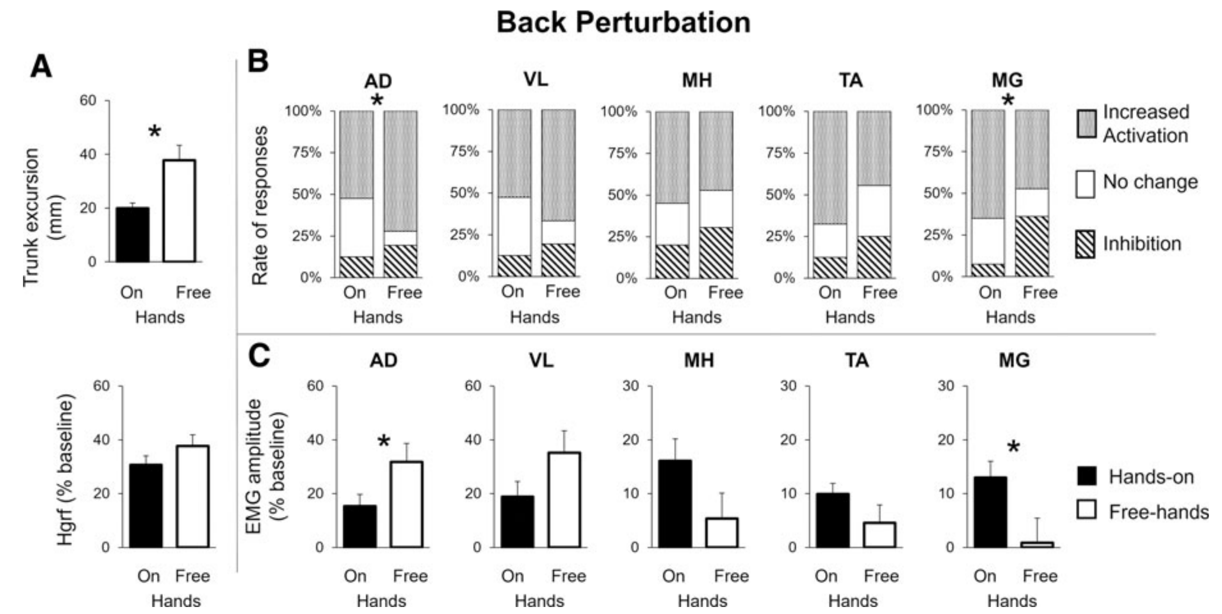


FIG. 4. Group averages ($n = 5$ participants) during hands-on (On) and free-hands (Free) back perturbations for (**A**) trunk excursion and resultant horizontal ground reaction force (Hgrf) perturbation response, (**B**) rate of electromyography (EMG) response types, and (**C**) EMG amplitude. Back free-hands perturbations lead to larger trunk excursion (**A**) and greater rate of increased activation responses in the adductor magnus (AD), but less increased activation responses and more inhibition responses in the medial gastrocnemius (MG) (**B**). EMG amplitude of the medial gastrocnemius was also lower with free-hands (**C**). VL, vastus lateralis; MH, medial hamstring; TA, tibialis anterior. Error bars represent the standard error. Successful attempts considered for analysis were 20 for hands-on and 18 for free-hands. Each attempt contributed to one data point for trunk excursion and two data points (i.e., left and right sides) for ground reaction force and EMG. *Significant difference between hands-on and free-hands.

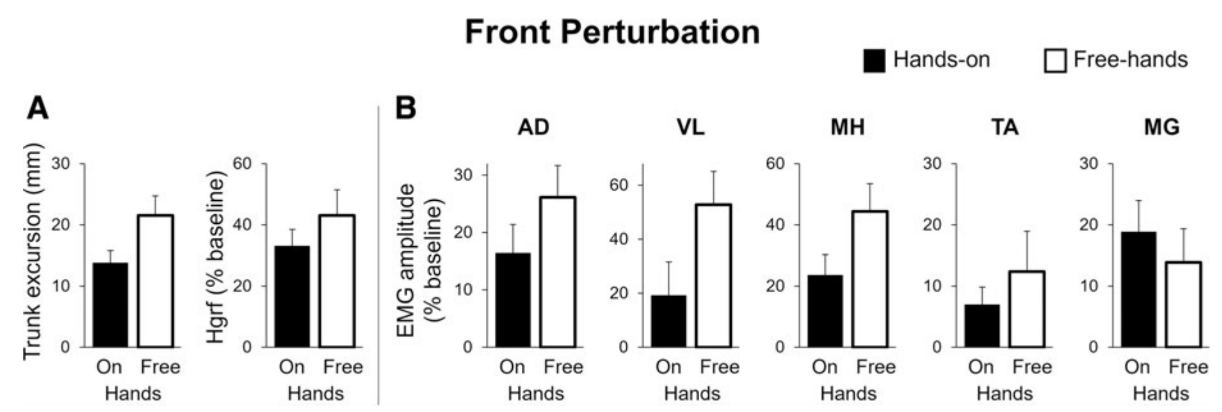


FIG. 5. Trunk excursion and resultant horizontal ground reaction force (Hgrf) (**A**) and lower limb electromyography (EMG) amplitude (**B**) responses to front perturbations controlled with hands-on (On) and free hands (Free). Data represent average + standard error resulting from eight successful attempts for hands-on and seven successful attempts for free-hands collected from Participants A96 and B23. Each attempt contributed to one data point for trunk excursion and two data points (i.e., left and right sides) for ground reaction force and EMG. Note the trends of larger trunk excursion and EMG amplitude of vastus lateralis (VL) and medial hamstrings (MH) with free-hands. AD, adductor magnus; TA, tibialis anterior; MG, medial gastrocnemius.

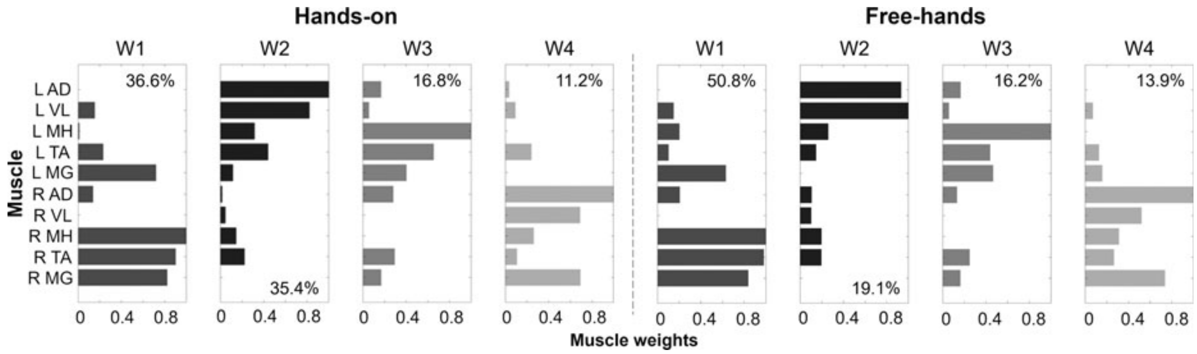


FIG. 6. Muscle synergies generated in response to trunk postural perturbations. Four-muscle synergy (W*i*) composition is defined for the hands-on and free-hands conditions. Percentages reported near each synergy describe the percent of the total variability accounted for (VAF) by the activation of each synergy. Each synergy shows the weights (0 to 1) of the following left (L) and right (R) side muscles: AD, adduction major; VL, vastus lateralis; MH, medial hamstrings; TA, tibialis anterior; MG, medial gastrocnemius.

consistent with those reported in able-bodied individuals receiving similar trunk perturbations by RobUST, as the use of handrails decreased ground reaction forces as well as EMG activity when compared with the free-hands condition.[26] We and other groups highlighted the ability of the mammalian spinal cord to interpret loading-related sensory information as a source of motor control for stepping and standing, demonstrating a positive association between loading and muscle activation.[4–6,39] The present study further provides evidence that the human spinal cord contains neuronal networks which, after SCI, are capable of generating side-specific reactive postural responses associated with loading-related sensory information when Stand-scES is applied and hands are not used for self-stabilization.

We interpret these findings as tonic Stand-scES having restored an appropriate level of spinal excitability that facilitates the recruitment of these postural networks by peripheral sensory information.[6,40–42] This view is overall in agreement with Deliagina and collaborators, who investigated the postural responses generated by a rabbit model in response to lateral platform tilting.[19] In that study, after decerebration, activation of extensor muscles was observed with limb flexion and loading. After subsequent spinalization, similar responses were facilitated by a preceding period of spinal stimulation (i.e., immediately after the cessation of scES), and were primarily explained by the engagement of stretch receptors of muscle spindles associated with limb flexion. However, the participants of the present study were standing with full lower limb extension and did not exhibit any meaningful flexion of the lower limb ipsilateral to the perturbation. Real-time as well as offline (i.e., by video recordings) visual inspection supports this assertion. Hence, the lack of lower limb flexion observed in the participants of this study following trunk perturbation suggests that the engagement of stretch receptors associated with limb flexion was not one of primary sensory information promoting the lower limb postural responses herein described, as instead it was the case for the rabbit model mentioned earlier.[19] Further, the increased loading on the ipsilateral limb of the participants of the present study was relevant (30% BW) in the free-hands condition (Fig. 3A), whereas it was relatively small in the spinal rabbit model (i.e., when compared with intact animals).[19] Taken together, these findings suggest that the detection of sensory information associated with vertical ground reaction force modulation without limb flexion plays a key role in the generation of lower limb postural responses related to lateral trunk perturbations in humans with motor complete SCI receiving Stand-scES. However, it remains unclear which receptors (e.g., Golgi tendon organs, plantar sole pressure receptors, and/or muscle spindles)[43,44] are primarily involved in the afferent inputs that are interpreted by the spinal circuitry of this population to result in meaningful lower limb postural activation patterns.

However, stretch receptors of muscle spindles may be the primary controller of back and front perturbation responses. In the experimental setup of this study, constant RobUST assistance at the pelvis contributed to maintaining the pelvis position while the trunk was displaced toward the perturbation direction. Backward and forward trunk displacement leads to stretching of the anterior and posterior muscle chain, respectively, which is known to have critical inputs in gait[45] as well as in postural control[19] after SCI. Trunk excursion was substantially larger with free-hands (Figs. 4A and 5A), which conceivably led to increased stretch responses and consequently to the increased trends of EMG amplitude for some of the investigated thigh muscles (Figs. 4C and 5B).

The use of the upper limbs for self-stabilization not only tended to reduce the amplitude (e.g., Fig. 3C, ipsilateral side; Fig. 4C, AD and VL; Fig. 5B, VL and MH) and rate (e.g., higher rate of no change from baseline for MG, Figs. 3B and 4B; and AD, Fig. 4B) of lower limb postural responses; it also promoted some postural activation patterns that were not consistent with the associated peripheral sensory information. For example, all contralateral lower limb muscles showed trends of increased EMG amplitude in response to relevant unloading (11% as average across participants) during lateral trunk perturbations with hands-on (Fig. 3C). To investigate this topic further, we implemented a muscle synergy analysis (Fig. 6). Briefly, the notion of synergies, proposed by Bernstein[46] and supported by more recent studies, is based on the concept that the nervous system may simplify the coordination of many muscles by using a limited set of control signals[47–50] each of which activates a group of muscles as a single unit.[51.] Such muscle coactivations facilitate control by reducing the number of degrees of freedom needed to be defined, while still achieving the flexibility and variability characteristic of natural behaviors.[52] A limited set of muscle synergies, showing different degrees of activation of each muscle across synergies, was also observed in an intact cat model receiving postural perturbations.[52] However, these synergies and their direction-specific contribution were disrupted after SCI,[53] leading the authors to suggest that muscle synergies for balance control may not be accessible by the spinal circuits alone.

Here, we observed that individuals with motor complete SCI receiving spinal cord stimulation also exhibited a relatively small number of discernible muscle synergies of the lower limbs during perturbed standing, showing different degrees of activation of each muscle across synergies (Fig. 6). Similarly, recent observations reported the restoration of meaningful muscle synergies during volitional lower limb movements enabled by scES after motor complete SCI.[54] These findings support the view that muscle synergies are assembled at the level of the spinal cord, as previously hypothesized,[48] and that the human spinal circuitry controlling lower limbs may retain the ability to generate meaningful muscle synergies for motor control following SCI when its excitability is properly modulated by scES. Further, the four synergies identified in this study were very similar in both the hands-on and free-hands conditions (Fig. 6). This supports the concept that a relatively small number of muscle synergies can generate a variety of motor outputs in response to sensory inputs, and that these synergies can be substantially robust and stable, as suggested by previous investigations that compared them between neurologically intact and affected sides (i.e., after stroke)[51] or before and after some treatments.[55]

The findings of this study also raise additional questions that could not be answered with the present experimental framework. For example, we originally planned to assess postural responses immediately after the cessation, and without Stand-scES. However, this was not possible because the participants began to experience symptoms of orthostatic hypotension when scES amplitude was reduced or was turned off, and needed to sit. This topic can be addressed in the future by recruiting individuals with lower (i.e., mid-thoracic) injury who tolerate upright posture without scES. Also, parallel experimental strategies might be implemented to assess whether any residual descending input (e.g., visual or vestibular) contributes to shaping the lower limb postural responses observed in a clinically motor complete population who conceivably presents with spared connectivity across the injury, which may become functionally relevant when Stand-scES is applied.[8,56,57] Finally, a larger sample size is warranted to assess whether the contribution of muscle synergies for postural control is perturbation direction-dependent and is impacted by self-balance assistance in this population. A similar experimental framework involving RobUST perturbation tasks demonstrated muscle synergy activation levels that were direction dependent in young able-bodied participants.[58]

The findings of the present study support the view that an appropriate sensory-rich environment promoting upright posture without self-stabilization by upper limbs can be critical for the human nervous system to generate enhanced lower limb postural responses after SCI. This concept should be considered when developing (1) experimental frameworks aimed at studying upright postural control in this population, as well as (2) activity-based recovery training protocols. In fact, if the nervous system is consistently exposed to enhanced sensory-motor postural processing during long-term rehabilitation with spinal cord neuromodulation, it is conceivable that the resulting neural plasticity and sensory-motor recovery would also be positively impacted. However, longitudinal studies involving more participants and populations with different injury severity are needed to test this hypothesis.

Transparency, Rigor, and Reproducibility Summary

This human translational, proof-of-principle study, which involved five individuals with motor complete SCI who were already implanted with a spinal cord epidural stimulation unit for the recovery of motor control, was not formally registered. The analysis plan was not formally pre-registered. A sample size of five participants was planned based on previous proof-of-principle studies that were successful in investigating mechanisms of human motor control with neuromodulation after SCI, and on the available grant support. Participants and investigators could not be blinded during data collection, and investigators were aware of relevant characteristics of the assessed motor tasks during data analysis. Biomechanical data were analyzed as they were collected. The RobUST was custom built by the investigators; schematics are available upon request. Key inclusion criteria and outcome evaluations are established standards. To our knowledge, there are no ongoing current or planned replication studies. All materials used to conduct the study were obtained by the investigators; de-identified data from this study and analytic code used for data analysis are not available in a public archive and will be made available through material transfer agreement upon reasonable request. This article will not be published with an open access license.

Acknowledgments

We thank the research volunteers for their valuable contribution to this study. We also gratefully acknowledge our research staff for their contribution to data collection, and our training staff for their support of the research volunteers. Dr. Maxwell Boakye performed surgical implantation and provided medical oversight; Dr. Sarah Wagers provided medical oversight; and Yukishia Austin, Lynn Robbins, and Kristen Johnson provided medical management.

Authors' Contributions

E.R., S.A., S.J.H., and C.A.A. conceived research; E.R., C.D.B., S.A., and S.J.H. designed research; E.R., C.D.B., T.P., and C.A.A. performed experiments; E.R., C.D.B., T.P., X.A., and C.Z. analyzed data; E.R., C.D.B., X.A., and C.Z. prepared figures; E.R., C.D.B., G.F., and S.J.H. interpreted results of experiments; E.R. and C.D.B. drafted the manuscript; and all authors edited, revised, and approved the final version of manuscript.

This work was supported by the New York State Spinal Cord Injury Research Board under Grant 8 C31290GG, Kessler Foundation, Leona M. & Harry B. Helmsley Charitable Trust, Christopher and Dana Reeve Foundation, UofL Health - University of Louisville Hospital, and Medtronic Plc.

Data Availability

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

Author Disclosure Statement

No competing financial interests exist.

References

1. Rowald A, Komi S, Demesmaeker R, et al. Activity-dependent spinal cord neuromodulation rapidly restores trunk and leg motor functions after complete paralysis. Nat Medicine 2022;28(2):260–271.
2. Gill ML, Grahn PJ, Calvert JS, et al. Neuromodulation of lumbosacral spinal networks enables independent stepping after complete paraplegia. Nat Med 2018;24(11):1677–1682.
3. Angeli CA, Boakye M, Morton RA, et al. Recovery of over-ground walking after chronic motor complete spinal cord injury. New Engl J Med 2018;379(13):1244–1250.
4. Rejc E, Angeli CA, Bryant N, et al. Effects of stand and step training with epidural stimulation on motor function for standing in chronic complete paraplegics. J Neurotrauma 2017;34(9):1787–1802.
5. Rejc E, Angeli C, Harkema S. Effects of lumbosacral spinal cord epidural stimulation for standing after chronic complete paralysis in humans. PLoS One 2015;10(7):e0133998; doi: 10.1371/journal.pone.0133998
6. Rejc E, Angeli CA. Spinal cord epidural stimulation for lower limb motor function recovery in individuals with motor complete spinal cord injury. Phys Med Rehabil Clin 2019;30(2):337–354; doi:10.1016/j.pmr.2018.12.009
7. Mesbah S, Gonnelli F, Angeli CA, et al. Neurophysiological markers predicting recovery of standing in humans with chronic motor complete spinal cord injury. Sci Rep 2019;9(1):1–18.
8. Smith AC, Angeli CA, Ugiliweneza B, et al. Spinal cord imaging markers and recovery of standing with epidural stimulation in individuals with clinically motor complete spinal cord injury. Exp Brain Res 2022; 240(1):279-288. doi: 10.1007/s00221-021-06272-9
9. Horak F, Macpherson J. Postural orientation and equilibrium. In: Handbook of Physiology. (J. S, L. R. eds.) Oxford University Press: New York; 1996; pp. 255–292.
10. Macpherson J, Deliagina T, Orlovsky G. Control of body orientation and equilibrium in vertebrates. In: Neurons, Networks and Motor Behavior. (Stein P, Grillner S, Selverston A, et al. eds.) MIT Press: Cambridge, MA; 1997; pp. 257–267.
11. Orlovsky T, Orlovskiĭ GN, Deliagina T, et al. Neuronal control of locomotion: from mollusc to man. Oxford University Press: Oxford, United Kingdom, 1999.
12. Massion J, Dufosse M. Coordination between posture and movement: why and how? Physiology 1988;3(3):88–93.
13. Beloozerova IN, Sirota MG, Orlovsky GN, et al. Activity of pyramidal tract neurons in the cat during postural corrections. J Neurophysiol 2005;93(4):1831–1844.
14. Beloozerova IN, Zelenin PV, Popova LB, et al. Postural control in the rabbit maintaining balance on the tilting platform. J Neurophysiol 2003;90(6):3783–93; doi: 10.1152/jn.00590.2003
15. Deliagina TG, Beloozerova IN, Popova LB, et al. Role of different sensory inputs for maintenance of body posture in sitting rat and rabbit. Motor control 2000;4(4):439–452.
16. Deliagina TG, Orlovsky GN, Zelenin PV, et al. Neural bases of postural control. Physiology (Bethesda) 2006;21:216–125; doi: 10.1152/physiol.00001.2006
17. Deliagina TG, Orlovsky GN. Comparative neurobiology of postural control. Curr Opin Neurobiol 2002;12(6):652–657; doi: 10.1016/s0959-4388(02)00376-8
18. Lyalka VF, Hsu L-J, Karayannidou A, et al. Facilitation of postural limb reflexes in spinal rabbits by serotonergic agonist administration, epidural electrical stimulation, and postural training. J Neurophysiol 2011;106(3):1341–1354.
19. Musienko PE, Zelenin PV, Orlovsky GN, et al. Facilitation of postural limb reflexes with epidural stimulation in spinal rabbits. J Neurophysiol 2010;103(2):1080–1092.
20. Lyalka VF, Zelenin PV, Karayannidou A, et al. Impairment and recovery of postural control in rabbits with spinal cord lesions. J Neurophysiol 2005;94(6):3677–3690; doi:10.1152/jn.00538.2005.
21. Fung J, Macpherson JM. Attributes of quiet stance in the chronic spinal cat. J Neurophysiol 1999;82(6):3056–3065; doi: 10.1152/jn.1999.82.6.3056
22. Edgerton VR, Tillakaratne NJ, Bigbee AJ, et al. Plasticity of the spinal neural circuitry after injury. Annu Rev Neurosci 2004;27:145–167.
23. Musienko PE, Gorskiĭ OV, Kilimnik VA, et al. Neuronal control of posture and locomotion in decerebrated and spinalized animals . Ross Fiziol Zh Im I M Sechenova [Article in Russian.] 2013;99(3):392–405.
24. Musienko PE, Gorskii OV, Kilimnik VA, et al. Regulation of posture and locomotion in decerebrate and spinal animals. Neurosci Behav Physiol 2015;45(2):229–237.
25. Baldan A, Alouche S, Araujo I, et al. Effect of light touch on postural sway in individuals with balance problems: a systematic review. Gait Posture 2014;40(1):1–10.
26. Luna TD, Santamaria V, Omofuma I, et al. Postural control strategies in standing with handrail support and active assistance from Robotic Upright Stand Trainer (RobUST). IEEE Trans Neural Syst Rehabil Eng 2021;29:1424–1431; doi: 10.1109/tnsre.2021.3097301
27. Khan M, Luna T, Santamaria V, et al. Stand trainer with applied forces at the pelvis and trunk: response to perturbations and assist-as-needed support. IEEE Trans Neural Syst Rehabil Eng 2019;27(9):1855–1864.
28. Harkema S, Gerasimenko Y, Hodes J, et al. Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and

assisted stepping after motor complete paraplegia: a case study. Lancet 2011;377(9781):1938–1947; doi: 10.1016/s0140-6736(11)60547-3
29. Ibáñez J, Angeli CA, Harkema SJ, et al. Recruitment order of motor neurons promoted by epidural stimulation in individuals with spinal cord injury. J Appl Physiol 2021;131(3):1100–1110.
30. Angeli C, Rejc E, Boakye M, et al. Targeted selection of stimulation parameters for restoration of motor and autonomic function in individuals with spinal cord injury. Neuromodulation 2023; doi: 10.1016/j.neurom.2023.03.014 Epub ahead of print.
31. Bowersock CD, Pisolkar T, Omofuma I, et al. Robotic upright stand trainer (RobUST) and postural control in individuals with spinal cord injury. J Spinal Cord Med 2023; 46(6):889–899; doi: 10.1080/10790268.2022.2069532
32. Carpenter MG, Allum JH, Honegger F. Directional sensitivity of stretch reflexes and balance corrections for normal subjects in the roll and pitch planes. Exp Brain Res 1999;129(1):93–113.
33. Leonard JA, Brown RH, Stapley PJ. Reaching to multiple targets when standing: the spatial organization of feedforward postural adjustments. J Neurophysiol 2009;101(4):2120–2133.
34. Tresch MC, Saltiel P, Bizzi E. The construction of movement by the spinal cord. Nat Neurosci 1999;2(2):162–167.
35. Cheung VC, d'Avella A, Tresch MC, et al. Central and sensory contributions to the activation and organization of muscle synergies during natural motor behaviors. J Neurosci 2005;25(27):6419–6434.
36. Torres-Oviedo G, Macpherson JM, Ting LH. Muscle synergy organization is robust across a variety of postural perturbations. J Neurophysiol 2006;96(3):1530–1546.
37. Torres–Oviedo G, Ting LH. Muscle synergies characterizing human postural responses. J Neurophysiol 2007;98(4):2144–2156.
38. Chvatal SA, Torres-Oviedo G, Safavynia SA, et al. Common muscle synergies for control of center of mass and force in nonstepping and stepping postural behaviors. J Neurophysiol 2011;106(2):999–1015.
39. Harkema SJ, Hurley SL, Patel UK, et al. Human lumbosacral spinal cord interprets loading during stepping. J Neurophysiol 1997;77(2):797–811.
40. Harkema S, Gerasimenko Y, Hodes J, et al. Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: a case study. Lancet 2011;377(9781):1938–1947.
41. Musienko P, Courtine G, Tibbs JE, et al. Somatosensory control of balance during locomotion in decerebrated cat. J Neurophysiol 2012;107(8):2072–2082.
42. Gerasimenko Y, Roy RR, Edgerton VR. Epidural stimulation: comparison of the spinal circuits that generate and control locomotion in rats, cats and humans. Exp Neurol 2008;209(2):417–425.
43. Blum KP, Lamotte D'Incamps B, Zytnicki D, et al. Force encoding in muscle spindles during stretch of passive muscle. PLoS Comput Biol 2017;13(9):e1005767.
44. Horak F, Macpherson J. Postural orientation and equilibrium. In: Handbook of Physiology. (J. S, L. R. eds.) Oxford University Press: New York; 1996; pp. 255–292.
45. Onushko T, Hyngstrom A, Schmit BD. Hip proprioceptors preferentially modulate reflexes of the leg in human spinal cord injury. J Neurophysiol 2013;110(2):297–306.
46. Bernstein N. The co-ordination and regulation of movements. Pergamon Press: Oxford; 1967.
47. Bizzi E, Cheung VC, d'Avella A, et al. Combining modules for movement. Brain Res Rev 2008;57(1):125–133.
48. d'Avella A, Saltiel P, Bizzi E. Combinations of muscle synergies in the construction of a natural motor behavior. Nat Neurosci 2003;6(3):300–308.
49. Saltiel P, Wyler-Duda K, D'Avella A, et al. Muscle synergies encoded within the spinal cord: evidence from focal intraspinal NMDA iontophoresis in the frog. J Neurophysiol 2001;85(2):605–619.
50. Saltiel P, Wyler-Duda K, d'Avella A, et al. Localization and connectivity in spinal interneuronal networks: The adduction–caudal extension–flexion rhythm in the frog. J Neurophysiol 2005;94(3): 2120–2138.
51. Cheung VC, Piron L, Agostini M, et al. Stability of muscle synergies for voluntary actions after cortical stroke in humans. Proc Natl Acad Sci 2009;106(46):19,563–19,568.
52. Ting LH, Macpherson JM. A limited set of muscle synergies for force control during a postural task. J Neurophysiol 2005;93(1):609–613.
53. Chvatal SA, Macpherson JM, Torres-Oviedo G, et al. Absence of postural muscle synergies for balance after spinal cord transection. J Neurophysiol 2013;110(6):1301–1310.
54. Singh RE, Ahmadi A, Parr AM, et al. Epidural stimulation restores muscle synergies by modulating neural drives in participants with sensorimotor complete spinal cord injuries. J Neuroeng Rehabil 2023;20(1):59.
55. Shuman BR, Goudriaan M, Desloovere K, et al. Muscle synergies demonstrate only minimal changes after treatment in cerebral palsy. J Neuroeng Rehabil 2019;16:1–10.
56. Angeli CA, Edgerton VR, Gerasimenko YP, et al. Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans. Brain 2014;137(5):1394–1409.
57. Rejc E, Smith AC, Weber KA, et al. Spinal cord imaging markers and recovery of volitional leg movement with spinal cord epidural stimulation in individuals with clinically motor complete spinal cord injury. Front Syst Neurosci 2020;14:559313.
58. Ai X, Santamaria V, Omofuma I, et al. Effects of boundary-based assist-as-needed force field on lower limb muscle synergies during standing posture training. IEEE Trans Neural Syst Rehabil Eng 2023; 31:2306-2314; doi: 10.1109/TNSRE.2023.3273990