Trunk Control and Postural Stability in Individuals with Spinal Cord Injury : Noninvasive Enabling Strategies and Modeling

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Trunk Control and Postural Stability in Individuals with Spinal Cord Injury

Noninvasive Enabling Strategies and Modeling

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Engineering

by

Mrinal Rath

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ABSTRACT OF THE DISSERTATION

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Doctor of Philosophy in Biomedical Engineering

University of California, Los Angeles, 2018

Professor Victor R. Edgerton, Chair

Electrical neuromodulation of spinal networks improves the control of movement of the paralyzed limbs after spinal cord injury (SCI). However, the potential of noninvasive spinal stimulation to facilitate postural trunk control during sitting in humans with SCI has not been investigated. This body of work demonstrates 1) that the spinal networks can be modulated transcutaneously with tonic electrical spinal stimulation to physiological states sufficient to improve trunk stability and postural control in the acute and chronic setting in individuals with chronic paralysis and 2) the feasibility of developing a personalized neuromusculoskeletal modeling. The conjunction of transcutaneous spinal cord stimulation and personalized neuromusculoskeletal modeling can be used to develop novel rehabilitation programs to improve and track functional recovery of trunk stability and postural control in individuals with spinal cord injury.

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2018

I dedicate this thesis to my Aai for having such an impact on my life and being a big part of the man I am today. I also dedicate this thesis to my twin Rutwik (Ricky) Rath, my parents, Mihira and Gitanjali Rath, and my family for their unconditional love and support. I love you all dearly. I lastly would like to acknowledge my colleagues, friends, fellow coaches, and our EGSA team for providing motivation and support to make a lasting impact.

"Be honest, humble, diligent, and kind

Then the world becomes yours

Yours to design"

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List of Acronyms

3D – three-dimensional

A-P – anteroposterior

COP – center of pressure

EMG – electromyography

E-T7 – erector spinae level T7

E-L3 – erector spinae level L3

FES – functional electrical stimulation

EMG – electromyography

L1 – interspinous space between the first and second lumbar (L1 and L2) vertebrae

LoS – limits of stability

M-L – mediolateral

NS – no stimulation

Obl - external obliques

RA – rectus abdominis

RAE – response to rapid arm extension

RF – rectus femoris

SCI – Spinal cord injury

Stim – transcutaneous spinal cord stimulation

T11 – interspinous space between the eleventh and twelfth thoracic (T11 and T12) vertebrae

tSCS - transcutaneous spinal cord stimulation

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Chapter 4 reprinted with permission from “Trunk Stability Enabled by Noninvasive Spinal Electrical Stimulation after Spinal Cord Injury” (Journal of Neurotrauma, 2018 May 5, 2018. doi: 10.1089/neu.2017.5584)

Chapter 5 contains work currently in submission

Chapter 7 contains work modified from papers in submission and performed in collaboration with Dimitry Sayenko and Kun Li. I contributed all the experimental data, parts of the analysis, significant portions of the discussion and writing and future directions. The work is included as it pertains to next steps and supports the feasibility and need for modeling as well as supports the story of stimulation facilitating trunk and postural control and the feasibility to model and quantify training and rehabilitation. Information included is with approval from all authors and collaborators.

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Trunk Stability Enabled by Noninvasive Spinal Electrical Stimulation after Spinal Cord Injury. *Journal of Neurotrauma 2018*.

Inverse Reinforcement Learning Via Function Approximation for Clinical Motion Analysis. *IEEE International Conference on Robotics and Automation 2018.*

Acute effects of regaining Trunk Stability After Spinal Cord Injury. *In Biomedical Engineering Society Annual Meeting 2018.*

Regaining trunk stability after spinal cord injury. *In Society for Neuroscience Annual Meeting 2018.*

Regaining trunk stability after spinal cord injury. *Southern California Graduate Symposium 2018.*

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The complex structure of simple devices: A survey of trajectories and forces that open doors and drawers. *Biomedical Robotics and Biomechatronics 2010*.

Epidural Stimulation and/or Pharmacological Neuromodulation Facilitates Standing in Spinal Rats. *In Biomedical Engineering Society Annual Meeting 2013.*

Assistive Robot Design and Fabrication. *In Georgia Institute of Technology 5th Annual Undergraduate Research Spring Symposium 2010.*

Chapter 1: Introduction

1.1 Significance and Scope

Spinal cord injury (SCI) is a most devastating affliction, not only because of the impact on individual participants, who suffer loss of both motor and sensory functions, but also because of the economic costs incurred by both the victims and the health care system. The NSCISC estimated SCI affected 282,000 persons in the United States in 2016, of which the average age is 29 years. Roughly 21.3% are incomplete paraplegic and 20% complete paraplegic (injury levels T1 and below) They also estimated the lifetime costs to be between $1,580,148 and $4,729,788 per participant, depending on the age and severity of the injury (NSCISC 2016).

Until recently, little could be done to change prospects for these participants. There is no single current standard of care because therapies are tailored to individual participants, depending on the level of injury and the kinds of impairments and functional limitations they have. Chest straps and passive trunk braces are often used to facilitate and correct upright sitting. Rehabilitation in SCI participants typically involves pressure relief movements, a regimen of stretching, strengthening, gait training, and prescription of appropriate assistive devices to compensate for motor deficits.[2]

We have shown that appropriate stimulation of the spinal cord can result in substantial improvements in voluntary movement during sitting, standing, and locomotion as well as improved control of bladder, bowel, sexual, and autonomic functions. [3, 4] As a result, this thesis aims to advance neuromodulation therapies to minimize the impact of SCI and improve a wide range of functions of these SCI participants. The ultimate goals of this thesis are to 1) quantify control and stability of the trunk and core in individuals with spinal cord injury with severe to moderate deficits (AIS A,C) and injuries above T11; 2) determine the effectiveness of targeted spinal cord stimulation, i.e., transcutaneous spinal electrical stimulation (tSCS) between T10 and L3 on improving seated trunk control and postural stability in SCI participants; 3) create subject specific 3D neuromusculoskeletal models and a methodology that could be used to assess the functional recovery and improvement of trunk control and postural stability in participants with spinal cord injury during quiet and dynamic seated tasks.

1.2 Background

1.2.1 AIS Impairment Scale

The AIS impairment scale describes a person's functional impairment as a result of their spinal cord injury. Clinically, the AIS impairment assessment is used to document sensory and motor function after spinal cord injury. It is used to diagnose and characterize SCI, as an outcome measure in studies to treat spinal cord pathology, as well as a tool to predict outcomes such as independence with activities of daily living, employment, life satisfaction, and life expectancy.

Participants categorized as AIS A have a complete lack of motor and sensory function below the level of injury (including loss of control of postural muscles and leg muscles); AIS B participants have some sensation below the level of injury (sensations in the lower back, abs and legs); and AIS C participants have residual muscle function below the level of injury but 50 percent of those muscles cannot move against gravity. AIS D is characterized by motor function preserved below the level of injury and at least half of the key muscle groups below neurologic level have a muscle grade 3. An AIS category of E is normal sensory and motor function (uninjured, able-bodied individuals).

1.2.2 Trunk Control and Postural Stability

SCI results in a variety of neurological deficits; there is a need for a variety of treatment approaches as well as tools to assess the functional recovery in persons with spinal cord injury. Common neuromotor deficits include the inability to maintain upright posture and typically results in persistent compensatory trunk position in persons with thoracic spinal cord injury.[5] Maintaining upright posture requires active alignment of the spinal column and head with respect to gravity as well as muscle coordination for a stable center of gravity (COG) and center of mass (COM) [6]and relies on soft tissue and surrounding musculature. [7]Trunk impairments significantly impede a participant's ability to regulate postural stability while sitting.[8, 9] Since over half of a participant's mass is above the waist, trunk stability is critical for controlling balance and mobility[10] and is required to perform activities of daily living [11] such as self-feeding, personal hygiene, operating a wheelchair, transfers, and pressure relief. In persons with upper thoracic spinal cord injury, the ability to maintain quiet sitting is compromised and is biomechanically different than the postures assumed by people without SCI.[5, 12, 13] Biomechanically, the "C"-shaped sitting seen in persons with SCI, involves a kyphotic thoracolumbar spine, flattened lumbar spine, and posteriorly tilted pelvis. [5, 12, 13] In this position, a person has increased base of support by posteriorly rotating the pelvis, shifting the center of mass backward. [5, 13]. It is suggested that people with quadriplegia or paraplegia prioritize the recovery of trunk stability overwalking function. [14, 15]

The ability to maintain posture varies with the level and extent of injury, which determines whether the participant can stabilize the trunk, especially the spine, during symmetric and asymmetric weight loading. Biomechanically the postural system has redundancies such that a functional movement can be performed in a range of muscle activation patterns and requires a complex coordination control system[16] These redundancies, i.e. has more postural variables and degrees of freedom than necessary to perform a task, [17] provide multiple strategies for controlling posture. Postural stability strategies involve multiple combinations of patterns of co-activation of trunk flexors and extensors (Stokes et al 2000), tonic stiffness, and feedback based phasic inputs to maintain stability throughout movement[18-20]

Traditional approaches in the regaining of balance function often focus on the use of compensatory strategies that emphasize the use of stronger muscles rather than on the restoration of function in the weaker and/or paretic muscles.[21] Achieving sufficient trunk stability and control not only allow persons to lift and use his or her arms without falling, it also improves independence and has clinical implications including decreased tissue trauma due to redistribution of pressure onto the ischial tuberosities, decreased kyphosis, improved pelvic alignment, improved circulation and improved postural support.[5, 22]

It has been suggested that the main positive effects of functional improvement based rehabilitation, i.e. training of movements with assistance, electrical stimulation, robotic devices and engaging a range of control strategies, of postural control can be attributed to sensorimotor integration,[23-28] as well as the improved coordination that can be attributed to task-specificity of training, [4, 29-32] with concomitant changes in muscle properties contribute to functional improvement. [33] The training of a task engages multiple modes of afferent input from load- related receptors, [34, 35] a fundamental feature of use-dependent adaptation. [36, 37]

The importance of learning to use sensory inputs from neurologically intact parts of the body has been emphasized to help maintain safe balance. [21, 27] In addition, it has been shown to have several therapeutic and functional benefits[38] aimed at overcoming physiological problems. Clinical benefits from improvements in trunk control, seated dynamic trunk movements and the ability to perform quiet sitting include: improvements in diaphragmatic breathing, decrease in neck pain from trying to keep the head up to look straight, ability to perform pressure relief, expand bimanual work-space, positively impact pelvic tilt and seated posture, facilitate forward reaching and active pulling, [39, 40] improve deep breathing, decrease incidences of bladder infections,[38] decrease spasticity, [41] improve blood pressure homeostasis,[42] and bone demineralization [43] and restore upright sitting[5]

Other not-so-traditional approaches to seated postural control have been under investigation including game-based visual bio-feedback, kayak ergometer training, sitting tai chi, and virtual reality, and functional electrical stimulation.[1, 44-47] In the SCI population, the importance of bio-feedback has been emphasized to help maintain safe balance, [21, 48] and the benefits of game-based exercises have been suggested for dynamic sitting balance.[1, 49]

Functional electrical stimulation (FES) has been proposed as a means to facilitate and restore trunk and postural control during sitting and standing in the SCI population.[50-53] FES is used to activate paralyzed muscles when there is no voluntary control such as in SCI.[54] Specifically, stimulation of hip extensors and trunk allow for seated equilibrium positions with a more natural anterior pelvic tilt and lordotic curve.[53]

FES of the thoracic and lumbar spinal cord has been shown to improve multi-directional seated stability in the SCI population,[46] increase bimanual workspace, [39] improve lateral vertebral alignment and posture,[55] and improve functional movements related to activities of daily living.[56] Furthermore, Yang et al. studied the impact of FES intensity on functional results and found that high-intensity stimulation was more effective in improving wheelchair propulsion as compared to low-intensity stimulation.[57]

More recently, other spinal cord stimulation techniques, such as transcutaneous spinal electrical stimulation (tSCS), have been developed and are promising for use in the SCI population.[50] tSCS has been previously shown to reduce spasticity, [58] modulate descending and ascending neural circuitries from the spinal cord,[59, 60] facilitate postural and locomotor patterns during weight supported walking and zero g (gravity-neutral) stepping [61, 62] and improve voluntary movement.[61, 63-65] tSCS has not been evaluated in facilitating and restoring trunk and postural control during quiet sitting and seated dynamic movements.

This thesis work demonstrates that targeted spinal cord stimulation, i.e., tSCS between the levels T10 and L3 improve trunk control and postural stability in persons with spinal cord injury (AIS A, C). In order to be able to evaluate the effectiveness of such stimulation, a reliable means of assessing trunk stability and function in SCI individuals is used. 3D kinematics (inertial and vision-based 3D motion capture technology) in combination with electromyography (EMG) of select lower trunk muscles, such as rectus abdominus, external oblique, erector spinae T7, erector spinae L3, force plate data and video recordings were used to assess trunk function and postural stability. The effects of transcutaneous spinal cord stimulation (non-invasive stimulation) of the thoracic and lumbar spinal cord in the acute setting and when combined with non-task-specific balance training on seated voluntary trunk control and postural steadiness in persons with SCI are demonstrated. Specifically, the ability to perform stereotyped seated dynamic movements and maintain a stable upright-seated position with visual biofeedback in the presence of non-invasive spinal stimulation and motor training are shown.

1.2.3 Regulation of Postural Control

The postural system is a highly functional control system that maintains body orientation in space and stabilizes the body from internal and external perturbations.[17] Maintaining balance requires the center of mass to remain within the base of support. [66] Detailed analysis of body stability and control has been performed in simpler animal models, predominately in sitting and standing and have contributed to our knowledge of the control system in humans. Deliagina et al. studied the postural system in cats and rabbits during standing and postural tasks in response to unexpected perturbations.[67-69] The studies in intact animals found that these unexpected external perturbations evoked a postural reaction. i.e. flexion in the perturbed side and extension in the contralateral. These findings suggest the somatosensory system and proprioceptive information from the limbs play a role in postural reactions to tilt.[70, 71] In spinalized rabbits, Musienko et al. studied whether spinal networks contribute to the generation of postural limb reflexes.[72] The test was performed before and after spinalization and found that spinalization resulted in the disappearance of postural limb reflexes but reappeared in the presence of epidural spinal stimulation suggesting that the spinal cord contains the neuronal networks to maintain posture. Animal studies have revealed two types of supraspinal influences: i) phasic postural commands[72-74] and ii) tonic drive for activation of spinal postural networks.[72, 75] The studies indicate an underlying postural network responsible for the organization and execution of responses to maintain stability.

In addition to the animal studies, significant work in humans has been performed. Although an extensive body of work exists on postural control in able-bodied individuals and postural stability during standing and locomotion, our knowledge on postural networks and trunk control in SCI during sitting is not well known.

There is currently a critical need to understand how the capability of the spinal cord for sophisticated processing of somatosensory information [76, 77] is used in different postural tasks in human, including multi-joint muscle synergy during quiet sitting, standing and postural corrective responses. Stabiliographic studies in able-bodied individuals looked at balance regulation and execution during quiet sitting and standing and found the body sway size and velocity were smaller and the power-weighted average frequency of movement were larger for quiet sitting as compared to quiet standing.[78] These results indicate that the balance control strategies differed between quiet sitting and standing. Biomechanically speaking, these strategies have supported the model that the trunk behaves like an underdamped oscillator.[79] Furthermore, Masani et al. investigated the direction-dependent effects of the trunk when perturbed during sitting in able-bodied individuals.[80] The study measured the tonic muscle activity prior to perturbation, and the phasic response following perturbation and found that tonic activity was 1-3% above the maximum volitional contraction for the abdominal muscles, and 4-6% for the back muscles and each trunk muscle showed a direction-specific, phasic activation in response to perturbation, above these tonic levels of activation.[80] These studies support the findings by Horak and Macpherson who studied the postural control system in terms of both the musculoskeletal and sensorimotor components and identified that there are multiple postural control strategies for any given task dependent on neural and biomechanical states.[17]

Similar to results found in the animal studies, regulation of the use of the different postural strategies in humans is based on the dynamic integration of multiple channels of information including proprioception, somatosensory, vestibular, and visual channels. Each individual channel’s effect on maintaining postural stability is highly task dependent. Work from Nasher et al. and Black et al. sought to identify the impact of the somatosensory, vestibular, and visual channels on postural sway by systematically blocking a channel and measuring its effects.[81, 82] The studies found that blocking one or more additional incrementally increased postural sway and are key in providing spatial orientation and reference in response to varying environments. These strategies are commonly described in terms of kinematics, kinetics, and muscle activity.

1.2.4 Epidural Spinal Cord Stimulation

Epidural stimulation is the application of continuous electrical current to the spinal cord via an implanted device. In humans, after motor complete SCI, epidural stimulation of lumbosacral spinal cord in the supine position has been shown to generate extension at lower stimulation frequencies, 5-15 Hz, [4, 83] and tonic and rhythmic motor patterns of the lower limbs at higher frequencies, 30-70 Hz.[83-87] Furthermore, lumbosacral epidural stimulation when combined with the sensory input associated with weight-bearing facilitate independent self-assisted weight-bearing.[4] More specifically, when a man with an epidural stimulator applied at T11 and L1 levels at sub-motor threshold intensity, the patient was able to transition sit-to-stand as well as stand with minimal support. The study found that weight-bearing activity altered the EMG activity and that shifting of poses modulated the EMG activity to higher amplitudes.[4] These findings are significant in that they show 3 key insights: 1) the spinal stimulation can modulate the physiological state of the spinal circuitry to perform functional tasks, 2) stimulation of afferent fibers in the dorsal root engage populations of interneurons whose activity is task-dependent, and 3) proprioceptive input, such as weight bearing, are integrated by the spinal cord even without supraspinal input to coordinate motor pool activity.[4, 88] In sitting, however, epidural stimulation had little or negligible EMG activity of lower limb muscles and analysis of changes in trunk and postural muscles were not evaluated.[88] Although there is sufficient supporting evidence that epidural stimulation can functional excite the spinal circuitry to facilitate quiet and dynamic seated tasks. Epidural stimulation was critical in paving the way for neuromodulation strategies but does have some key limitations; namely that an intensive surgery requiring skilled neurosurgeons limits the addressable population and overall impact potential. This limitation supports the need for alternative methods of neuromodulation of the spinal circuitry that are comparable or exceed the proven effectiveness of epidural stimulation in a range of functional tasks and support the development of tSCS.

1.2.5 Transcutaneous Spinal Electrical Stimulation (tSCS)

tSCS was developed from transcutaneous electrical nerve stimulation which involves controlled current to treat pain. tSCS is a form of noninvasive stimulation that improves lower limb motor function [61-64] and upper limb grip and hand function (Gad et al. 2018). However, the ability of tSCS to improve trunk stability, steadiness and motor control of persons with spinal cord injury during sitting (dynamic and static) and standing has not been tested.

Evidence supporting the effectiveness of spinal cord neuromodulation would include work by Gerasimenko, Rejc and Triolo.[3, 40, 64, 88]. Work by Gerasimenko[61] and Rejc[88] has reported that noninvasive electrical spinal cord stimulation, i.e., tSCS, can be used to gain access to the spinal circuits to induce involuntary stepping-like activity and standing in the legs of non-injured humans respectively. Furthermore, there is evidence that spinal cord neuromodulation can improve trunk stability, steadiness and motor control during seating and functional seated tasks utilized in activities of daily living [40] and supports the direction and assessment to evaluate the effects of tSCS on trunk and postural control.

We have previously established the methods needed to rigorously assess postural stability in persons with spinal cord injury, thereby supporting the feasibility of this work. Therefore, we tested the effectiveness of tSCS in facilitating trunk control and postural stability persons with spinal cord injury with varying levels of severity (AIS A, B or C with an injury level between T1 and T11). The long-term goal is to 1) improve a participant's quality of life and reduce his/her medical care costs and 2) aide clinicians and practitioners to be more effective in developing rehabilitation and training protocols by utilizing patient-specific models and being able to track and quantify functional improvement.

1.2.6 Biomechanical Modeling

Biomechanical and neuromusculoskeletal (NMS) modeling and simulation is gaining traction and being widely implemented in the field of healthcare. Modeling the neuromuscular system involves methods to represent neural control, musculoskeletal geometry, muscle-tendon dynamics, contact forces, and multibody dynamics.[89] Not only do these models and simulations map the internal musculature, depict muscle forces and joint loads and are task specific, they also have great impact on the design and development of rehabilitative interventional therapies and medical device design respectively. Computational modeling and simulation of the human NMS system also shows potential for improving the diagnosis and treatment of conditions that limit human mobility such as SCI, stroke, MS etc.[89] Modeling of the human NMS during locomotion and upper limb movement have provided great insight into the neural control of movement and have helped in the development of rehabilitative strategies as well as the development of assistive robotic devices and neuroprosthesis. [46, 90-93] Limited modeling and simulation of the NMS system, however, has been conducted for trunk control and postural stability in persons with spinal cord injury as well as with varying levels and severity of injury.

Models and simulations of the trunk in SCI participants during quiet upright sitting and seated flexion and extension movements can be used to provide insight into internal muscle and joint forces and the internal states that are nearly impossible to measure experimentally. These models can enhance our fundamental understanding of SCI human movement. This knowledge can then be used to identify the interventional therapies that will most likely enhance functional mobility, enhance performance and enable functional voluntary control of movement which will improve a participant's quality of life by enhancing independence.

This work included testing the ability to model and simulate real patient movements during trunk control and postural stability tasks in persons with SCI and with varying levels and severity of injury.

Existing models of the human trunk NMS system do exist, but patient specific models are needed, and models of SCI are limited, therefore this thesis includes models, modeled in OpenSim, as well as experimental data that will be provided to the OpenSim community for future directions. These models provide insight into the normal and altered activation and recruitment patterns of specific seated postural tasks in SCI participants and can be used to identify the limiting factors that prevent normal trunk control and affect a participant's dynamic and quasi-static trunk control and postural stability. Anticipated limiting factors include joint angles and moments, trunk muscle activations and forces (timing and/or magnitude), internal joint loads, and muscle fiber velocities.

1.3 Project Summary and Scientific Problem

The main body of work demonstrates that balance training with visual feedback effectively to improve the postural balance of individuals with incomplete spinal cord injury in the acute and chronic setting. It further illustrates the use and potential of non-invasive stimulation of the thoracic and lumbar spinal cord to improve motor function following neurological disorders in postural regulation beyond sitting such as sit-to-stand and standing maneuvers. More specifically, we demonstrated that, after more than two years following the onset of complete or partial paralysis, tSCS over the lumbosacral enlargement improved self-governing control of upright sitting. the studies demonstrate the use of non-invasive stimulation of the thoracic and lumbar spinal cord to improve voluntary trunk control and postural stability in spinal cord injury participants. These results demonstrate that targeted spinal cord stimulation, i.e., tSCS between T10 and L3 improves trunk control and postural stability in individuals with spinal cord injury with injury levels above T11 and AIS A or C classification, can modulate the synaptic efficacy of monosynaptic and polysynaptic motor responses as well as the functional state of descending motor pathways at different stages of motor recovery. These functional improvements are then characterized in terms of reward functions and subject-specific predictive modeling serving as a proof of concept of the potential of enhanced training and rehabilitation paradigms.

Specifically, this work takes a step towards beginning to understand the underlying mechanisms for this seated motor recovery in the presence spinal stimulation and bio-feedback using the inherent properties and plasticity of the neuromuscular system in spinal cord injured populations. The clinical implications of these mechanisms our approach provides further evidence of the acute neuroplastic capacity of spinal and potentially supraspinal networks and provides a conceptional rationale for the development of a longer-term seated postural control protocol enabled by non-invasive spinal stimulation. The present results are indicative for planning an activity-based rehabilitation program for improving balance. Finally, this study highlights the importance of including assessments of postural-specific networks while seated, as outcomes that might be extrapolated to the potential to control standing and warrant further investigation.

Chapter 2: Methods and Protocols

2.1 Participants

Experiments were conducted in four male participants (summarized in the Table 1 below) The participant gave written informed consent to the experimental procedure, which was approved by the UCLA institutional review board and is in accordance with the declaration of Helsinki on the use of human subjects in experiments.

Table 1. Clinical characteristics and anthropometrics of study participants

Participant ID	Sex	NLI	AIS Grade	Age (yrs)	Height (cm)	Body Mass (kg)	Post-SCI (yrs)	Stimulation Intensity Threshold (mA)		Stimulation Intensity Used (mA)	
								T11 30 Hz	L1 15 Hz	T11 30 Hz	L1 15 Hz
P1	M	T4	A	25	180	91	7	50	60	40	50
P2	M	T2	A	23	169	80	5	140	120	100	80
P3	M	T9	A	26	156	50	2	110	80	100	60
P4	M	T2	A	26	157	57	8	40	15	25	5
P5	M	C4	C	26	183	79	7	55	60	50	50
P6	M	T3	A	30	188	84	10	70	70	60	65
P7	F	C5	C	32	160	51	13	30	25	25	20
P8	M	T3	A	47	188	84	6	80	40	75	35

NLI – Neurological level of injury; AIS – American spinal injury association scale (AIS) classification

2.2 Balance Training

The training in the experimental group will be performed with the force plate analysis system ‘‘Stabilan-01’’ (Rhythm, Russia). During the training, participants will either sit or stand on the force plate and will be instructed to look at the monitor that was placed at eye level approximately 1.5 m in front of the force plate. The center of pressure (COP) position signal will be used as a visual input feedback to game-based exercises. During the first day of the study, participants will undergo an acclimation session in which they will become familiarized with the force plate and game-based exercise. During the training, each participant will perform a single testing trial (‘‘exam’’) of each game-based exercise. Participants will be instructed to reach the maximal score for the entire training program. After this exam, the second measurement will be performed.

2.3 Training Protocols

Six game-based exercises have been adopted from previous studies[1, 94] in the trunk control training: Circle, Target, Hunting (Static and Dynamic), Octagon, Basketball, and Brick Breaker. Details of the training intervention have been reported elsewhere. [1, 94] During the balance training, two types of supervised learning conditions will be implemented in random order. In the first condition, stereotyped patterns of movement are generated, requiring a high precision of movement performance. For the second type, participants will apply a general strategy of voluntary postural control that included attention, decision-making, and performance of the task with different movement patterns. In brief, the training paradigms included three types of learning conditions: a) a set path of seated dynamic movements (‘circle’ game and ‘octagon’ test); b) unset path requiring decision-making goal-oriented movement patterns (‘basketball’, ‘brick breaker’, ‘hunting static’ and ‘hunting dynamic’ games); c) ability to maintain upright quiet sitting without and with visual feedback (‘target’ game and ‘self-perturbation’ test). Postural control assessment was performed prior to the first training session and after the last seated balance or stand training session. Each game, or exercise, lasted between 30 secs to 2 minutes and 2 min of rest was provided between games and/or tests. For motivation purposes, the participant was instructed to maximize his score in each game. When the participant was able to achieve a consistent score in a game, the difficulty level of the exercise was increased. Experimental sessions lasted for 90 mins and the ability to translate COP was trained via visual feedback and game-based exercises. Each training session started by assessing threshold and optimal stimulation parameters.

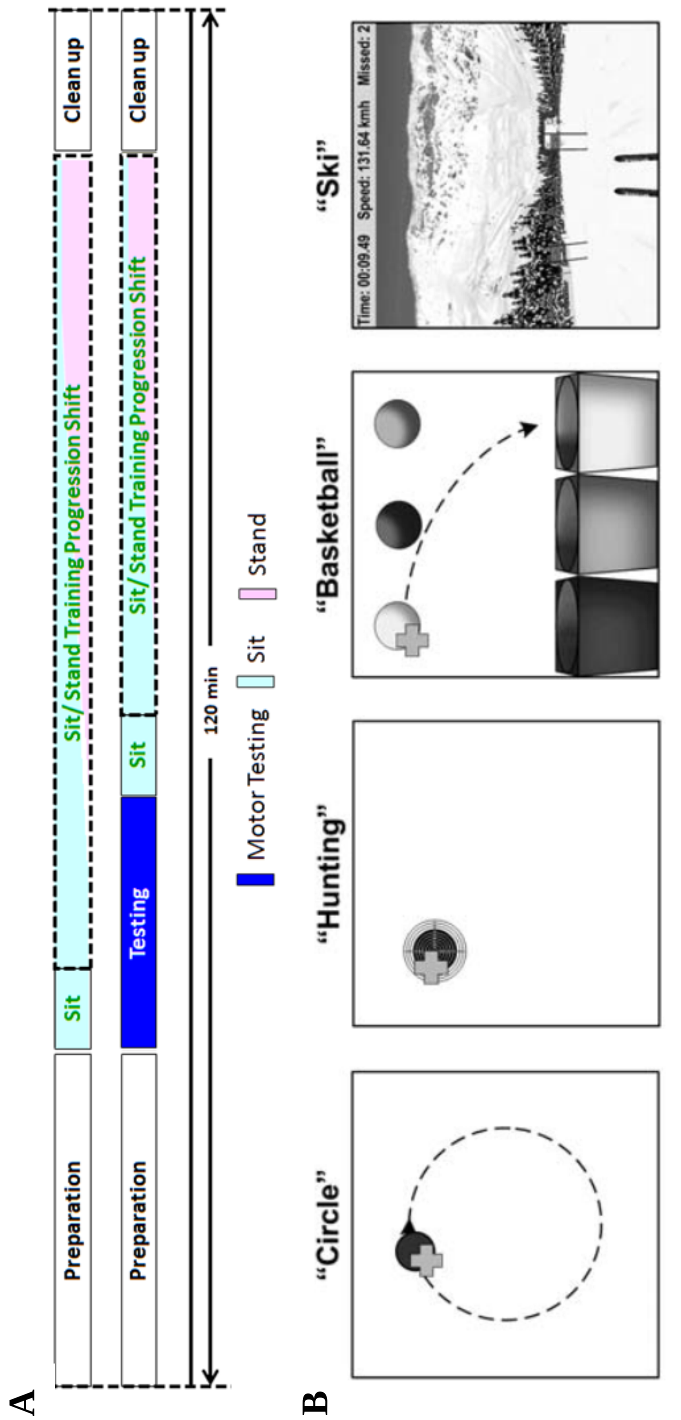


Figure 1. Outline of Training Protocol. A) Intrasession breakdown on testing vs training and the progression from sit training to stand training. B) Training game-based exercises. [modified from Sayenko et al. 2010[1]]

2.4 Transcutaneous Electrical Spinal Cord Stimulation Protocol

Strategies for enhancing the functional capabilities of persons with spinal cord injury have been developed that rely on residual capacities.[95] However, most of these traditional approaches run into limits. tSCS is a form of noninvasive stimulation that improves lower limb motor function.[95] [64]However, the ability of tSCS to improve trunk stability, steadiness and motor control of persons with spinal cord injury during sitting (dynamic and static) and standing has not been tested.

tSCS includes electrically activating the spinal circuitry via electrodes placed on the skin overlying the vertebrae of the lower thoracic and/or lumbosacral vertebrae A custom-built, 3-channel constant-current stimulator with a range of 0 to 250 mA was used to deliver transcutaneous spinal cord stimulation. The stimulation was administered using two self-adhesive electrodes (ValuTrode, Axelgaard Ltd., Fallbrook, CA, USA) with a diameter of 3.2 cm placed as cathodes on the skin over the T11 and L1. In addition, two 7.5 × 13 cm self-adhesive electrodes serving as anodes (ValuTrode) were placed symmetrically on the skin over the iliac crests. A foam rubber pad was placed over the cathodes and secured using adhesive tape, and an elastic belt was wrapped tightly around the trunk above the waist to ensure a constant pressure between the electrodes and the skin. The stimulation waveform consisted of monophasic, rectangular 1-ms pulses at a frequency of 30 Hz during stimulation over the T11, and 15 Hz during stimulation over the L1, with each pulse filled with a carrier frequency of 10 kHz[64] In the beginning of each experimental session, the participants were instructed to maintain a “relaxed” sitting posture, that is without actively trying to extent the trunk. During these preliminary tests, the stimulation intensity, ranging from 10 to 150 mA at each location, was gradually increased to generate threshold motor outputs as detected via the COP movements recorded by the force plate and/or via changes in trunk extension and improved trunk curvature as confirmed by visual inspection (see Supplementary Video 1). After that, the stimulation intensity at each location was adjusted to a sub-motor threshold level, which was then kept constant during the main tests with stimulation.

2.5 Assessment of Postural Control Protocol

Three primary tests were performed: quiet sitting, multidirectional leaning (‘Octagon’), and response to rapid arm extensions (RAE). During each test, participants were instructed to sit unsupported on the force place and attempt to actively maintain their trunk as upright as possible, maintain balance, and minimize the use of their arms and head. One researcher was standing behind the participant to ensure safety of the tests and provide assistance to prevent falls if needed. During the quiet sitting test, participants were instructed to sit as quietly as possible for 60 seconds with eyes open. After 2 minutes of rest, the task was repeated with eyes closed. During the multidirectional leaning test, the ability to voluntarily displace the center of pressure (COP) to a maximum distance without losing balance was assessed. Participants were instructed to lean from the center position as far as possible in the indicated direction without losing balance, while keeping their back extended. The COP position was visualized on the monitor to provide feedback on body displacement. Eight targets were presented at 45-degree angle increments around the center starting in the forward right direction. The participant was asked to move the COP indicator to each target, which was present for 5 seconds, hold the position during that time, and return back to the starting position.

Then, a response to rapid arm extension test was performed in seven participants (P1-4, P6-8) to assess the efficiency of postural corrective responses. The data of participant P5 were omitted from the group analysis due to incomplete video and 3D kinematics recordings during the RAE test. In agreement with previous literature,[1] the participants were instructed to rapidly extend the right arm forward from their side to a fully extended position then return the arm back to the initial position based on verbal cues.

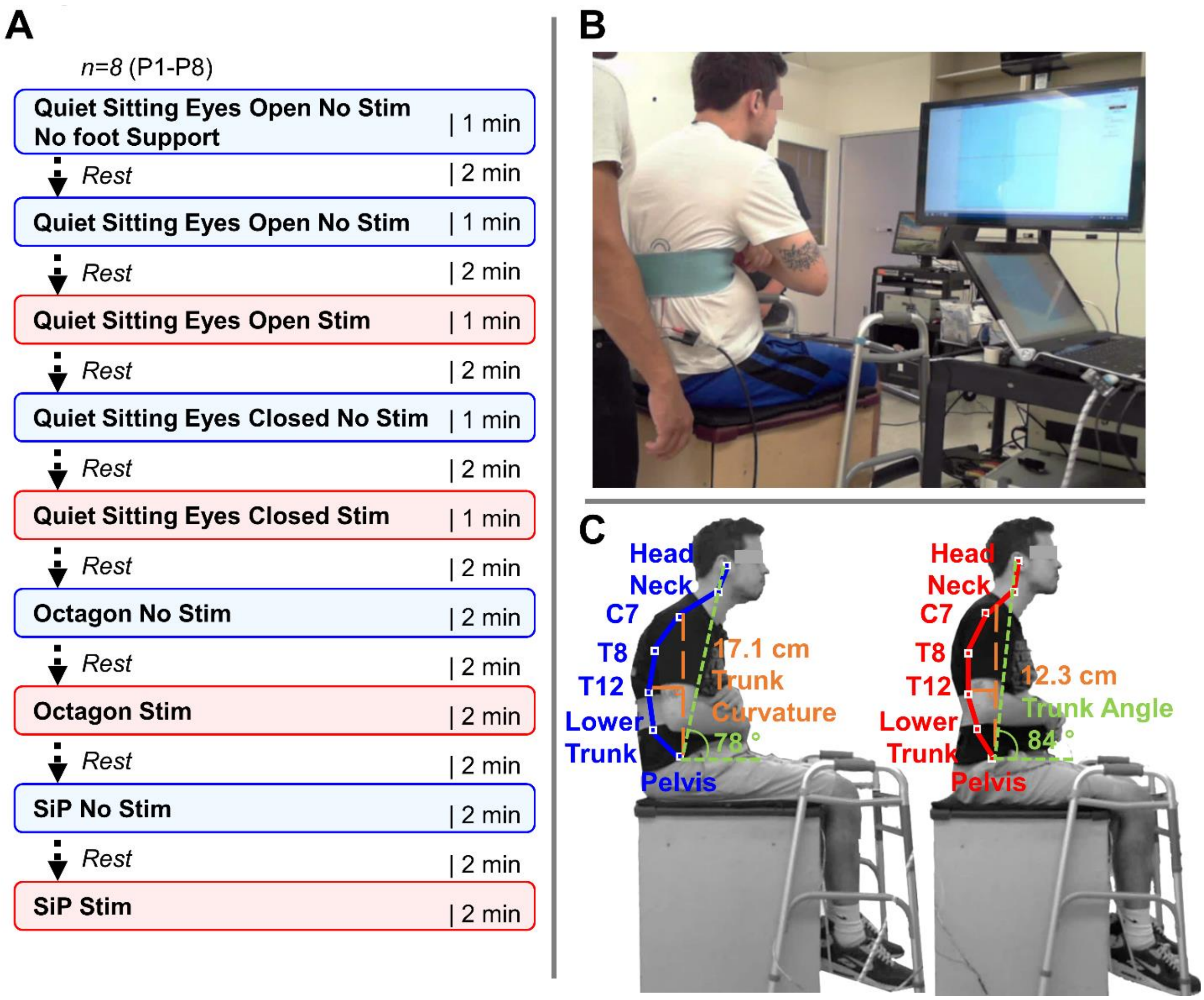


Figure 2. (A) Schematic representing the experimental design protocol and interventions. Eight individuals were tested in a single experimental session without and in the presence of transcutaneous electrical spinal cord stimulation. (B) Testing room layout and experimental setup. (C) Representative participant (P5) without (left) and with sub-motor threshold spinal stimulation (right). Note the decrease in trunk curvature (orange), increase in trunk angle (green) and the improvement in upright sitting posture and spinal alignment. Key anatomical landmarks are shown without (blue) and with stimulation (red).

2.5 Assessment of Force Plate Protocol

COP trajectory data from the force plate were analyzed in the A-P and M-L directions. The COP characteristics were quantified via total excursion, mean displacement, and mean acceleration. COP excursions were calculated where (xi, yi) is the COP position at frame i and N the total number of samples:

$$Total\ CoP\ Excursion = \sum_{i=1}^{N} \sqrt{(x_i - x_{i-1})^2 + (y_i - y_{i-1})^2}$$

The maximum COP displacement for both the quiet and dynamic sitting tasks was defined for each direction as the mean COP position maintained for 0.24 s at the extreme points of a given direction; the primary directions (forward, backward, right, and left) were used to define the limits of stability (LoS).

2.6 Assessment of EMG Protocol

The digitized EMG time series were full-wave rectified and filtered with custom Matlab code as outlined in Figure 2A. Each individual raw trunk muscle EMG (Obl, RA, E-T7, E-L3) was first passed through a median filter with a 7.5 ms sample window to reduce the magnitude of the noise signal and remove any significant outliers while retaining prominent features i.e. muscle activation, peaks etc. Next, this signal was then passed through a high pass filter with a .0001 Hz cutoff frequency (Eh) to bring the EMG signal to baseline, and full -wave rectified (Er). The filtered and rectified signal, Er, was finally passed 10 times through a 15th order linear adaptive filter with delta set to 1 x 10-9 s. The input signal was Er and the reference signal was the summation of both stimulation channels (Stim T7 and Stim L3). The linear adaptive filter was used to isolate the EMG artifact resulting from stimulation from both the T-7 and L-3 stimulation electrodes. An example of the EMG processing prior to filtering and the same signal post filtering is shown in Figure 2B, C. Note that for the raw signals, the y limit range indicates magnitude and the signal was centered for comparison purposes. Muscle activity was quantified by calculating the mean EMG signal amplitude, after measurement windows were normalized in duration for each trial. Incidences of lost balance were excluded from analysis. The EMG data of participant P3 were excluded from the group analysis because of the relatively low, T9 neurological level of SCI.

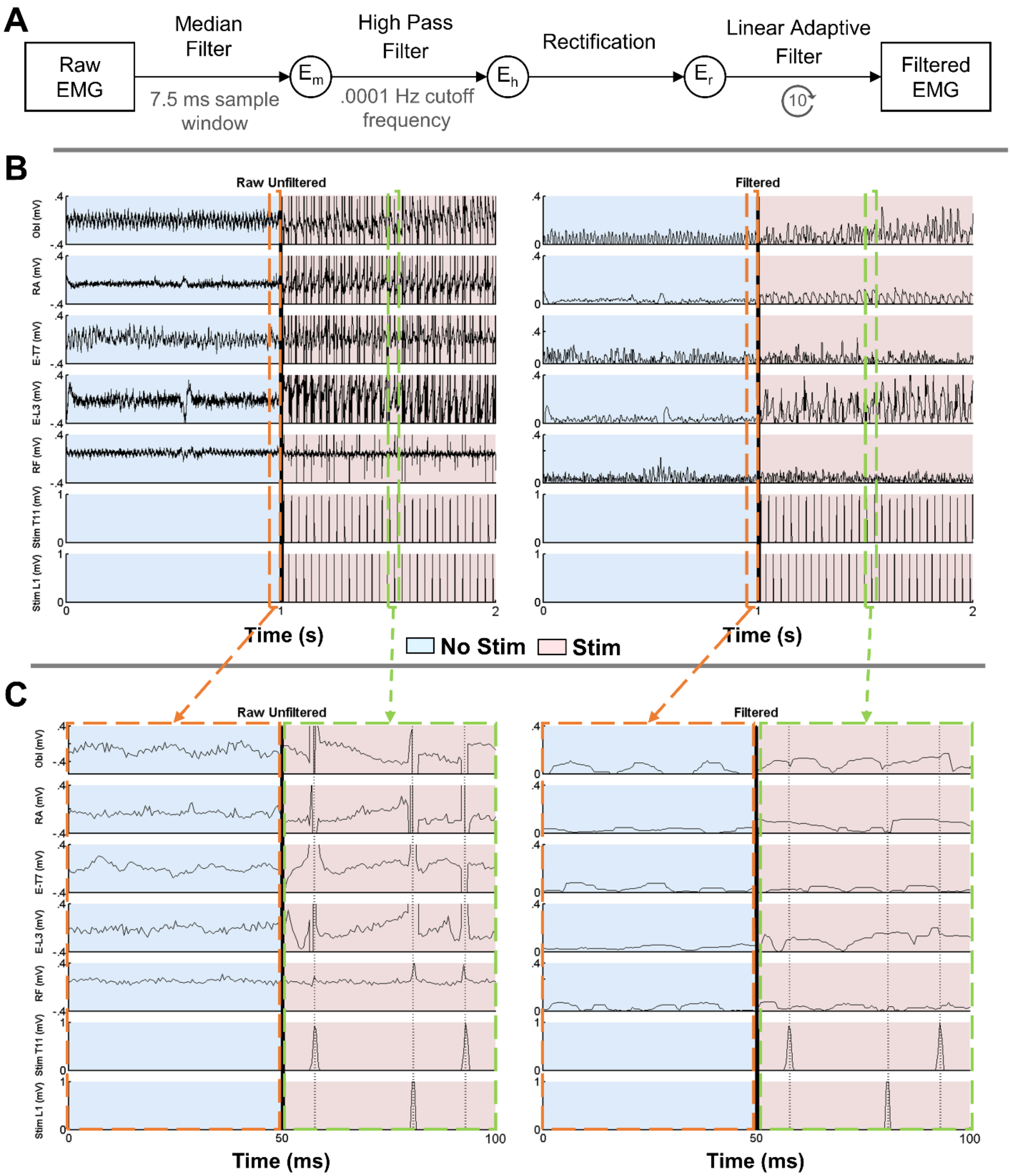


Figure 3. (A) Schematic representing EMG processing. Each trunk muscle EMG channel was filtered. Note for the linear adaptive filter, the reference signal was the sum of T11 and L1 stimulation. (B) Representative raw unfiltered (left) and filtered (right) EMG sample from P1 without (light blue) and with (light red) the presence of stimulation. (C) Zoomed in 50 ms sample of raw unfiltered (left) and filtered (right) EMG without (light blue) and with (light red) stimulation. The orange and green dashed lines indicate the enlarged segments without and with stimulation respectively.

2.7 Assessment of 3-Dimensional Kinematics Protocol

Custom source code with a graphical interface was used to extract image, joint, and depth data from the Xbox One Kinect motion capture system. Custom Matlab (Mathworks, USA) code was used to plot and analyze the COP and kinematic joint location data and associated trajectories to determine the limits of stability, quantify spinal alignment, and graph EMG data during each test.

Joint positions were used to calculate the joints' displacements over time. These displacements were then used to determine the velocity and acceleration profiles of each joint via single and double derivatives of the position profile, respectively. Joint displacements and joint angles of select joints were calculated from 3D kinematic data. COP velocity and acceleration as well as coordinates of the head, neck, and lower trunk during quiet sitting, multidirectional leaning, and RAE were used to verify the limits of stability via COP projection onto the two-dimensional x-y plane.

2.8 Statistical Protocol

Statistical analyses were performed using a within-subject statistical design. Comparisons between force plate data, EMG, and 3D kinematic positional data for all assessment tasks without and with the presence of stimulation were performed using the two-tailed nonparametric Wilcoxon Signed-Ranked test ($\alpha < .05$). The results for the pooled data are presented as mean values and standard deviations (SD). In addition to EMG comparisons for quiet sitting, multi-directional leaning and RAE, comparisons between no stimulation in quiet sitting vs no stimulation in multidirectional leaning as well as stimulation in quiet sitting vs stimulation in multidirectional leaning were performed. Correlation coefficients between arm velocity and COP displacement for the RAE were determined using the nonparametric Spearman's rank correlation coefficient, with rho and p values indicated ($\alpha < .05$). Statistical test comparing the correlation coefficients, where the null hypothesis was that the difference between no stimulation and stimulation conditions equals 0, was performed using the cocor R package web-based interface (http://comparingcorrelations.org/) developed by the CRAN project (http://cran.r-project.org/package=cocor) with $\alpha = .05$ and a confidence interval of 95%.d[96]. Pearson and Filon's z test results are reported.

2.9 Potential Risks

2.9.1 Risk from Transcutaneous Spinal Cord Stimulation

The transcutaneous stimulation device is noninvasive and meets US safety regulations. All procedures have been approved by the UCLA Institutional Review Board (IRB#14-000158). There is a minor risk of discomfort during the stimulation procedure that stops after stimulation.

2.9.2 Risk from Interventions and Experimental Procedures

Because subjects must meet the criteria listed above, we expect all subjects to be in good health. The studies described may involve the following physical risks and/or discomforts:

1) increased respiration or shortness of breath;

2) increased heart rate

3) muscle and joint soreness

4) lowering or elevation of blood pressure

5) dizziness

6) skin irritation from recording electrodes, or hand placements of trainers

7) skin abrasion from hand placements of trainers

8) muscle strain or joint sprain from leg movement, or from the force exerted by the trainers.

Most subjects will have increased respiration and heart rate due to an increase in activity. However, we did not expect the increase in respiration and heart rate to be greater than what is normally experienced during regular exercise. SCI participants may sustain skin irritation from the recording electrodes, or hand placements of the trainers. These conditions are considered to be minimal risks and are reversible. There is some chance that participants may sustain muscle and joint soreness, lowering or elevation of blood pressure, dizziness, or skin abrasion from hand placements of the trainers. If these events occur the experiment was ceased immediately. These conditions are considered to be minimal risks and are reversible.

It is highly unlikely that a participant would feel chest pain or high blood pressure that did not resolve within several minutes. These events have not occurred in our past experience. However, if this did occur the individual would be immediately transported to the University of California, Los Angeles Emergency Unit and the on-call physician notified. It is also highly unlikely that a participant would suffer a muscle strain, joint sprain, or fracture from lower extremity physical therapy. These conditions are considered to be moderate risks but rarely occur. However, if these events should occur, the participant would immediately stop training and would be immediately evaluated by the on-call physician. Standard medical procedures will be provided. The participant primary physician would be notified as needed. These conditions are considered to be moderate risks and are reversible.

There are no identifiable psychological, sociological, economical, or legal risks to the participants.

2.10 Adequacy of Protection against Risk

2.10.1 Recruitment and Informed Consent

Recruitment of participants was performed through the Neurological Rehabilitation Service at UCLA, which evaluates approximately 70 chronic SCI outpatients each year. Our current database includes approximately 600 chronic SCI participants with approximately 75 potential participants matching the eligibility requirements who have expressed interest in participating in our research program. In addition, physicians and physical therapists at rehabilitation sites in the Los Angeles area were provided with the purpose of the research, selection criteria for referral, and flyers for advertisement. The research aims and a summary of the criteria for eligibility was posted on Dr. Edgerton's website, at NextStep Fitness, ProjectWalk, Christopher and Dana Reeves Foundation website upon initiation of study.

All eligible subjects were invited to the UCLA Boyer Hall, where the research was performed, to discuss the complete protocol and its risks and benefits with Dr. Havton. Afterwards, all potential participants were encouraged to read the informed consent given by Dr. Havton and discuss the study with their physician, family, and friends, before signing the IRB approved informed consent. The informed consent forms were written so that it could be understood by an eighth-grade language student and contain information on all studies to be performed as well as contact information should the subject or his/her associates have any questions. The original signed informed consent and two copies which are kept in a secured drawer in a secured office in the Edgerton Lab.

2.10.2 Protection against Risk

No participant was allowed to participate in the study without being examined by Dr. Havton. In addition, all eligible participants were encouraged to discuss the study with their primary physician. Furthermore, to minimize the risks, certain measures were implemented to protect the participants; For example, each participant was closely monitored (blood pressure, oxygen saturation, respiratory function and heart rate) at the beginning, during and after each experiment and training session. The experiment would have immediately come to a halt if these values become abnormal or the participant feels tired or out of breath or has chest pain. If these conditions persisted, Dr. Havton was to be contacted immediately to assess the subject and notify the person's primary care provider when necessary.

Before and after every experiment and training session, the participant's skin was checked and monitored for irritations and abrasions. If skin irritations or abrasions were caused by the recording electrodes or hand placements of trainers, electrode and hand placement were modified appropriately. Furthermore, constant monitoring of the participant's skin and muscle for signs of muscle strain, joint sprain, and skin irritation (e.g., temperature and redness) occurred. Furthermore, continuous monitoring of the participant was conducted by the staff for potential injuries. For example, signs of skin redness, swelling of joints, or spasticity can be indicators of injury when participants have impaired sensation. The physical therapist or trained staff member will stretch the muscles of the participants before and after each training session to prevent injury.

If any signs of the risks or discomfort are noted, the experiment or training session was immediately discontinued. If any complications arose, training was immediately stopped and Dr. Havton was immediately informed. Dr. Havton, or a designated associate, was available on campus during all experimental sessions involving persons with spinal cord injury.

To protect confidentiality, each participant was assigned a coded identification number with no association to the identity of the participant. This number was used to distinguish all evaluations and analyses. Data was stored on computer media and videotape and was secured in a locked storage area of the laboratory. Only members of the research team including research assistants, post-doctoral students, and graduate students had access to the data for analyses. Only a designated researcher had access to the coding of the identification number to the participants.

2.11 Data and Safety Monitoring Plan

Dr. Edgerton, Mrinal Rath, research personnel, therapists, and nurse managers (if appropriate) met on a weekly basis to discuss the progress of the individuals participating in the study. Any adverse events were to be reported to the UCLA's Institutional Review Board. All fatal or life-threatening events were to be reported to the IRB within 72 hours of discovery. All other events were to be reported within 5 working days. The PIs and medical monitor were to review the adverse events report, follow the recommendations of the IRB, and put in place additional safety guidelines as needed to prevent recurrence of the event.

Throughout the study procedure all safety and risk mitigation efforts were made. One participant withdrew from the study due to an adverse event independent of the intervention, and the data was excluded from the analysis. No major adverse events occurred throughout the study. The stimulation procedures were well tolerated by all participants, with no pain or discomfort associated with tSCS being reported. The participants noted tightness in the trunk muscles during stimulation and the feeling of "falling backwards" at higher intensities, however it was readily tolerated and not reported at sub-motor threshold intensities which were used throughout the duration of the assessments.

Chapter 3: Materials and Equipment

3.1 Stabilan-01 Force Plate System

The Stabilan-01 force plate is used for collecting center of pressure measurements sampled at 50 Hz. The field for CoP coordinate recording is a circle with the center at the origin of the platform and a 200 mm radius. The CoP coordinate tolerance is no more than 1% at the resolving power (~ 0.01 mm). The platform supports up to 150 Kg and the minimum measurement has accuracy is 10g. The Stabilan-01 Force Plate System complies with the medical device requirements relating to the safety.

During the training, participants sat on a force platform and were instructed to shift their center of pressure in the indicated directions as represented by a cursor on a monitor. The performance was monitored throughout the training period and the difficulty was adjusted to challenge the postural system with a range set near the participant's limit of stability.

3.2 Electromyography (EMG)

PowerLab 16/35 series DAQ and Octal Bio Amp

Electromyography (EMG) signals of selected trunk muscles were recorded using bipolar surface electrodes. Signals from the right rectus abdominis (RA), external obliques (Obl), erector spinae at the levels of the seventh thoracic vertebra (E-T7) and the third lumbar vertebra (E-L3), rectus femoris (RF), and anterior deltoid (AD) muscles were recorded using the PowerLab 16/35 series DAQ system with a low-noise, high-gain differential amplifier (Octal Bio Amp). An EKG Reference was placed over the sternum.

EMG signals were differentially amplified with a band-pass filter of 10 Hz–2 kHz (−3 dB) and digitized at a sampling rate of 2 kHz. The digitized EMG time series were full-wave rectified after subtraction of the mean background EMG. The magnitudes of EMG activation were calculated by measuring the area under the curve during each directional. Measurement windows were normalized in duration for each trial such that incidences of lost balance were excluded from analysis. Total EMG activity and percent contribution by the external oblique, rectus abdominus, and erector spinae level T7 and L3 were determined.

3.3 3D Inertial Motion Capture

3D Visual-based Motion Capture – Xbox KinectOne

Biomechanical data was collected using the Xbox KinectOne (Microsoft Corp., Redmond, WA, USA). The KinectOne is a markerless computer vision system that uses an RGB camera and an Infrared laser. 3D positioning is determined via the point cloud generated by the infrared laser and a triangulation process described in Freedman 2010. Essentially a laser light source is split via refraction after exiting a specialized lens that creates a point cloud on an object. These refractions are transmitted back to the Kinect receiver which then processes the data using onboard firmware.

The KinectOne was placed approximately 1.5 meters directly in front of the testing apparatus at approximately 2 meters from the ground angled 60° downward. The testing apparatus was used to calibrate the system. Video and kinematic data was acquired at 640 × 480 pixels @ 30 Hz (RGB camera) and 640 × 480 pixels @ 30 Hz (IR depth-finding camera).

The biomechanical model consists of 24 segments: head, neck, C7/8, T12, L5 and right and left: shoulder, elbow, wrist, hand, thumb, hip, knee, ankle and toes. Each joint data has 3 degrees of freedom; rotational information is inferred from the relative orientation of three or more markers, i.e. ankle, knee and hip markers provide the knee angle.

Custom source code with a graphical user interface was used to play and extract image, joint, and depth data from the KinectOne. Custom Matlab code was then used to read, plot and analyze the biomechanical joint data.

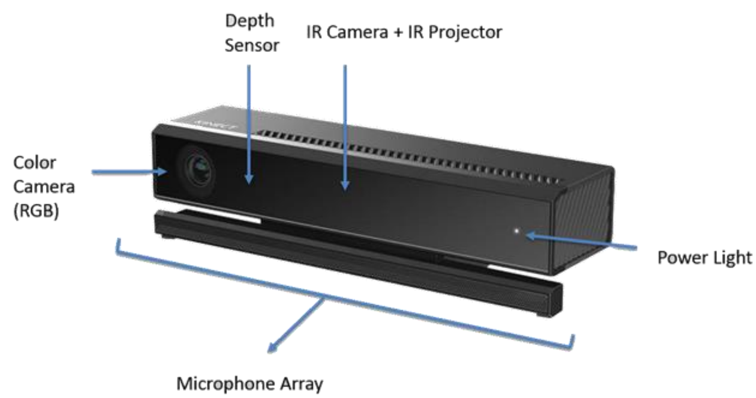


Figure 1. Xbox KinectOne Sensor Labeled. (http://blogs.microsoft.co.il/lironr107/wp-content/uploads/sites/1568/2015/01/k1.png)

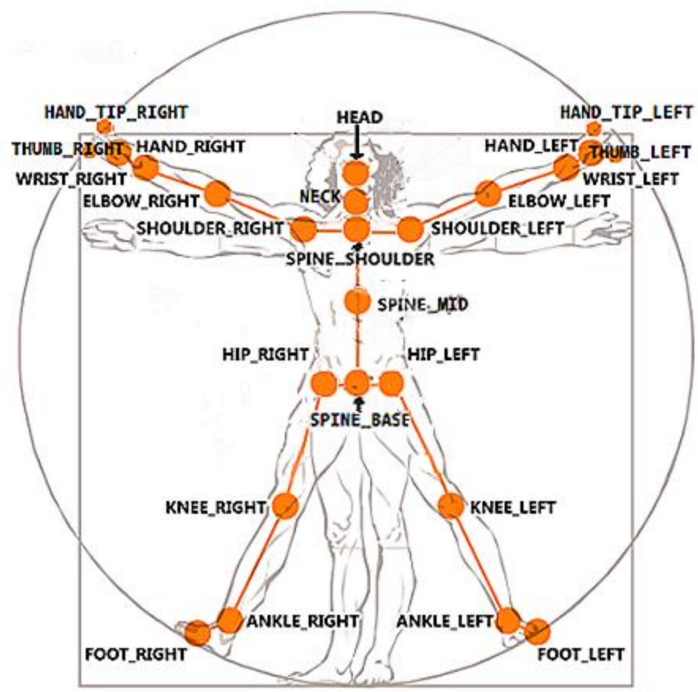


Figure 2. Xbox Kinect Studio's Joint Locations (https://i-msdn.sec.s-msft.com/dynimg/IC741371.png)

Xbox KinectOne - Custom software

Kinect Studio is a utility application that you can use to preview Kinect sensor array data, record and play eXtended Event File (XEF) files, control the timeline position, and select 2D or 3D views. Kinect Studio allows users to record and play back body data using XEF files (https://msdn.microsoft.com). Each ". XEF" file contains a sequence of data frames captured by Kinect, and each frame includes a point cloud that describes the human body in three-dimensional space. A point cloud means a large set of 3D points that lie on human body surface. The task of tracking can be viewed as matching the point clouds in two consecutive frames. For example, in frame 1, point 1 lies on the human head, and to track point 1 means that we need to find a point in frame 2 identical to point 1. If we want to track all the points in frame 1, we need to find a matching scheme that pairs the points between frame 1 and frame 2. A visual representation of the point cloud and tracking is shown in Figure 3.

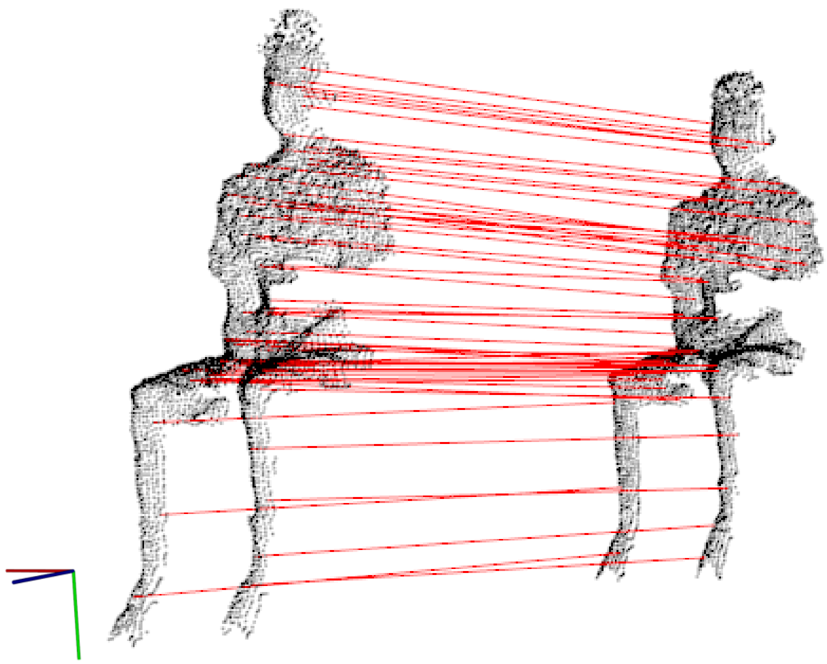


Figure 3. Point cloud tracking from one video frame to the next frame. Representative participant is seated on the sitting platform and red lines indicate the tracking of the point location to the subsequent frame.

We developed a custom algorithm match point cloud schema between any two frames of data. For any point in frame 1, a corresponding point in frame 2 is generated and used to track joints and movement with respect to time. For instance, if you select the right acromion from an initially starting set of points in frame1, a corresponding set of points in frame 2 are used to represent the right acromion in frame 2. The frames are tracked in 3D space and traced frame by frame with the cloud matching schema.

We also developed a custom algorithm using two Xbox Kinects to better capture 3D kinematic movements not discretely seen in just a single coronal view. The two Kinect's capture the testing apparatus and the participant from 2 different angles/planes. We specifically position the cameras to capture the coronal and sagittal plane movements. For each Kinect, a transformation matrix is computed based on the pose of the testing apparatus in the view of the Kinect. Based on the two transformation matrices, the data streams are synthesized.

3.4 Coulomb-3M Transcutaneous Spinal Cord Stimulator

The Coulomb-3M transcutaneous spinal cord stimulator was employed in this study. It is an investigational custom-built device designed to modulate the spinal cord to promote restoration of movement and function to participants with paralysis. It is intended to deliver a localized therapeutic electrical stimulus to the spinal cord with electrode pads placed on the skin. The Coulomb-3M stimulator is a three-channel stimulator where each channel was designed to generate 10 kHz radio pulses of different duration (0.1 ms to 3.0 ms with a step of 0.1 ms), repetition rate (1−10 Hz with a step of 1 Hz, 10−100 Hz with a step of 5 Hz) and current control intensity (0 – 220 mA).

3.5 Sitting Apparatus

Quantifying upright sitting biomechanically is the main outcome of the proposed interventions. A custom built seated platform implemented with the 'Stabilan-01' (Rhythm, Taganrog, Russia) force plate analysis system was used. During testing a walker was placed around the platform while the participant was seated on the apparatus via a seated transfer. Spotters were used to maintain participant safety during the testing and training process. A 3D computer-aided design model of the apparatus including the force plate is shown in Figure 4. Note a thin .5” gel cushion with a removable washable cover was placed over the force plate to minimize risks of the patient developing pressure sores.

Figure 4. Computer-aided design model of sitting apparatus system with force plate

3.6 Stand Frame Apparatus

Upright standing is an essential part of the proposed interventions. Two major paradigms were used depending on the individual sensory-motor function: *active standing* defined as involving muscular effort on the part of the participant to come to and maintain the standing position, and *assisted standing* defined as standing that depended on the standing frame to assist the participant to maintain an upright position. In both paradigms, the participants were instructed to stay as actively as possible by performing movements and weight shifts. The participants were encouraged to increase their independence during standing by receiving the qualitative visual feedback on their performance during the training sessions. A custom designed standing frame was utilized. Figure 5 shows a computer-aided design model of the standing frame.

A point cloud model of the standing apparatus with force plate acquired from the KinectOne sensor is shown in Figure 6.

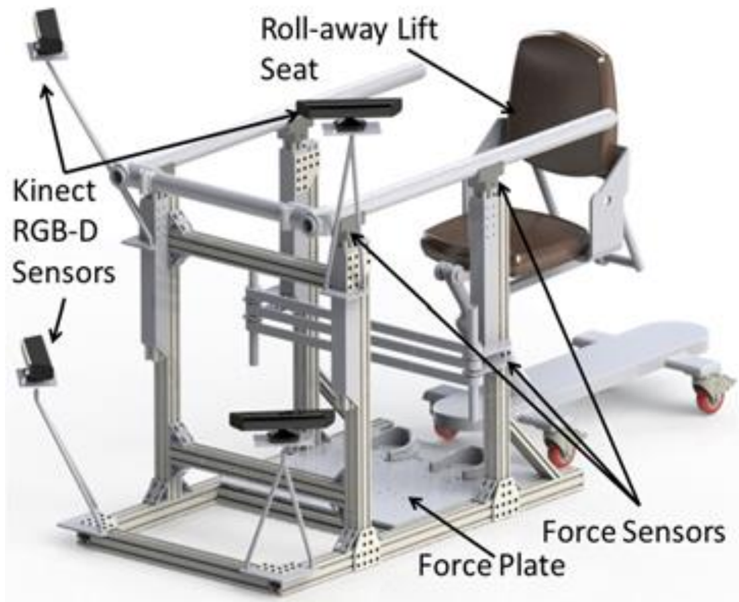


Figure 5. Computer-aided design model of stand frame training system, with safety and sensing features.

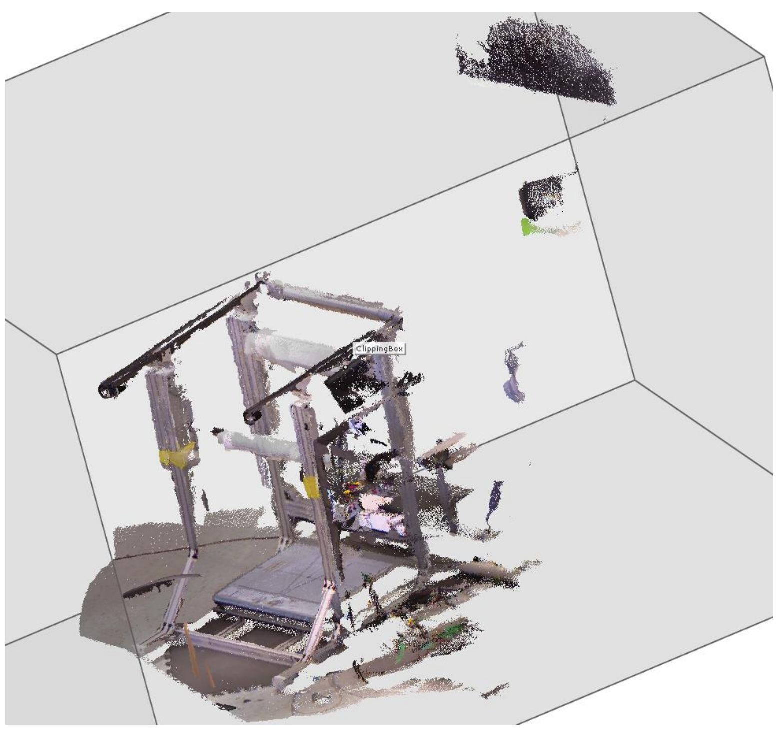


Figure 6. Point Cloud model of stand frame training system

Chapter 4: Acute Effects of tSCS on Trunk Stability

4.1 Introduction

Sensory-motor impairments that affect trunk, upper extremity, and lower extremity functions are common in individuals with spinal cord injury (SCI).[9, 97] The severity of these impairments primarily relates to the neurological level and degree of completeness of the lesion sustained by the spinal cord. As a result, the complex synergies required to regulate postural stability while performing routine daily tasks, such as reaching from a wheelchair to lift objects, or transferring from a wheelchair to a bed or into a car, can be affected to varying degrees.[40, 98] Individuals with SCI are consequently exposed to a higher risk of instability and falling even in a quiet seated posture, increasing the probability of fall-related pain, bone fractures, and other injuries.[99, 100] In addition to restoring seated quiet and dynamic ability,[5] clinical and physiological benefits of improving trunk posture and control have been shown to include a decrease in neck and back pain,[101, 102] the ability to perform pressure relief,[101] improvements in bimanual workspace,[40] pelvic tilt, lateral vertebral alignment,[39, 55] enhanced forward reaching and active pulling,[39, 40] and improvements in diaphragmatic and deep breathing.[103] Hence, reaching an optimal level of quiet and dynamic seated postural capability is generally one of the key objectives in SCI rehabilitation, with the ultimate goal of enhancing affected individuals' health as well as performance and independence in daily activities.[51]

Postural regulation of trunk is also one of the key elements of locomotor control.[69, 104-107] While the importance of studying seated postural control is frequently acknowledged, the success of restoring stability during quiet and dynamic sitting in individuals with SCI is limited. Current clinical practice has established an emphasis on the reduction of pressure sores, the control of abnormal tone, and skeletal alignment, and utilizes almost exclusively repetitive reaching movements towards a target while sitting on the edge of a treatment table.[108, 109] In addition, such practice often focuses on the use of compensatory strategies that emphasize the engagement of stronger muscles, rather than on the restoration of function of the weaker and/or paretic muscles.[110, 111] As such, instead of promoting the recovery of motor control,[112-114] these rehabilitation strategies are aimed at strengthening muscles above the spinal lesion and using leverage, momentum, and substitution to move weak or paralyzed parts of the body.[110]

Prior efforts have clearly demonstrated that the spinal neuronal circuitries below a paralyzing site of injury have a functional potential that far exceeds what has been thought possible, allowing significant levels of voluntary control of standing, stepping, and leg movements.[115-119] These functional outcomes depend on multiple factors, including the stimulation location, intensity, and frequency, as well as the specific motor task practiced. Recently, a non-invasive electrical neuromodulatory technique was proposed as an alternative to the invasive epidural approach to augment the functional state of the spinal locomotor-specific networks, enabling the recovery of rhythmic stepping movements in individuals with paralysis.[61, 65, 120-122] Neural regulation of locomotion and posture may occur in a synergistic manner because both systems rely on similar peripheral (visual, vestibular, neck and trunk proprioception) input sources, and afferent inputs are projected to anatomically overlapping neural networks comprising projections to the lower trunk and leg muscles.[69, 105, 123, 124] In this light, the objective of this study was to quantify the electrophysiological, kinematic, and kinetic characteristics of postural control of trunk during sitting in response to non-invasive electrical neuromodulation of postural-specific networks of the lumbosacral enlargement. We hypothesize that: (1) the physiological states of the lumbosacral spinal networks can be electrically modulated, resulting in improved seated trunk control and stability of individuals with SCI; and (2) postural-specific networks can perform multiple motor control strategies when appropriately neuromodulated spinally.

4.2 Results

4.2.1 Quiet Sitting

With a gradual increase of spinal stimulation intensity during preliminary test in “relaxed” sitting, the participant assumed a more erect posture (Supplementary Video 1). During the main test, SCI participants were instructed to sit unsupported on the force place and attempt to actively maintain their trunk as upright as possible, maintain balance, and minimize the use of their arms and head for one minute. During quiet sitting the COP displacements decreased to 1.36 ± .98 mm as compared to 4.74 ± 5.41 mm without stimulation ($Z = -2.418$, $p = .0156$). The COP acceleration decreased from 4.33 ± 3.00 m/s2 without stimulation to 1.55 ± 1.24 m/s2 in the presence of stimulation ($Z = -2.661$, $p = .0078$) (Fig. 3A, B). There was also an increase in the coactivation of Obl and E-T7, as shown in the normalized pooled scattergram (Fig. 3A) and a change in the distribution of the trunk muscle activation (Fig. 3C). The EMG activity of E-T7, E-L3, and Obl changed from .12 ± .10 mV, .03 ± .02 mV, and .05 ± .06 mV without stimulation, to .05 ± .03 mV ($Z = -1.9872$, $p = .0469$), .37 ± .26 mV ($Z = 2.418$, $p = .0156$), and .16 ± .14 mV ($Z = 2.153$, $p =.0313$) in the presence of stimulation, respectively. There were no significant changes in the RA and RF EMG activity (Fig. 3C). Greater extension was observed in the lower trunk during stimulation, thus, sitting became more upright, with a mean trunk curvature of 12.30 ± 1.83 cm as compared to 15.08 ± 1.71 cm without stimulation ($Z = -2.4181$, $p = .0117$); the mean trunk angle increased from 83.88 ± 3.72° with stimulation as compared to 81.38 ± 3.66° without stimulation ($Z = 2.305$, $p = .0106$) (Figs. 2.5.2C and 4).

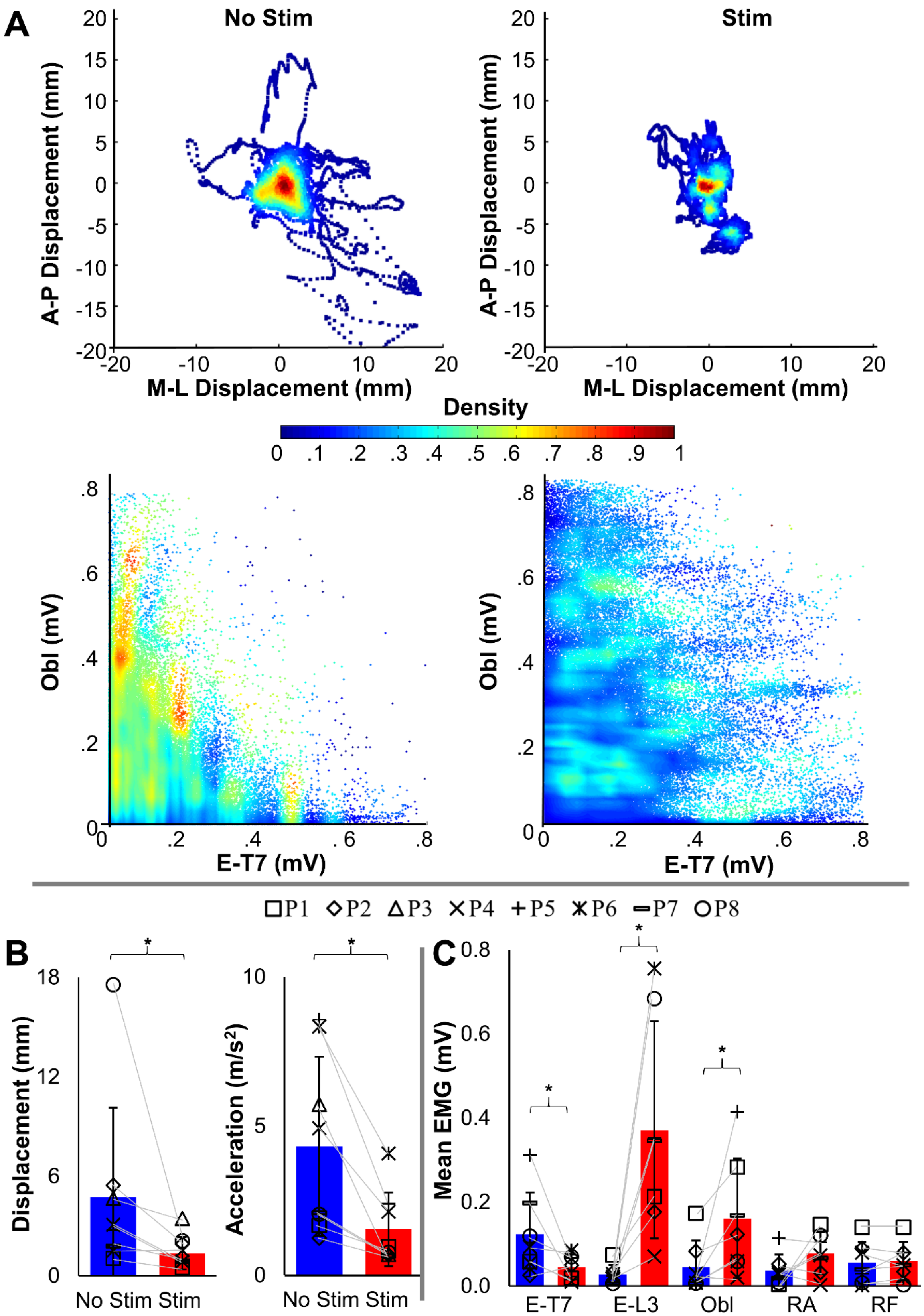

A
No Stim
Stim
A-P Displacement (mm)
M-L Displacement (mm)
Density
Obl (mV)
E-T7 (mV)
P1 P2 P3 P4 P5 P6 P7 P8
B
Displacement (mm)
Acceleration (m/s²)
No Stim Stim
C
Mean EMG (mV)
E-T7
E-L3
Obl
RA
RF

Figure 3. Acute effects of sub-motor threshold spinal stimulation on center of pressure (COP) parameters during unsupported quiet sitting for eight participants: (A) Normalized COP excursion density for all eight participants during eyes open without (left) and with sub-motor threshold spinal stimulation (right). The density indicates time spent at each position for all participants. Below, a scattergram between the erector spinae at the T7 level (E-T7) and external obliques (Obl) without and with stimulation in one representative participant (P2) is shown. (B) Mean amplitude and standard deviation of mean COP displacement (left) and of mean COP acceleration (right) without (blue) and with (red) stimulation; A two-tailed non-parametric Wilcoxon Signed-Ranked Test was used for assessing differences between stimulation conditions; *n=8*, * indicates statistical significance, $\alpha < .05$. A lower COP amplitude and acceleration are indicative of better control. (C) Mean EMG between stimulation conditions of E-T7, erector spinae at the L-3 level (E-L3), Obl, rectus abdominus (RA) and rectus femoris (RF). Note the significant change in activity of the E-T7, E-L3, and Obl; two-tailed non-parametric Wilcoxon Signed-Ranked Test where $n=7$ and $\alpha < .05$. P3 was omitted from EMG calculations due to a NLI of T9. Note no significant change in the RF.

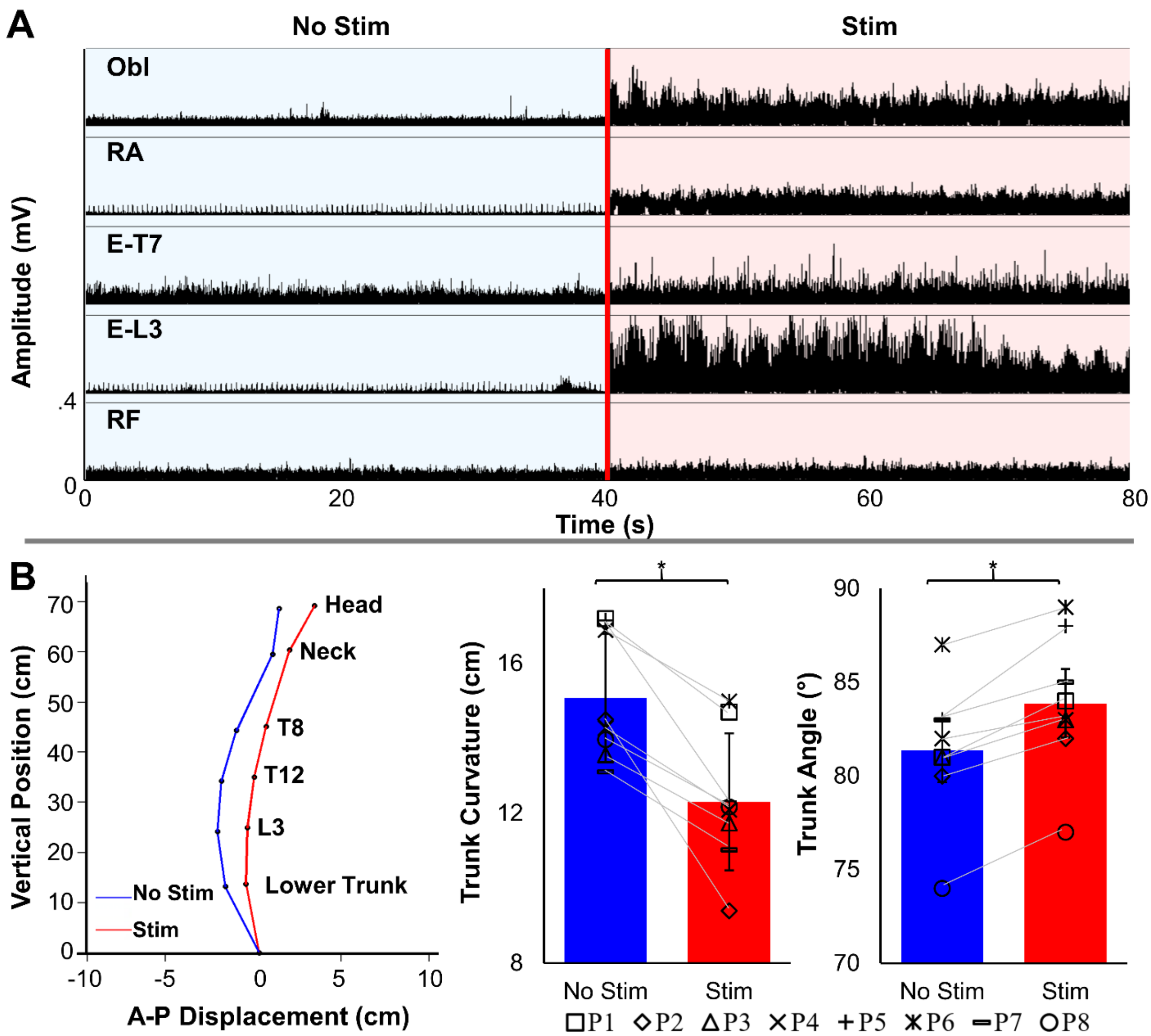


Figure 4. Characteristics of spinal stimulation during quiet sitting. (A) EMG recordings of four trunk muscles from a representative participant (P2) without (blue) and with (red) sub-motor threshold stimulation during unsupported quiet sitting. The external obliques (Obl), rectus abdominis (RA), erector spinae at levels T7 (E-T7) and L3 (E-L3), and rectus femoris (RF) are shown. (B) Spinal alignment (left), mean trunk curvature (middle), and trunk angle (right) during quiet sitting without (blue) and with (red) spinal stimulation. A 5-second window was used (4 to 9 seconds after trial onset) to determine the mean trunk curvature, horizontal distance between the hip (anterior-superior iliac crest), and maximal trunk displacement during quiet upright sitting. The pelvis is assumed to be fixed at the origin. Higher values in

trunk curvature indicate a decrease in trunk extension and more kyphotic (C-shaped) sitting. Higher values of trunk angle indicate more upright sitting. Individual data for all participants are shown via symbols. * indicates statistical significance, two-tailed non-parametric Wilcoxon Signed-Ranked Test where n=8 and $\alpha < .05$.

4.2.2 Multidirectional Leaning

During the multidirectional leaning ('Octagon') test (Fig. 5, Supplementary Video 2), participants were asked to lean as far as possible in the indicated direction without losing balance, hold the position and return to the initial position based on visual cues while minimizing movement of the arms and head to maintain balance and keeping the back extended. In the presence of stimulation, the mean limits of stability increased by 46.92 ± 35.66% (Z = 2.4181, p = .0156), 36.92 ± 30.48% (Z = 2.4181, p = .0156), 54.67 ± 77.99% (Z = 2.267, p = .0234), and 22.70 ± 26.09% (Z = 2.063, p = .0391) in the forward, backward, right, and left directions, respectively. The LoS increase was also associated with a less multimodal and a more uniformly shaped distribution of the A-P and M-L movement profiles of the COP displacements (Fig. 5A), indicating better temporospatial coordination; that is, participants were able to perform a more continuously controlled trunk leaning movement, hold the extended position for a greater duration of time, and return to the starting position without falling (Fig. 5B).

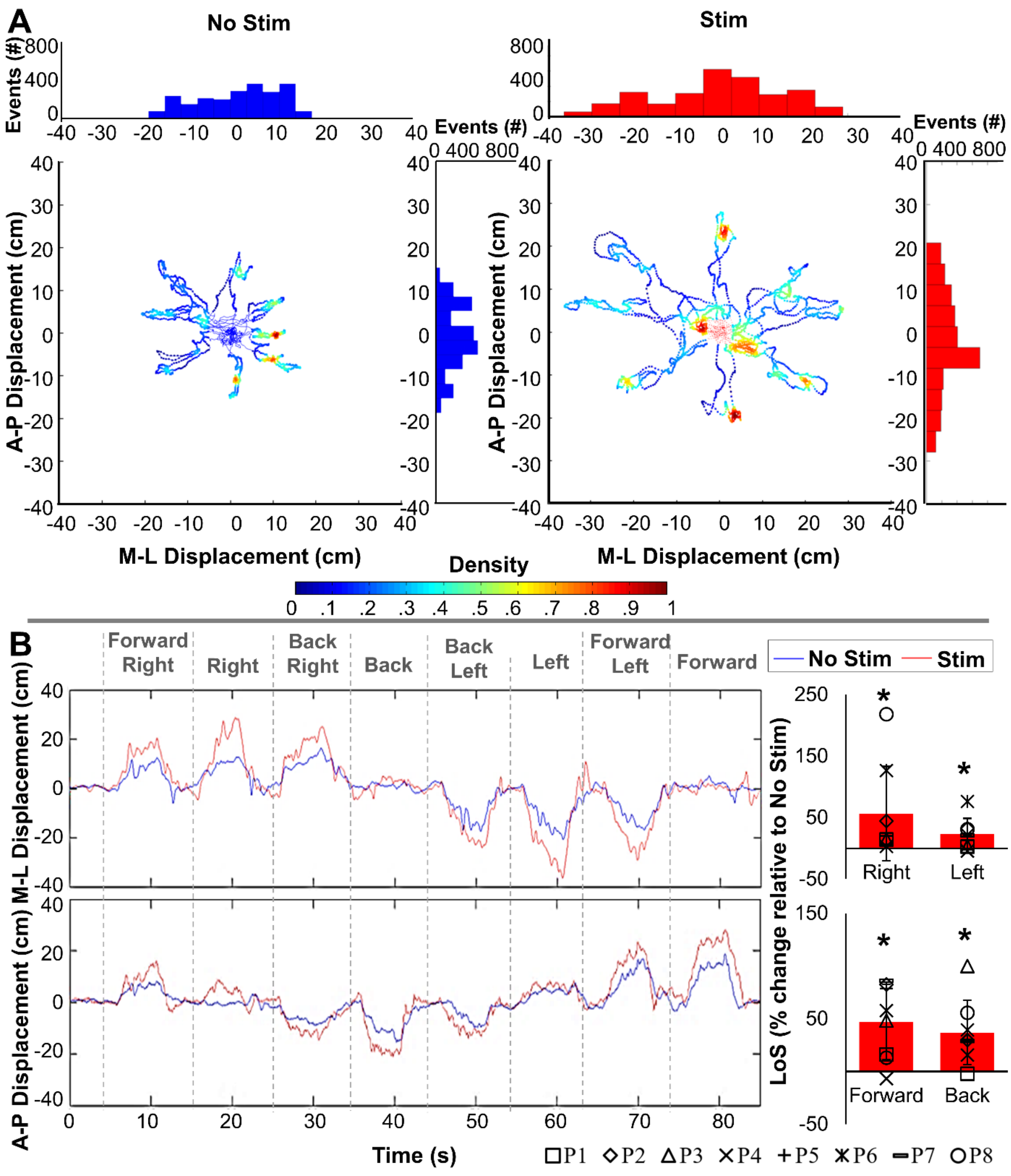


Figure 5. Acute effects of sub-motor threshold spinal stimulation on the limits of stability (LoS) during the 'octagon' multidirectional leaning test. (A) Density plot of the center of pressure (COP) excursions during the ‘octagon’ test for a representative participant (P2) without (left) and with (right) spinal stimulation. The distribution of directional displacement events, occurrence of a magnitude of displacement binned into

uniform time windows, is shown in both the M-L direction above each density plot and in the A-P direction to the right of each density plot. Note the distribution of the bins; the presence of spinal stimulation results in a more normal distribution of movement. (B) The mediolateral (M-L) and anteroposterior (A-P) time series, with positive values representing the directions right and forward, and negative values representing the directions left and backward. The pooled percent increases in the limits of stability (LoS) in the presence of spinal stimulation compared to no stimulation for all participants (n=8) are shown to the right of each time series plot. Note the significant increase in all leaning directions. * indicates statistical significance; two-tailed non-parametric Wilcoxon Signed-Ranked Test where n=8 and $\alpha < .05$.

Individual EMG data during multidirectional leaning are presented in Supplementary Tables 2 and 3. During multidirectional leaning, more neutral spinal alignment and decreased trunk curvature occurred and were maintained in either of the leaning directions (Fig. 6A) in the presence of spinal stimulation when compared to no stimulation. This was most notable for trunk extension, i.e., the backward leaning direction in the sagittal plane where ‘leaning’ was the newly adopted strategy as opposed to ‘slouching’. The improvement in seated spinal stability was associated with increases in trunk extensor (E-T7 and E-L3) and flexor (Obl and RA) activity in the presence of spinal stimulation (Fig. 6B).

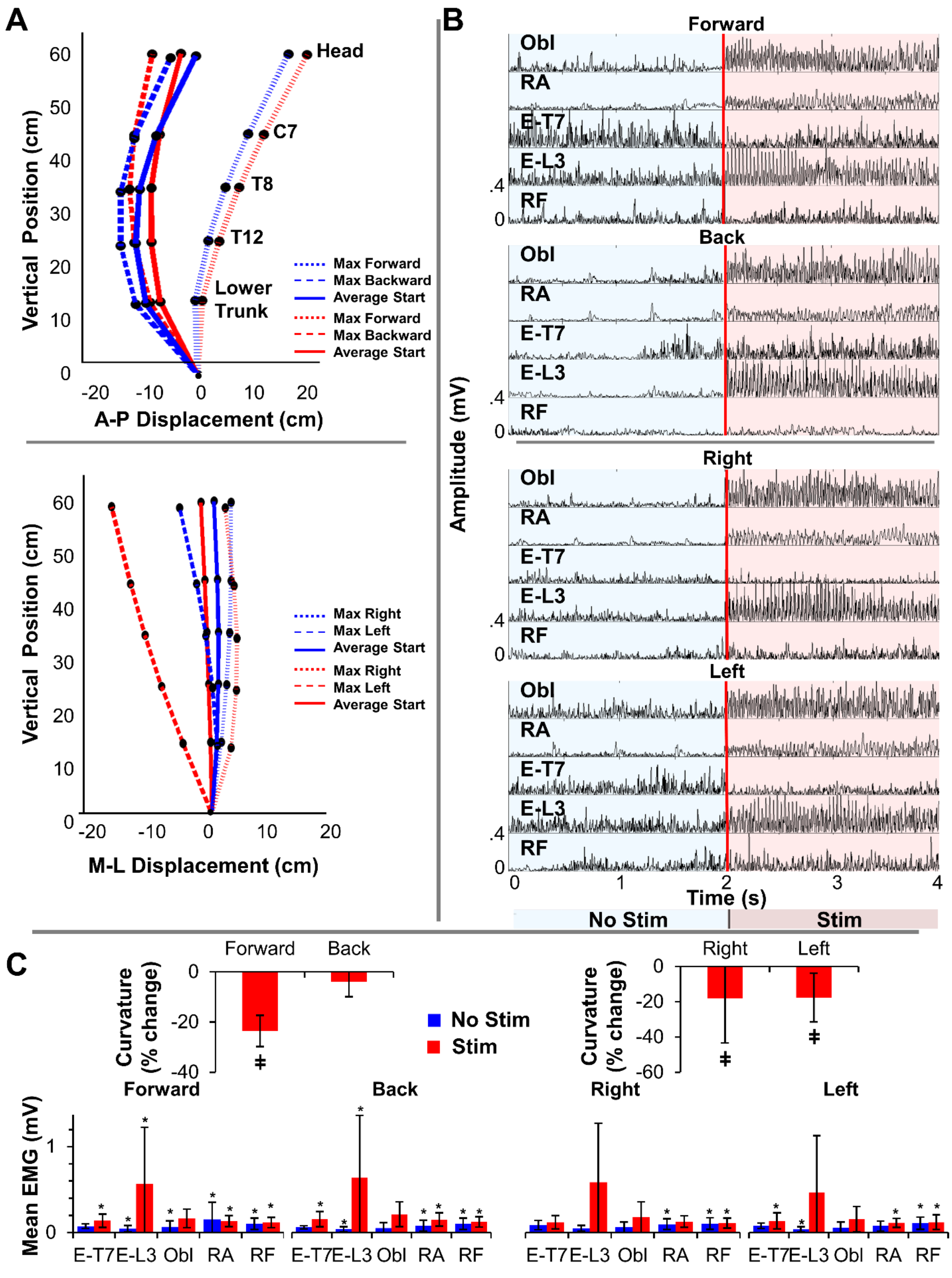

A
Head
C7
T8
T12
Lower Trunk
Max Forward
Max Backward
Average Start
Max Forward
Max Backward
Average Start
Vertical Position (cm)
A-P Displacement (cm)
Max Right
Max Left
Average Start
Max Right
Max Left
Average Start
Vertical Position (cm)
M-L Displacement (cm)
B
Forward
Back
Right
Left
Obl
RA
E-T7
E-L3
RF
Amplitude (mV)
Time (s)
No Stim
Stim
C
Forward
Back
Right
Left
Curvature (% change)
No Stim
Stim
Forward
Back
Right
Left
Mean EMG (mV)
E-T7
E-L3
Obl
RA
RF

Figure 6. Acute effects of sub-motor threshold spinal stimulation on the limits of stability (LoS) during the 'octagon' multidirectional leaning. (A) Three-dimensional (3D) joint kinematics showing the spinal alignment during directional leaning without (blue) and with (red) spinal stimulation in a representative participant (P6): Leaning in the anteroposterior (A-P) direction (top) and mediolateral (M-L) direction (bottom). 3D joint kinematics during the averaged start and extreme forward, backward, right, and left positions. The pelvis is assumed to be fixed at the origin. (B) Electromyographic data from a representative participant without (blue) and with (red) stimulation for four trunk muscles in the forward, backward, right, and left directions. The external obliques (Obl), rectus abdominis (RA), erector spinae at levels T7 (E-T7) and L3 (E-L3), and rectus femoris (RF) are shown. Note the change in magnitude of muscle activity. (C) The change in trunk curvature in the presence of stimulation during the A-P (left) and M-L (right) directions ($n=8$, $\alpha <.05$). A decrease in trunk curvature indicates more upright neutral spinal alignment. ǂ indicates statistical significance. The mean EMG activity levels and their standard deviations during each directional leaning without (blue) and with (red) spinal stimulation are shown ($n=7$, $\alpha <.05$, P3 was omitted from EMG calculations due to a NLI of T9). * indicates statistical significance between the corresponding values during quiet sitting and leaning in the indicated direction.

During leaning forward, there was a significant increase in E-L3 mean EMG activity from 0.05 ± 0.03 mV without stimulation to 0.57 ± 0.66 mV with stimulation (Z = 2.4181, p = .0156). The activity in E-L3, Obl, RA and RF increased as compared with the quiet sitting without stimulation (Z = 2.4181, p = .0156, Z = 2.4181, p = .0156, Z = 2.1532, p = .0313, and Z = 2.1532, p = .0313, respectively). In the presence of stimulation, the activity in E-T7, E-L3, RA, and RF was higher during leaning forward, as compared with quiet sitting (Z = 2.4181, p = .0156, Z = 2.1532, p = .0313, Z = 2.4181, p = .0156, and Z = 2.1532, p = .0313, respectively). During leaning backwards, mean EMG activity increased in E-T7, E-L3, Obl, and RF from .06 ± .02, .04 ± .03, .05 ± .06, and .09 ± .06 mV without stimulation, to .14 ± .08 mV (Z = 2.1532, p = .0313), .59 ± .66 mV (Z = 2.4181, p = .0156), .19 ± .13 mV (Z = 2.1532, p = .0313), and .11 ± .05 mV

(Z = 2.1532, p = .0313) in the presence of stimulation, respectively. The activity in E-L3, RA and RF increased as compared with the quiet sitting without stimulation (Z = 2.4181, p = .0156, Z = 2.4181, p = .0156, and Z = 1.9872, p = .0469, respectively). In the presence of stimulation, the activity in E-T7, E-L3, RA, and RF was higher during leaning backward, as compared with quiet sitting (Z = 2.4181, p = .0156, Z = 2.4181, p = .0156, Z = 2.4181, p = .0156, and Z = 2.1532, p = .0313, respectively). During leaning to the right, mean EMG activity increased in E-L3, Obl, RA, and RF from .08 ± .05, .06 ± .06, .09 ± .06, and .09 ± .06 mV without stimulation, to .11 ± .07 mV (Z= 2.4181, p=.0156), .16 ± .16 mV (Z = 2.4181, p = .0156), .12 ± .06 mV (Z = 2.1532, p = .0313), and .10 ± .06 mV (Z= 2.4181, p=.0156) in the presence of stimulation, respectively. The activity in RA and RF increased as compared with the quiet sitting without stimulation (Z = 2.4181, p = .0156 and Z = 2.4181, p = .0156, respectively). In the presence of stimulation, the activity in RF was higher during leaning to the right, as compared with quiet sitting (Z = 2.1532, p = .0313). Lastly, during leaning to the left, there was a significant increase in the E-L3 mean EMG activity from .03 ± .03 without stimulation to .43 ± .61 mV in the presence of stimulation (Z = 2.4181, p = .0156). The activity in E-L3 and RF increased as compared with the quiet sitting without stimulation (Z = 2.1532, p = .0313 and Z = 1.9872, p = .0469, respectively). In the presence of stimulation, the activity in E-T7, RA and RF was higher during leaning to the left, as compared with quiet sitting (Z = 1.9872, p = .0469, Z = 1.9872, p = .0469 and Z = 1.9872, p = .0469, respectively). This finding is consistent with the results in quiet upright sitting where the EMG contribution supported an altered spinal alignment and sitting posture that was more spine-neutral, upright, and less kyphotic. The percent change in curvature was –23.55 ± .34% (Z = -2.3863, p = .017), –3.96 ± 1.68% (Z = -1.2951, p = .1953), –18.05 ± 2.65% (Z = -2.2014, p = .0277), and –17.65 ± .62% (Z = -2.1004, p = .0391) during leaning in the forward, back, right, and left directions, respectively. Increased lordosis and decreased kyphosis were maintained throughout multidirectional leaning in the presence of stimulation when compared to no stimulation (Fig. 6C). This improved posture can be attributed to increased tonic activity of the trunk flexors and extensors, especially in the E-L3.

4.2.3 Response to Rapid Arm Extension

During the response to rapid arm extension, participants rapidly extended the right arm forward from their side to a fully extended position, then returned the arm back to the initial position based on verbal cues. Without spinal stimulation, the participants' arm extension was often slower and more limited in range compared to with stimulation, because the participants had to interrupt the motion in order to maintain balance and not fall. The magnitude of the COP displacement during the perturbation varied across the trials to a great extent and was dependent on the arm velocity/angular displacement. EMG responses from the trunk muscles were of lower amplitudes without spinal stimulation (Fig. 7A), and the relationship between their magnitude and the arm velocity/angular displacement was low (Fig. 7B). During the recovery phase from the response to rapid arm extension, i.e. 1-3s after the onset of the movement, there was an observable decrease in COP displacement and COP variance without as compared to with stimulation as shown in the last two seconds of Supplementary Video 3 and recreated in Figure 8.

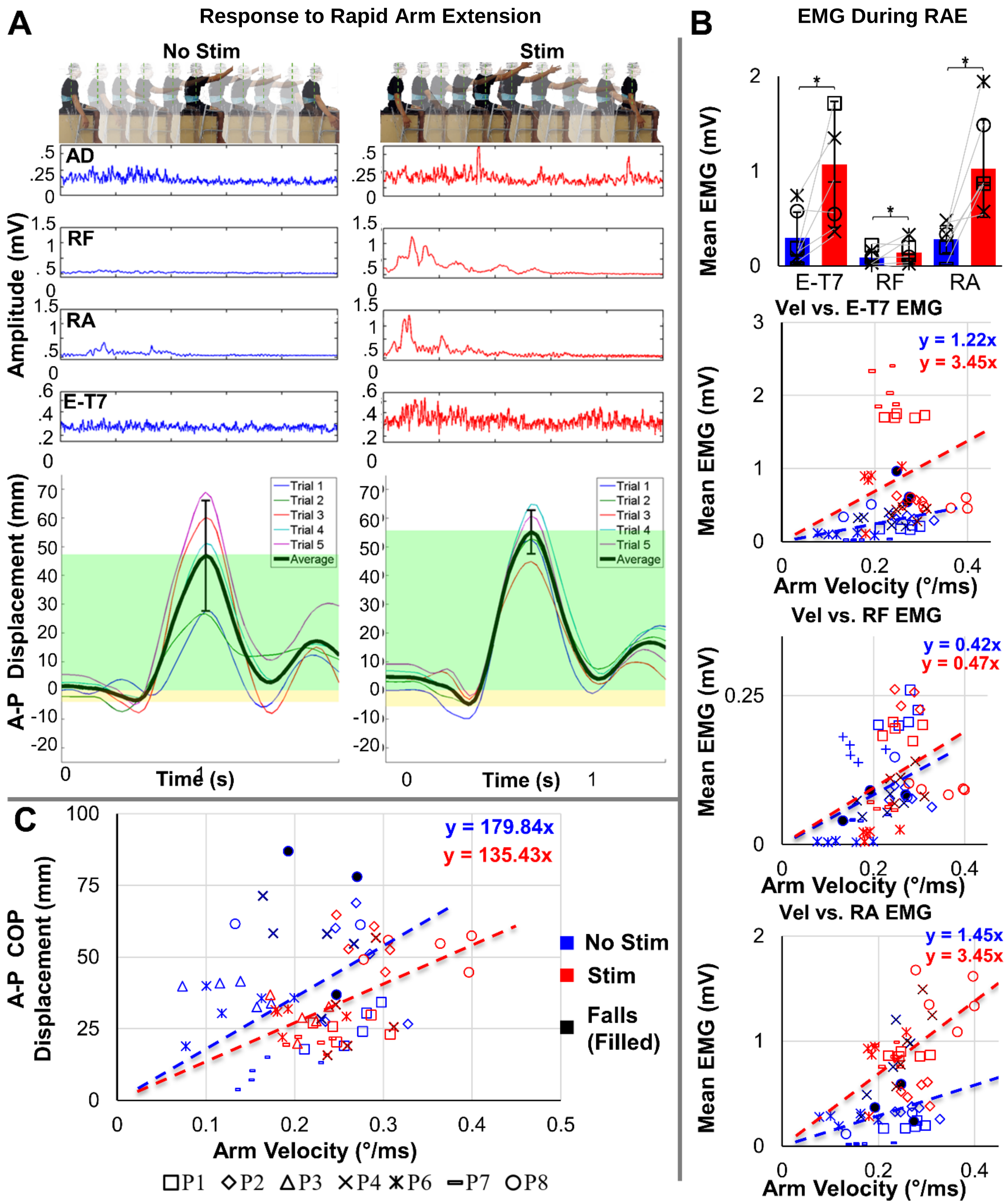


Figure 7. Acute effects of transcutaneous spinal stimulation on anteroposterior center of pressure (COP) excursion during the response to rapid arm extension (RAE) test. (A) Response to rapid arm extension.

Below, the average EMG activity of the anterior deltoid (AD), rectus femoris (RF), rectus abdominis (RA), and erector spinae at level T7 (E-T7) along with the anteroposterior (A-P) COP displacement of one representative participant (P2) without (left) and with (right) spinal stimulation is shown. Individual (colored traces) as well as the average COP displacements (black trace) are shown. The magnitude of average anterior (green) and posterior (yellow) displacement are shown. (B) Pooled EMG activity (EMG) of the E-T7, RF, and RA during the response to rapid arm extension without (blue) and with (red) stimulation. Note the change in EMG activity in the indicated muscles. (C) Mean angular arm velocity versus A-P COP for all trials. Note the increase in arm velocity with stimulation, compared to without stimulation (blue). $n=6$, $\alpha < .05$. * indicates statistical significance between the mean EMG with stimulation as compared to mean EMG without stimulation. All statistical significance was determined by using a non-parametric Wilcoxon Signed-Ranked Test.

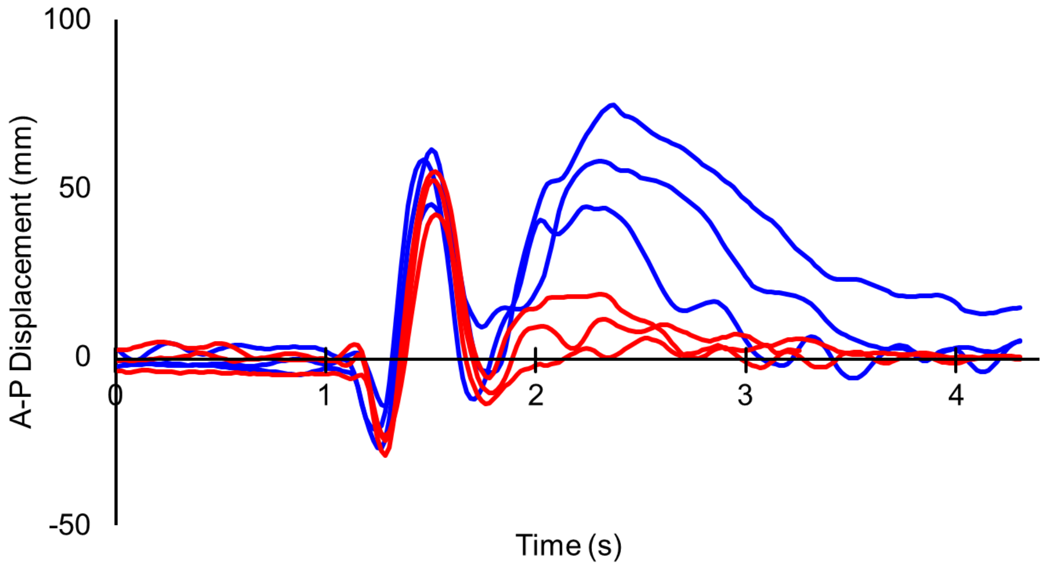


Figure 8. Acute effects of transcutaneous spinal stimulation on anteroposterior center of pressure (COP) excursion during the rapid arm extension for P8 without (blue) and with (red) spinal stimulation is shown. Note the decrease in COP displacement and variance during the recovery (~2-4s) with the presence of stimulation.

In the presence of spinal stimulation, the effectiveness of postural corrections in response to the rapid arm extensions was considerably enhanced (Fig. 7). Consistent with the quiet and dynamic seated tests, the participants' upright seated posture was improved as revealed by decreased trunk curvature; during the perturbations, the arm extension was faster, with a larger range of motion, and the participants were able to maintain balance during the test (Supplementary Video 3). The EMG responses in the trunk muscles were significantly higher during the response to rapid arm extension, with a pronounced activity in E-T7 and RA following the arm extension, which highly depended on the arm velocity/angular displacement. We observed changes in correlation between arm velocity and mean EMG of the E-T7, RF, and RA from .46 ($p = .0104$), 0.30 ($p = 0.0663$), and .30 ($p = .1122$) without to .50 ($p = .1769$), .53 ($p=.0024$), and .26 ($p = .1614$) with stimulation. The Pearson and Filon's z test retained the null hypothesis, the difference between no stimulation and stimulation is 0, for E-T7 ($Z = .2593$, $p = 0.7954$), RF ($Z = 1.3405$, $p = 0.1801$) and RA ($z = 1.1204$, $p = 0.2625$). Interestingly, there was also an emergence of RF activity in response to the response to rapid arm extension (Fig. 7A, B). In addition, the amplitude of the mean COP displacement during and following the perturbation was lower, more consistent and more highly correlated with the arm velocity/angular displacement (Fig. 7C). During response to rapid arm extensions the correlation between anteroposterior arm velocity and COP displacement became statistically significant from $r = .5821$ ($p = .2397$) without to $r = .5115$ ($p = .0043$) with stimulation. The Pearson and Filon's z test rejected the null hypothesis, difference between no stimulation and stimulation is 0, with $z = -2.0402$, $p = 0.0413$ indicating that there was a significant change in the correlation between arm velocity and COP displacement. In the presence of stimulation, larger arm velocities occurred as well as a smaller A-P COP displacement, indicating that a higher degree of stability is maintained in the presence of stimulation as the participants are able to exhibit a faster and larger range of motion and maintain balance without falling.

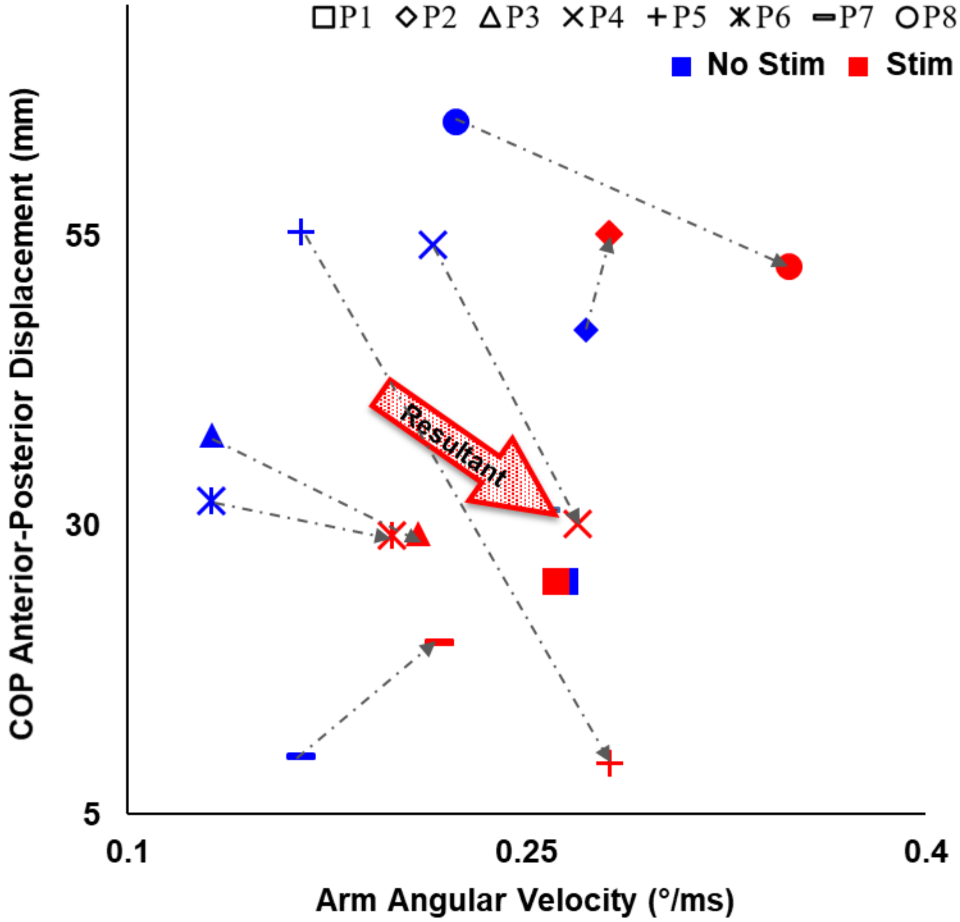


Figure 9. Acute effects of transcutaneous spinal stimulation on anteroposterior center of pressure (COP) excursion during the response to rapid arm extension (RAE) test. Individual (symbols) mean angular arm velocity versus A-P COP for all trials without (blue) and with (red) the presence of stimulation. Note the individual acute effects are shown via dashed grey arrows and the resultant between all participants is indicated in the large red arrow.

In the presence of spinal stimulation, the effectiveness of postural corrections in response to the rapid arm extensions was considerably enhanced (Fig. 8). The pooled mean arm velocity displacement increased from .20 ± .06 °/ms without to .26 ± .05 °/ms ($p = .028$, $z = 2.1974$) with the presence of stimulation and the A-P COP decreased from 38.72 ± 18.49 mm without to 34.46 ± 13.68 mm ($p = .40$, $z = -0.8452$) with the presence of stimulation. The resultant change without to with the presence of stimulation was .06 ± .05 °/ms and -9.47 ± 18.44 mm for the mean arm velocity and mean A-P COP displacement respectively.

4.3 Discussion

Our results indicate the feasibility and effectiveness of non-invasive spinal stimulation in regaining postural control during sitting following chronic SCI. We demonstrated that kinematics, kinetics, and neuromuscular activity patterns are modified in the presence of spinal stimulation, resulting in enhanced performance during quiet sitting and during dynamic tasks related to trunk control. Our data show that improved postural control during sitting can be achieved within a single experimental session in individuals with complete or partial paralysis diagnosed more than two years earlier.

4.3.1 Potential Mechanisms of Improved Seated Postural Control During Spinal Stimulation

During the Neuromodulation in combination with performing a motor task can facilitate restoration of supraspinal-spinal connectivity and reactivation of spinal networks even after chronic, severe spinal injury.[96, 125-127] Regaining of significant levels of clinically relevant functions, such as stepping, standing, and voluntary leg movements, after SCI has been demonstrated using both invasive[128-130] and non-invasive[61, 65, 120, 122] spinal stimulation. In the present study, we observed that multiple features of seated postural control, including quiet and dynamic tasks, immediately improved during spinal stimulation. With neuromodulation, the participants could actively maintain a more upright seated posture, and improve various balance strategies, both quantitatively and qualitatively.

The primary spinal stimulation parameters chosen to neuromodulate spinal networks in the present study were consistent with previous studies performed during supine position, standing, or stepping.[3, 88, 118, 131] For instance, it has been demonstrated that stimulation of the rostral portion of the lumbosacral enlargement (corresponding approximately to the T11-T12 vertebral level) at a frequency of 30 Hz is more specific for facilitating voluntary movements,[4, 61, 65, 83, 128] whereas stimulation delivered over the caudal area of the lumbosacral enlargement (corresponding approximately to the L1-L2 vertebral level) at a frequency of 15

Hz results in facilitation of tonic extensor activity specific for postural control.[129, 130, 132] Finally, our stimulation locations approximated the myotomal maps of the lumbosacral spinal cord projecting to E-L2, RA, Obl, and the internal oblique from the rostral segments, and to E-L2, Obl, and the internal oblique from the caudal segments.[133] The average activity of the trunk muscles during multidirectional leaning was not characterized by muscle specificity that depended on movement direction i.e. we observed improved motor performance, which was accompanied by the trunk muscles' co-contraction, e.g., of Obl and E-L3 during any direction. Moreover, with increased muscle activity of the E-L3, RA, and Obl we observed improvements in all directional leaning; this contrasts the direction dependent balance control previously reported who mainly cited improvements in the anteroposterior directions.[39, 40, 56, 80, 134-136] Such lack in muscle specificity overserved in our study may be attributed to impaired function of the sublesional networks, and/or to adaptive compensatory strategies aimed to overcome de-creased postural steadiness by increasing trunk core stiffness. This is similar to what has been shown in the lower leg muscles during standing in the elderly,[137] or during stepping in stroke survivors.[138]

In the presence of stimulation during quiet sitting, we observed decreases in mean COP displacement, velocity and acceleration. COP displacement is a means to assess postural steadiness[8] whereas velocity and acceleration are indicative of postural activity to maintain stability.[139, 140]

With spinal stimulation, seated balance responses to rapid arm extensions were more successful than when attempted without stimulation. These improvements are likely due to a combination of three different mechanisms: improved anticipatory response primed by stimulation facilitating the feed forward mechanism, increased trunk stiffness due to increased coactivity of the trunk flexor and extensors, and reorganization and learning of the postural system post-injury neuromuscular control features of the trunk and head.

During rapid arm movements, normally the CNS initiates anticipatory postural adjustments (APA) prior to the onset of the movement in order to maintain balance in a feed-forward manner[141] but are less prominent or inexistent during rapid arm raises in the seated posture.[142] When the postural system was challenged during the perturbations using rapid arm extension, the increase in extensor activity and emergence of novel, subject specific, hip- and trunk-based synergies occurred. This suggests adaptive and enabling effects of spinal stimulation on postural-specific networks to engage them to a physiological state that prepared spinal networks to respond to voluntary effort with a more predictable, consistent outcome. The results support prior studies and seems to be a feed-forward mechanism that enables the spinal networks to process, in real-time, the more extensive range of sensory inputs and motor commands for the successful execution of an intended task and to maintain a more stable sitting posture.

Maintenance of posture during sagittal rapid arm extensions was observed to increase contractions of the trunk and are likely to improve postural stability and trunk control.[51] Increased activity of the RA and E-T7 and E-L3 are significant in maintain anteroposterior stability.[143] More specifically, trunk flexor activation prior to the arm raise with low trunk extensor activity followed by deactivation of trunk flexors and activation of trunk extensors immediately after the arm raise while maintaining greater tonic baseline activity of the trunk muscles occurred throughout the duration of the assessment. This is consistent with work by Cholewicki, who studied external load perturbations in able-bodied individuals during trunk flexion, extension, and lateral bending under quick release of trunk loading,[135] Reeves, who showed trunk muscle co-activation resulted in significantly higher CoP velocity and improved responses to rapid loading generated by the arm extension,[136] Lee who showed recruitment of trunk muscle co-contraction increases trunk stiffness,[144] and Kukke who showed increased bimanual work space and improved balance with FES enabled sitting applied to the lumbar erector spinae.[39]

Furthermore, within the five successive rapid arm raises per assessment, the A-P COP displacement included greater levels of pre-activation of the trunk extensors resulting in decreased COP displacements which is consistent with work from Stokes et al.[145] That is, corrective responses in the presence of stimulation became more effective in preparing the networks to respond to the magnitude of the perturbation, as revealed by the proportionally decreased COP displacements and increased trunk muscle responses relative to the arm velocity/angular movements. These observations suggest that modulation of the functional state of spinal networks not only resulted in an increased magnitude of EMG motor responses and COP displacement, but also improved their predictability, i.e., it improved accuracy while employing strategies more similar to able-bodied individuals. These notions are supported by findings in able-bodied individuals during standing where anticipation of rapid arm movements can lead to stiffening of the joints and adjustment of the initial posture before the onset of the movement thereby facilitating the postural goal of maintaining stability.[146] Furthermore, greater amplitudes of trunk muscle activity of both flexors and extensors (i.e. greater EMG amplitude) can be explained in part by increased trunk stiffness

It has been thought that automatic balance recovery strategies are attributed not only to spinal mechanisms but are also associated with supraspinal control.[147] Growing evidence suggests that supraspinal adaptations contribute significantly to improved balance performance even following externally challenged balance training,[69, 148-150] and have been shown to be facilitated by feed-forward mechanisms.[123] If the connections spared following SCI can be reinforced by spinal cord stimulation, functional improvement is possible by amplifying the potential of interneurons to plastically reorganize after SCI.[127] These observations are indicative that spinal postural-specific neural networks are highly flexible and adaptable, can function predictably as a feed-forward mechanism, and can effectively maintain equilibrium. In the presence of stimulation great synergizes at both sub- and potentially supralesional levels occur. These synergies affect the order and duration of postural muscle activity and are consistent with tests in able-bodied patients during standing.[151]

4.3.2 Spinal Stimulation versus Functional Electrical Stimulation to Facilitate Postural Control of Trunk

Can the observed enhanced postural control be primarily attributed to direct neuromuscular activation of paraspinal muscles adjacent to the stimulation sites, similar to the inducing effects of functional electrical stimulation (FES)? FES has been proposed as a means to facilitate and restore trunk and postural control during sitting and standing in the SCI population.[1, 40, 50, 67, 152, 153] Intramuscular stimulation delivered bilaterally at the L1-L2 spinal nerves coupled with erector spinae and gluteus maximus muscles stimulation showed increased isometric trunk extension moment essential for forward reaching to different heights.[52] Low-intensity FES delivered bilaterally over the rectus abdominis and erector spinae[53] muscles at the thoracic and lumbar regions have shown directional-dependent increases in trunk stiffness, specifically in the anteroposterior direction associated with the stimulated muscles.[53] FES can also improve anteroposterior stability during sitting,[53] increase bimanual workspace,[39] improve anteroposterior vertebral alignment and posture,[39, 55] improve active upright sitting, and increase shoulder height. However, these inducing strategies were tested in a single static upright posture, and substitute one statically stable posture for another requiring the use of the upper limb to transition postures.[52, 56]

In our study, the activity of the erector spinae, rectus abdominis, and external obliques, all contributors to seated posture, was elevated during voluntary efforts to sit upright, when combined with stimulation of the lumbosacral enlargement. These elevated activities and increased equilibrium during sitting were associated with a more natural anterior pelvic tilt and lordotic curve, and greater stability and control during movement in the left-anterior, anterior, and right-anterior directions. In contrast to the direction-dependent effects noted above using FES in a static posture, it appears that spinal stimulation not only facilitated stability during quiet upright sitting, but also improved multidirectional leaning and postural corrections during response to rapid arm extensions within the first experimental session. These effects occurred using the same stimulation locations and frequencies for each individual. FES is typically delivered over several trunk muscles, resulting in increased co-activation of antagonistic muscles, which, in turn, contributes to kinematically improved upright sitting,[46, 53] although not necessarily to improvement in energy efficiency. In the present study, however, spinal stimulation was delivered over the spine and resulted in improved trunk postural regulation through facilitation of postural synergies, independent of the motor tasks or direction of active movements. Previous electrophysiological[57, 154, 155] and computational[156-158] studies demonstrated that the structures, stimulated directly and electrically by epidural or transcutaneous spinal lumbar spinal cord stimulation, are primarily afferent fibers of the posterior roots. For lumbar and sacral roots, the exits of the spinal nerves from the spinal canal are relatively far from the electrode, and, thus, it is possible to activate predominantly sensory posterior root fibers during stimulation over the L1. However, the intervertebral foramina of some thoracic roots are close to the T11 stimulation electrode and, as such, mixed afferent and efferent fibers could be directly electrically activated.[159] Examining the properties of individual spinally evoked motor potentials in various trunk muscles could be revealing in characterizing afferent or efferent fibers vs. interneuronal circuitry targeted during spinal stimulation. However, due to the proximity of the stimulating and recording electrodes, spinally evoked potentials from the trunk muscles were obscured by a prominent stimulation artifact, which did not allow us to investigate the specific properties and contributions of the individual motor pools to trunk postural control during different tasks. This limits our understanding of the targeted neural structures during spinal stimulation.

Finally, FES often requires feedback controllers or manual assistance when transitioning between static postures, such as upright and leaning sitting.[97, 160, 161] The spinal stimulation delivered in our study (at constant intensity and frequency) facilitated postural control and improved stability in a variety of static and dynamic motor tasks. Based on these critical differences in the effects of FES and spinal stimulation, we suggest that the facilitatory effects of spinal stimulation can be attributed to its ability to potentiate the processing and projections of proprioceptive and descending inputs to broader components of the neural networks that contribute to sitting, including multi-segmental projections to the trunk and lower limb musculature, that execute corresponding supraspinal motor control.

4.3.3 Limitations and methodological considerations

A balanced, within-subject cross-over study design has been used, wherein each participant received an equal number of stimulation and no stimulation conditions within an experimental session. The blinded design was intended, however, even participants with complete paralysis could perceive facilitatory effects of spinal stimulation on upright posture due to increased tone in the trunk musculature. “Dose-dependent” effects of the stimulation intensity on EMG responses and the level of trunk extension, as well as the effects of “sham” stimulation delivered, for instance, distantly from the lumbosacral enlargement may provide further evidence on cause and effect in defining efficacy of a given intervention. Further research with larger sample sizes is warranted to test, using a multi-factorial ANOVA design, the effects of factors such as the participants' body composition, level and duration of injury, presence of hardware in the spine, as well as training or practice. Paired comparisons of individual variables between no stimulation and stimulation conditions, not multiple comparisons, were utilized in this exploratory study.

4.4 Conclusion

We demonstrated that, after more than two years following the onset of complete or partial paralysis, stimulation over the lumbosacral enlargement improved self-governing control of upright sitting. Spinal stimulation targeted similar networks to those that control rhythmic movements and upright standing, suggesting important functional and anatomical overlap between these systems. From a functional perspective, any strategy that can improve or regain sitting and postural control represents a substantial advancement for individuals with paralysis in their daily life activity.[95] The physiological implications of our findings are consistent with qualities that reflect independence, enhanced function of sensorimotor and autonomic systems, and improved quality of life of individuals with SCI. From a clinical perspective, our approach provides further evidence of the acute neuroplastic capacity of spinal and potentially supraspinal networks and provides a conceptional rationale for the development of a longer-term seated postural control protocol enabled by non-invasive spinal stimulation. The present results are indicative for planning an activity-based rehabilitation program for improving balance. Finally, this study highlights the importance of including assessments of postural-specific networks while seated, as outcomes that might be extrapolated to the potential to control standing.

Chapter 5: Chronic Effects of tSCS on Trunk Stability

5.1 Introduction

Promising long-term motor recovery for individuals with SCI include rehabilitation techniques associated with neural plasticity include body weight-supported treadmill training,[32, 88, 110] sit-to-stand training,[162] standing,[88] locomotion with exoskeleton,[163-165] transcutaneous neuromuscular electrical stimulation,[61, 62, 120] and biofeedback training.[1] The long-term effectiveness of physical therapy in treating patients with SCI is limited, especially during the outpatient setting. Individuals with SCI have reported problems with mobility and spasticity even after rehabilitation.[166] Although there is validity to the external treatment of SCI with physical therapy,[166] spinal stimulation and other intervention therapies, such as Transcutaneous Spinal Cord Stimulation (tSCS), are critical for long-term functional recovery of trunk and postural control.[50, 167] The long-term potentiation and chronic effects of spinal stimulation of improving trunk stability and postural control however, to our knowledge, have not been evaluated. As such we hypothesized that tSCS over the lumbosacral spinal cord in SCI individuals AIS A, C improved chronic trunk and postural control. We also hypothesized individuals with SCI employ unique task dependent strategies in order to perform functional tasks, and execute them in the physiological manner, when combined with spinal stimulation.

5.2 Results

Quiet sitting

Participants were instructed to actively maintain their upright posture for 60 seconds, decreased COP excursion, COP mean frequency, and COP mean velocity were observed. The COP excursion decreased to 93.09 ± 37.42 mm as compared to 104.84 ± 39.48 mm (Z = -.7764, p = .4375) with stimulation before training, 123.78 ± 48.44 mm (Z = -2.1532, p = .0313) without stimulation after non- task-specific training, and 143.75 ± 30.79 mm (Z = -2.1532, p = .0313) without stimulation before training (Fig. 2A). The COP mean frequency changed to 0.36 ± 0.07 Hz as compared to 0.27 ± 0.09 Hz (Z = .7764, p = .4375) with stimulation before training, 0.42 ± 0.08 Hz (Z = -2.1532, p = .0313) without stimulation after non- task-specific training, and 0.55 ± 0.07 Hz (Z = -2.1532, p = .0313) without stimulation before training (Fig. 2B). The COP mean velocity decreased to 3.66 ± 0.73 mm/s as compared to 4.33 ± 0.93 mm/s (Z = -.08760, p = .3125) with stimulation before training, 6.07 ± 1.15 mm/s (Z = -2.1532, p = .0313) without stimulation after non- task-specific training, and 6.91 ± 1.50 mm/s (Z = -2.1532, p = .0313) without stimulation before training (Fig. 2C). 95% confidence interval of the pooled COP area decreased to 25.30 ± 6.32 mm^2 with stimulation after non-task-specific training from 60.19 ± 18.10 mm^2 (Z = -2.1532, p = .0313) with stimulation before training, 200.74 ± 40.15 mm^2 (Z = -2.1532, p = .0313) without stimulation prior to training and 121.53 ± 36.46 mm^2 (Z = -2.1532, p = .0313) without stimulation after training (Fig. 2D).

Figure 1

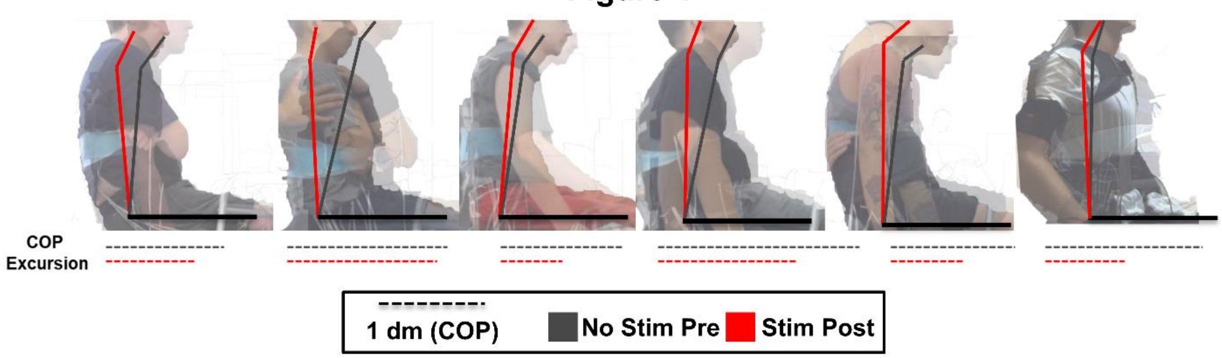


Figure 1. Effects of sub-motor threshold spinal stimulation on quiet sitting characteristics for six participants. Three-dimensional (3D) joint kinematics showing head and trunk angles (top), center of pressure excursion (dashed line) during quiet sitting without the presence of stimulation before

(grey) vs after training in the presence of sub-motor threshold stimulation (red). Note the increase in trunk angle, decrease in head angle, and decrease in COP excursion and curvature after training and with the presence of stimulation. Key joint landmarks are indicated.

Figure 2

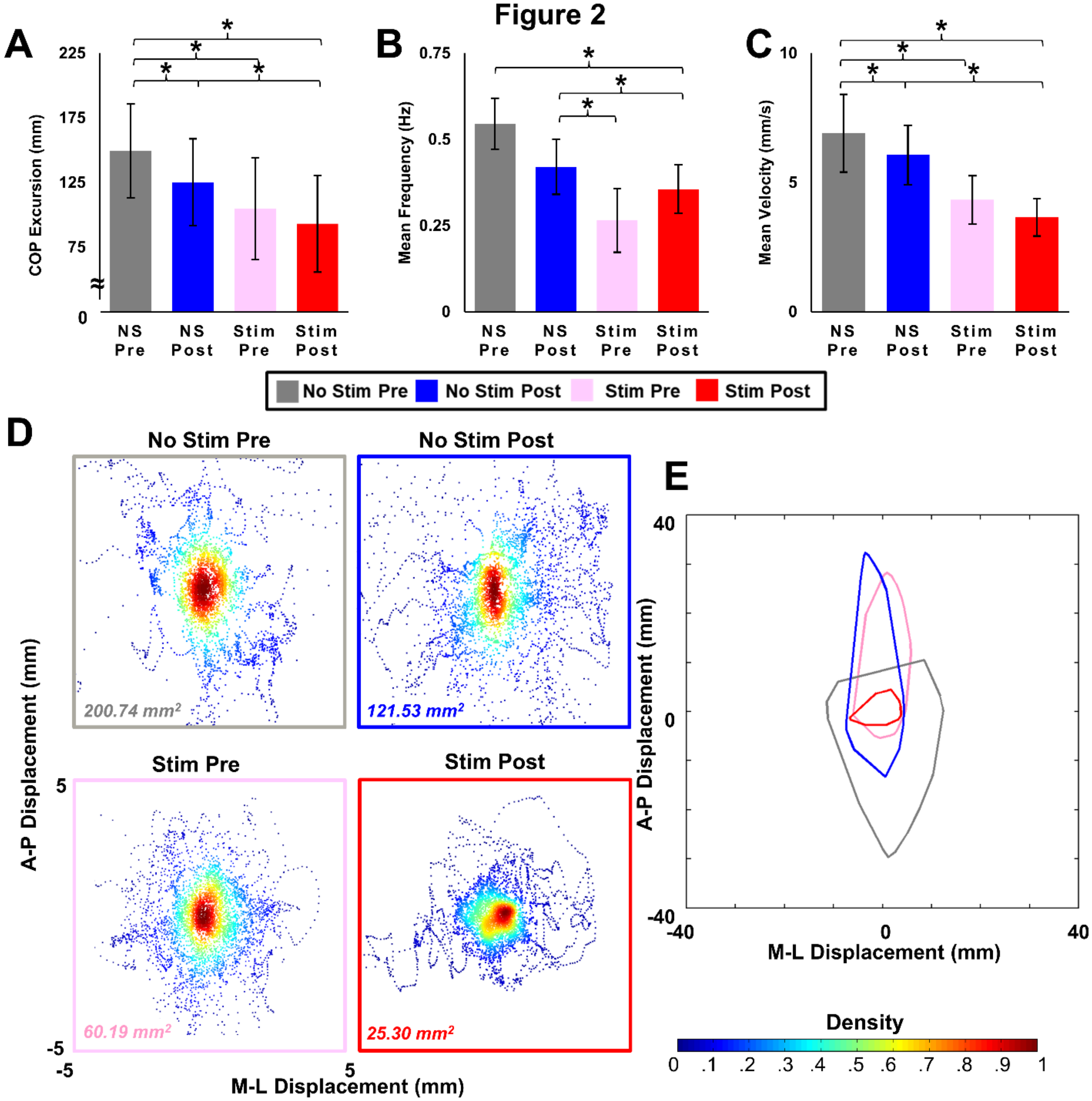


Figure 2. Effects of sub-motor threshold spinal stimulation on center of pressure (COP) characteristics during unsupported quiet sitting for six participants. Individual and mean A) COP

excursion, B) mean COP frequency, and C) mean COP velocity with standard deviations for quiet sitting without stimulation prior to training (grey), without stimulation after training (blue), with stimulation prior to training (pink), and with stimulation after training (red). Decreased COP excursion, frequency and velocity indicates improved balance. D) Normalized COP excursion density for all six participants during eyes open without stimulation prior to training (grey), without stimulation after training (blue), with stimulation prior to training (pink), and with sub-motor threshold spinal stimulation after training (red). The density indicates time spent at each position for all participants. 95% confidence interval of the COP area for all participants is indicated; a decrease in the confidence interval area indicates improved quiet upright sitting. E) overlaid contour plots of normalized COP area. Note the decrease in COP excursion area under the four conditions especially in the anteroposterior direction. A two-tailed non-parametric Wilcoxon Signed-Ranked Test was used for assessing all differences between training and stimulation conditions; n=6, * indicates statistical significance, $\alpha < .05$.

Quiet sitting in the presence of stimulation and training resulted in decreased head angle, increased trunk extension and more upright sitting, decreased curvature, were observed in the lower trunk during stimulation after non-task-specific training, with mean head angle of 153.54 ± 14.90° with stimulation as compared to 162.43 ± 11.19° with stimulation before training ($Z = -.08760$, $p = .3125$), 166.33 ± 15.05° without stimulation after non-task-specific training ($Z = -2.1532$, $p = .0313$) and 170.12 ± 16.26° without stimulation before training ($Z = -2.1532$, $p = .0313$) (Fig 3A); the mean trunk angle increased to 95.30 ± 3.46° with stimulation as compared to 89.37 ± 4.02° with stimulation before training ($Z = 2.1532$, $p = .0313$), 84.78 ± 5.07° without stimulation after training ($Z = 2.1532$, $p = .0313$) and 82.88 ± 5.33° without stimulation before training ($Z = 2.1532$, p = .0313) (Fig 3B). Mean trunk curvature decreased to 10.4 ± 2.80 cm as compared to 13.09 ± 2.07 cm with stimulation before training (Z = -2.1532, p = .0313), 15.6 ± 1.43 cm (Z = -2.1532, p = .0313) without stimulation before training and 13.6 ± 2.2 cm (Z = -2.1532, p = .0313) without stimulation after non- task-specific training (Fig. 3C).

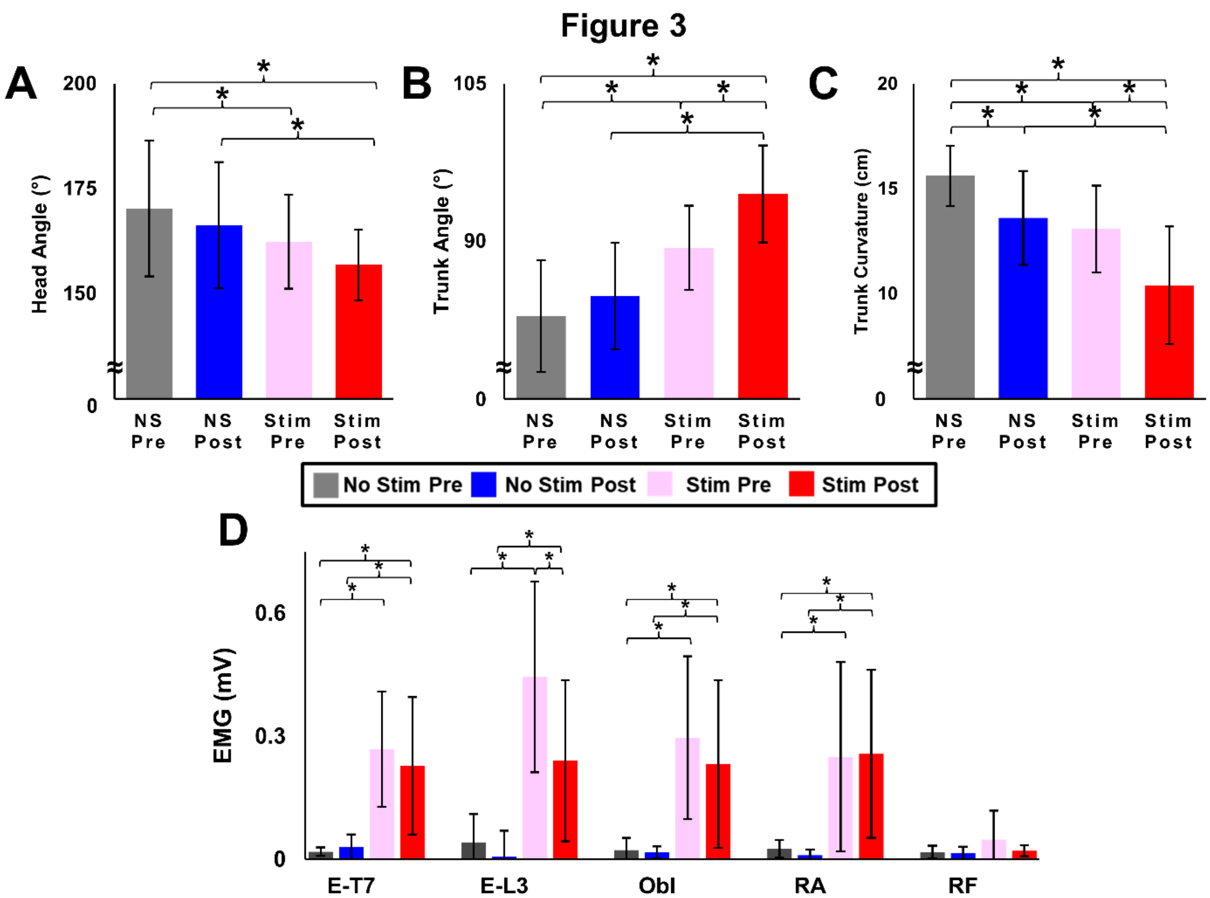


Figure 3. Effects of sub-motor threshold spinal stimulation on kinematics and muscle activity during unsupported quiet sitting for six participants. Individual and mean A) head angle, B) trunk angle, and C) trunk curvature with standard deviations for quiet sitting without stimulation prior to training (grey), without stimulation after training (blue), with stimulation prior to training (pink), and with stimulation after training (red). Decreases in head angle and curvature and increase in trunk angle indicate improved spinal alignment and upright sitting ability. D) Individual and mean

EMG activity of the erector spinae at the T-7 (E-T7) and L3 (E-L3) levels, external oblique (Obl), rectus abdominus (RA), and rectus femoris (RF). A two-tailed non-parametric Wilcoxon Signed-Ranked Test was used for assessing all differences between training and stimulation conditions. Note the increase in muscle activity in the presence of stimulation. n=6, * indicates statistical significance, $\alpha < .05$.

The EMG activity of E-T7, E-L3, Obl and RA increased to .23 ± .17 mV, .24 ± .20 mV, .23 ± .20 mV and .26 ± .20 mV from .27 ± .14 mV (Z =0, p = 1), .44 ± .23 mV (Z = -2.1532, p = .0313), .30 ± .20 mV (Z = -0.7764, p = .4375), and .25 ± .23 mV (Z = -1.6757, p = .0938) with stimulation before training, .03 ± .03 mV (Z = 2.1532, p = .0313), .01 ± .06 mV (Z = 2.1532, p = .0313), .02 ± .01 mV (Z = 2.1532, p = .0313), and .01 ± .01 mV (Z = 2.1532, p = .0313) without stimulation after non-task-specific training and .02 ± .01 mV (Z = 2.1532, p = .0313), .04 ± .07 mV (Z = 1.8627, p = .0625), .02 ± .03 mV (Z = 2.1532, p = .0313), and .03 ± .02 mV (Z = 2.1532, p = .0313) without stimulation prior to training. There were no significant changes in the RF EMG activity (Fig. 3D).

Multidirectional leaning

The limits of stability (LoS) during the multidirectional leaning ('Octagon') test increased in all directions with the presence of stimulation after training as compared to no stimulation (both before and after non-task-specific training) as shown in Fig. 4. Participants were to move their COP by leaning as far as possible in the indicated direction without losing balance and return to the starting position based on visual cues. In the presence of stimulation, the mean limits of stability increased to 58.54 ± 40.4 mm, 29.63 ± 8.80 mm, 49.15 ± 20.32 mm, and 48.71 ± 23.07 mm as compared to 45.63 ± 26.54 mm (Z = 0.7764, p = .4375), 24.00 ± 11.20 mm (Z = 2.1532, p = .0313), 41.49 ± 19.57 mm (Z = 2.1532, p = .0313), and 45.87 ± 20.43 mm (Z = 0.4023, p = .6875) with stimulation before training, 45.05 ± 25.81 mm ($Z = 2.1532$, $p = .0313$), 25.22 ± 8.01 mm ($Z = 2.1532$, $p = .0313$), 38.09 ± 14.267 mm ($Z = 2.1532$, $p = .0313$), and 39.99 ± 20.28 mm ($Z = 1.8627$, $p = .0625$) without stimulation after training and 26.25 ± 8.48 mm ($Z = -2.1532$, $p = .0313$), 18.27 ± 13.87 mm ($Z = 2.1532$, $p = .0313$), 27.87 ± 10.65 mm ($Z = 2.1532$, $p = .0313$), and 32.77 ± 17.44 mm ($Z = 1.4176$, $p = .1563$) without stimulation before non- task-specific training in the forward, backward, right and left directions respectively (Fig. 4A). The mediolateral (M-L) and anteroposterior (A-P) time series of a representative participant comparing stimulation after non-specific training (red) as compared to without stimulation before training (grey) is shown in Fig. 4C with positive values representing the directions right and forward, and negative values representing the directions left and backward.

Figure 4

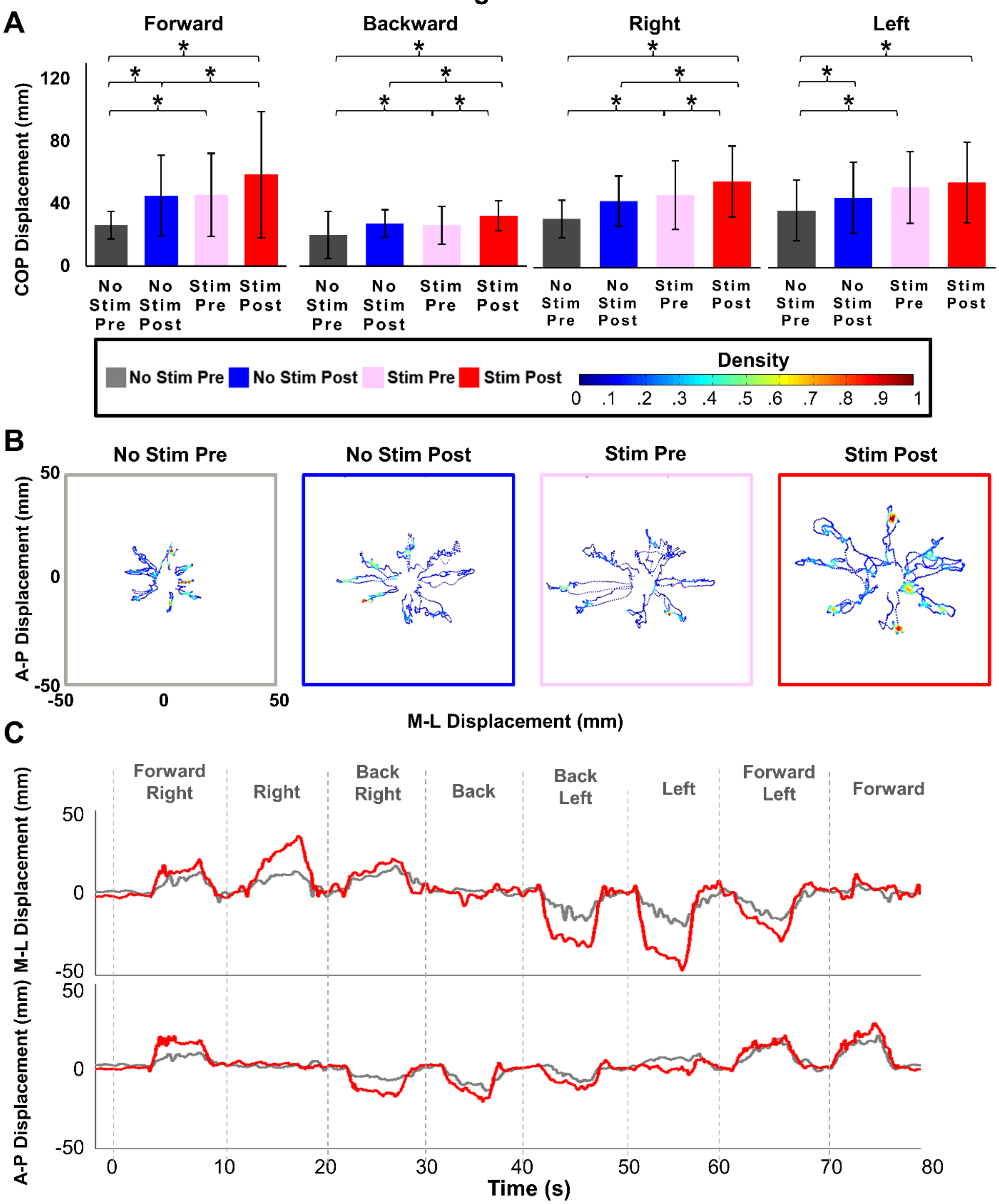


Figure 4. Effects of sub-motor threshold spinal stimulation on the limits of stability (LoS) during the 'octagon' multidirectional leaning test for six participants. A) Individual and mean limits of

stability with standard deviations during forward, backward, right and left leaning without stimulation prior to training (grey), without stimulation after training (blue), with stimulation prior to training (pink), and with stimulation after training (red). Increase in directional COP displacement indicates improved dynamic trunk control. Note the significant increase in all leaning directions. B) Density plot of the center of pressure (COP) excursions during the 'octagon' test for a representative participant (P5). C) The mediolateral (M-L) and anteroposterior (A-P) time series, with positive values representing the directions right and forward, and negative values representing the directions left and backward of a representative participant (P5). * indicates statistical significance; two-tailed non-parametric Wilcoxon Signed-Ranked Test where n=6 and $\alpha < .05$.

During multidirectional leaning, more neutral spinal alignment and decreased trunk curvature occurred in forward, right and left leaning, more neutral head angle during backward leaning, and trunk extension was observed in right leaning all in the presence of spinal stimulation after non-task-specific training as compared to no stimulation conditions (Fig. 5 and 6). There were newly adopted direction dependent strategies in the presence of stimulation after training.

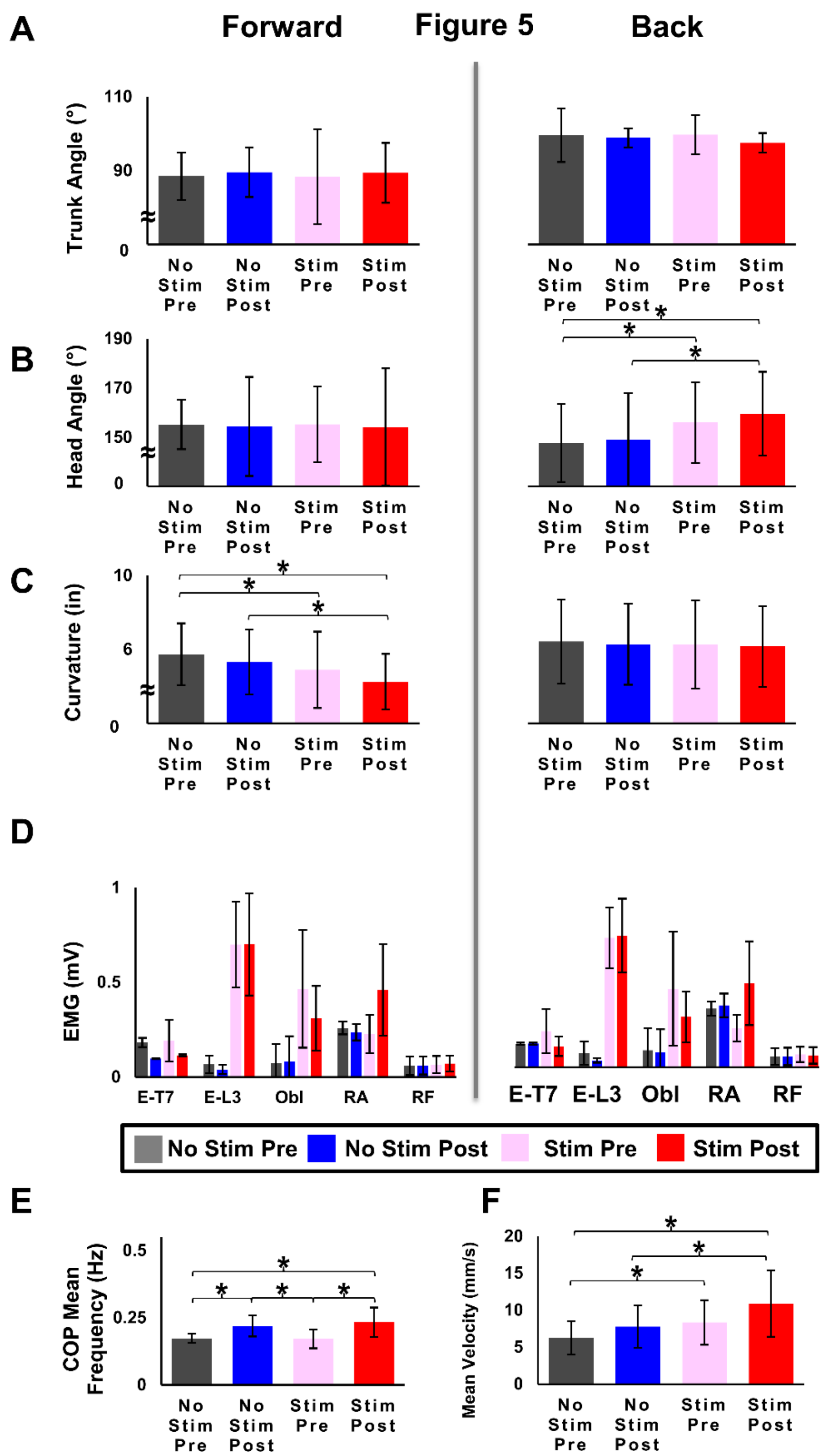


Figure 5. Effects of sub-motor threshold spinal stimulation on the anteroposterior (A-P) limits of stability (LoS) during the 'octagon' multidirectional leaning. Individual and mean A) trunk angle,

B) head angle, C) trunk curvature in the forward (left of median) and backward (right of median) directions without stimulation prior to training (grey), without stimulation after training (blue), with stimulation prior to training (pink), and with stimulation after training (red). A decrease in head angle, increase in trunk angle and decrease in trunk curvature each indicate more upright neutral spinal alignment that is maintained during the entirety of the leaning. D) Individual and mean EMG activity of the erector spinae at the T-7 (E-T7) and L3 (E-L3) levels, external oblique (Obl), rectus abdominus (RA), and rectus femoris (RF). Individual and mean E) mean COP frequency and F) mean COP velocity with standard deviations. An increase in frequency and velocity indicate faster responses and movement during leaning, * indicates statistical significance; two-tailed non-parametric Wilcoxon Signed-Ranked Test where $n=6$ and $\alpha < .05$.

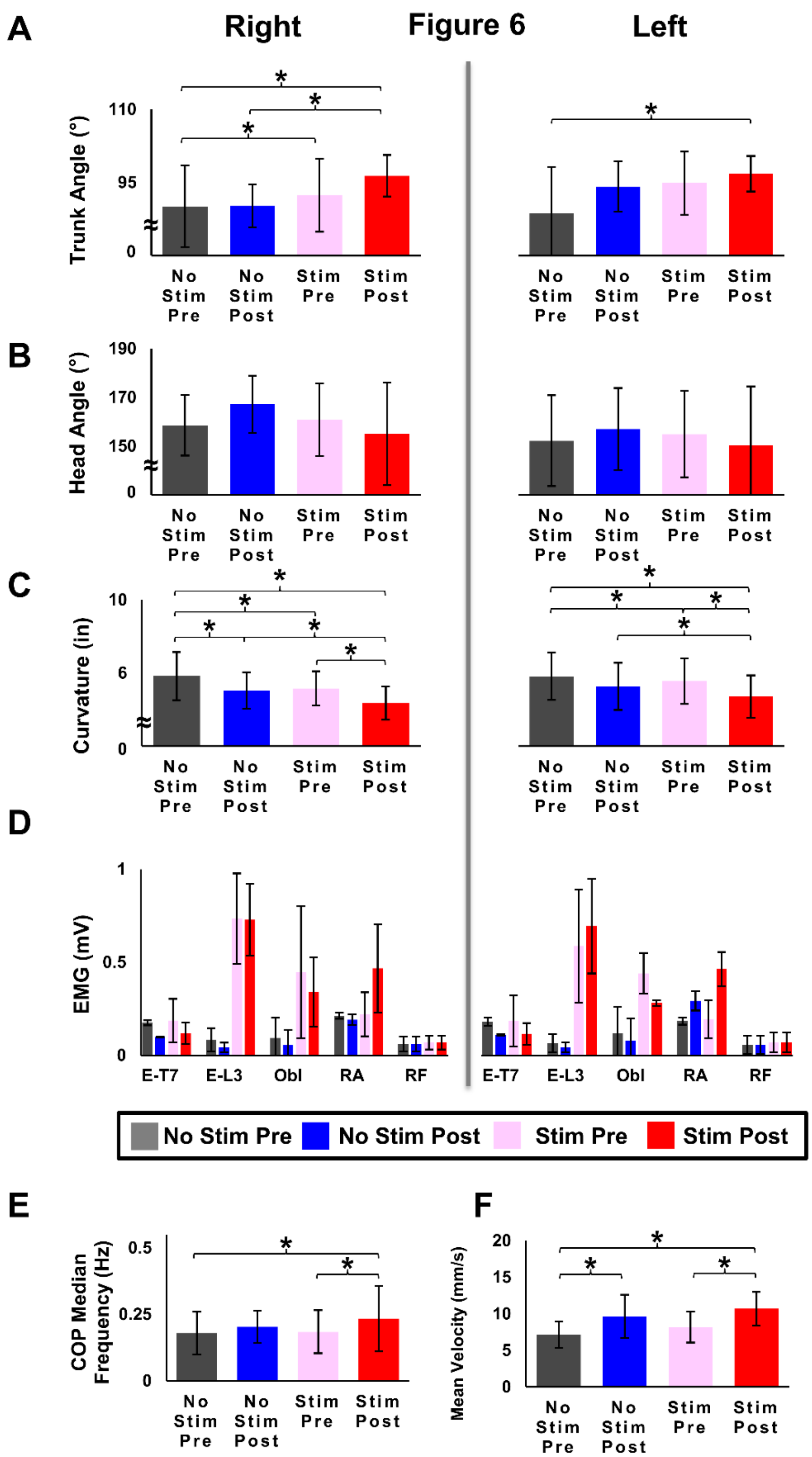


Figure 6. Effects of sub-motor threshold spinal stimulation on the mediolateral (M-L) limits of stability (LoS) during the 'octagon' multidirectional leaning. Individual and mean A) trunk angle,

B) head angle, C) trunk curvature in the right (left of median) and left (right of median) directions without stimulation prior to training (grey), without stimulation after training (blue), with stimulation prior to training (pink), and with stimulation after training (red). A decrease in head angle, increase in trunk angle and decrease in trunk curvature each indicate more upright neutral spinal alignment that is maintained during the entirety of the leaning. D) Individual and mean EMG activity of the erector spinae at the T-7 (E-T7) and L3 (E-L3) levels, external oblique (Obl), rectus abdominus (RA), and rectus femoris (RF). Individual and mean E) mean COP frequency and F) mean COP velocity with standard deviations. An increase in frequency and velocity indicate faster responses and movement during leaning, * indicates statistical significance; two-tailed non-parametric Wilcoxon Signed-Ranked Test where n=6 and $\alpha < .05$.

The mean trunk angle increased to 89.37 ± 8.08°, 97.50 ± 2.64°, 96.37 ± 4.25°, 96.82 ± 3.66° with stimulation after training as compared to 88.32 ± 1.45°, 99.69 ± 4.34°, 92.36 ± 6.69°, 94.88 ± 5.78° ($Z = 0$, $p = 1$; $Z = 0.5791$, $p = .5625$; $Z = 1.534$, $p = .125$; $Z = 0.1970$, $p = .8438$) with stimulation before training, 89.56 ± 6.75°, 98.90 ± 2.58°, 90.23 ± 4.40°, 94.17 ± 5.14° ($Z = 0.5791$, $p = .5625$; $Z = 0.5791$, $p = .5625$; $Z = 2.1532$, $p = .0313$; $Z = 2.1532$, $p = .0313$) without stimulation after non-task-specific training, and 88.49 ± 6.42°, 99.52 ± 7.22°, 90.10 ± 8.37°, 88.75 ± 9.43° ($Z = 0$, $p = 1$; $Z = 1.010$, $p = .3125$; $Z = 2.1532$, $p = .0313$; $Z = 2.1532$, $p = .0313$) without stimulation before training in the forward, backward, right and left leaning respectively (Fig 5A, 6A).

The mean head angle changed to 154.13 ± 23.78°, 159.58 ± 16.94°, 155.03 ± 21.06°, 150.39 ± 24.19° with stimulation after training as compared to 155.20 ± 15.38°, 155.98 ± 16.32°, 160.91 ± 14.94°, 154.95 ± 17.68° ($Z = 0$, $p = 1$, $Z = -0.4023$, $p = .6875$; $Z = 0$, $p = 1$, $Z = -0.1970$, $p = .8438$) with stimulation before training, 154.44 ± 20.08°, 149.00 ± 18.85°, 167.22 ± 11.70°, 157.01 ±

16.84° ($Z = 0.1970$, $p = .8438$; $Z = -2.1532$, $p = .0313$; $Z = -2.1532$, $p = .0313$; $Z = -0.4023$, $p = .6875$) without stimulation after non-task-specific training, 155.16 ± 9.99°, 147.69 ± 15.83°, 158.60 ± 12.51°, 152.24 ± 18.67° ($Z = -0.1970$, $p = .8438$; $Z = -2.1532$, $p = .0313$; $Z = -0.4023$, $p = .6875$; $Z = 0.1970$, $p = .8438$) without stimulation before training in the forward, backward, right and left leaning respectively (Fig 5B, 6B).

Mean trunk curvature decreased to 10.80 ± 1.51, 15.64 ± 2.19, 11.08 ± 0.92, 11.98 ± 1.16 cm as compared to 12.43 ± 2.07, 15.92 ± 2.39, 13.10 ± 0.94, 14.13 ± 1.25 cm ($Z = -1.010$, $p = .3125$; $Z = -0.4023$, $p = .6875$; $Z = -2.1532$, $p = .0313$; $Z = -2.1532$, $p = .0313$) with stimulation before training, 13.52 ± 1.76, 15.94 ± 2.19, 12.84 ± 1.00, 13.41 ± 1.29 cm ($Z = -2.1532$, $p = .0313$; $Z = -0.7764$, $p = .4375$; $Z = -2.1532$, $p = .0313$; $Z = -2.1532$, $p = .0313$) without stimulation after training, and 14.58 ± 1.67, 16.32 ± 2.28, 14.83 ± 1.31, 14.81 ± 1.30 cm ($Z = -2.1532$, $p = .0313$; $Z = -.5791$, $p = .5625$; $Z = -2.1532$, $p = .0313$; $Z = -2.1532$, $p = .0313$) without stimulation before non- task-specific training in the forward, backward, right and left leaning respectively (Fig. 5C, 6C).

The improvement in multi-directional leaning occurred due to increases in trunk extensor (E-L3) and flexor (Obl and RA) activity in the presence of spinal stimulation (Fig. 5E, 6E). The mean and standard deviations of the muscle activity during each directional movement is included in the supplementary table 1.

Leaning strategies varied based on leaning direction. Each strategy functionally increased the limits of stability in the presence of stimulation when compared to no stimulation. The COP mean frequency and mean velocity was assessed in the anteroposterior and mediolateral directions; the mean frequency changed to 0.23 ± 0.05 and 0.23 ± 0.11 Hz as compared to 0.17 ± 0.04 and 0.19 ± 0.07 Hz ($Z = 2.1532$, $p = .0313$; $Z = 2.1532$, $p = .0313$) with stimulation before training, 0.22 ±

0.04 and 0.20 ± 0.05 Hz ($Z = .5791$, $p = .5625$; $Z = 1.010$, $p = .3125$) without stimulation after training, and 0.17 ± 0.02 and 0.17 ± 0.07 Hz ($Z = 2.1532$, $p = .0313$; $Z = 2.1532$, $p = .0313$) without stimulation before non- task-specific training in the anteroposterior and mediolateral directions respectively (Fig. 5E, 6E). The COP mean velocity increased to 10.90 ± 4.49 and 10.72 ± 2.29 mm/s as compared to 8.35 ± 3.02 and 8.20 ± 2.13 mm/s ($Z = 1.4176$, $p = .1563$; $Z = 2.1532$, $p = .0313$) with stimulation before training, 7.78 ± 2.87 and 9.67 ± 2.94 mm/s ($Z = 2.1532$, $p = .0313$; $Z = .7764$, $p = .4375$) without stimulation after training, and 6.22 ± 2.25 and 7.17 ± 1.82 mm/s ($Z = 2.1532$, $p = .0313$; $Z = 2.1532$, $p = .0313$) without stimulation before non- task-specific training in the anteroposterior and mediolateral directions respectively (Fig. 5F, 6F).

Self-Initiated Perturbation

Participants were instructed to actively maintain their upright posture while rapidly flexing their right hand and returning it to the starting position based on verbal cues. There were no significant changes in mean head angle between testing conditions. The mean trunk angle increased to 90.36 ± 5.39° as compared to 82.10 ± 10.15° ($Z = 1.4176$, $p = .1563$) with stimulation before training, 85.97 ± 6.73° ($Z = 2.1532$, $p = .0313$) without stimulation after non- task-specific training and 80.50 ± 7.90° ($Z = 2.1532$, $p = .0313$) without stimulation before training (Fig. 7A). Mean trunk curvature decreased to 10.66 ± 3.84 cm as compared to 11.910 ± 3.90 cm ($Z = -1.6757$, $p = .0938$) with stimulation before training, 12.01 ± 3.42 cm ($Z = -2.1532$, $p = .0313$) without stimulation after non- task-specific training and 13.49 ± 4.35 cm ($Z = -1.4176$, $p = .1563$) without stimulation before training (Fig. 7B).

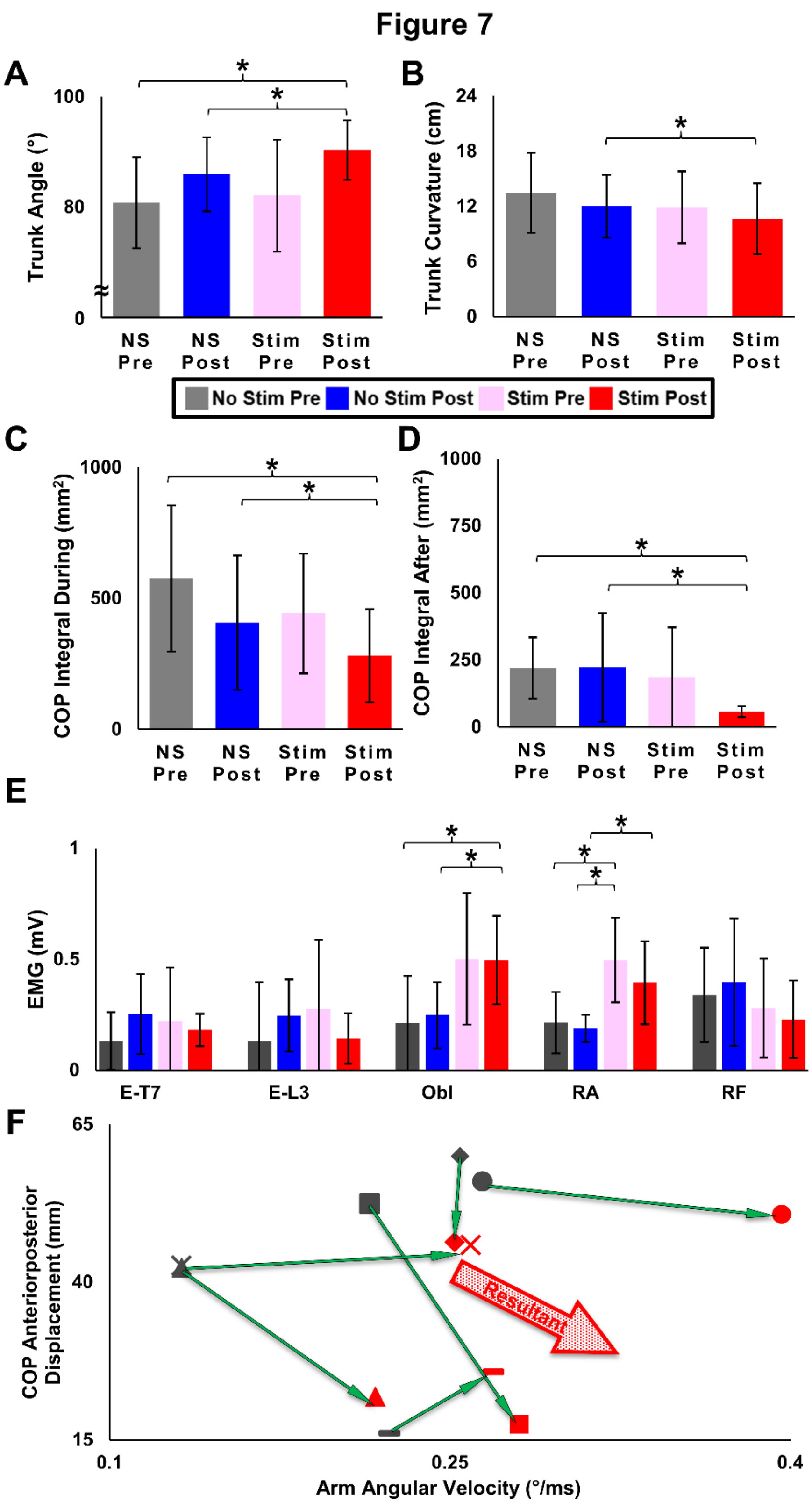


Figure 7. Effects of transcutaneous spinal stimulation on trunk characteristics during the self-

initiated perturbation (SiP) test. Individual and mean A) trunk angle and B) trunk curvature with standard deviations without stimulation prior to training (grey), without stimulation after training (blue), with stimulation prior to training (pink), and with stimulation after training (red). Anteroposterior COP excursion integral C) during and D) after rapid arm flexion. E) Individual and average electromyographic activity of the erector spinae at level T7 (E-T7), erector spinae at level L3 (E-L3), external oblique (Obl), rectus abdominus (RA), and rectus femoris (RF). F) Individual mean angular arm velocity versus anteroposterior COP displacement for all trials. Symbols indicate participant numbers. Green arrows indicate change between no training without stimulation and with training and in the presence of sub-motor threshold spinal stimulation. Red arrow indicates the resultant change under the trained simulation condition as compared to without training or stimulation. Decrease anteroposterior COP displacement and increased arm angular velocity indicate improved trunk stability and dynamic control. * indicates statistical significance; two-tailed non-parametric Wilcoxon Signed-Ranked Test where n=6 and $\alpha < .05$.

The mean COP integral during the self-initiated perturbation and 50 ms after the perturbation decreased to 281.22 ± 178.08 and 57.00 ± 20.63 mm^2 as compared to 442.49 ± 2.2872 and 185.29 ± 185.89 mm^2 (Z = -1.2297, p = .2188, Z = -1.8627, p = .0625) with stimulation before training, 406.71 ± 256.63 and 222.34 ± 202.97 mm^2 (Z = -2.1532, p = .0313, Z = -2.1532, p = .0313) without stimulation after non-task-specific training and 576.19 ± 279.28 and 220.13 ± 114.41 mm^2 (Z = -2.1532, p = .0313, Z = -2.1532, p = .0313) without stimulation before training (Fig. 7C,D).

The EMG activity of E-T7, E-L3, Obl and RA changed to 0.18 ± 0.07, 0.14 ± 0.11, 0.50 ± 0.20, 0.39 ± 0.19 mV after training with the presence of stimulation as compared to 0.22 ± 0.24, 0.28 ± 0.31, 0.50 ± 0.30, 0.50 ± 0.19 mV (Z = .1970, p = .8438, Z = .5791, p = .5625, Z = 0, p = 1, Z =

.5791, p = .5625) with stimulation before training, 0.25 ± 0.18, 0.25 ± 0.16, 0.25 ± 0.15, 0.19 ± 0.06 mV (Z = .7764, p = .4375, Z = .7764, p = .4375, Z = 2.1532, p = .0313, Z = 2.1532, p = .0313) without stimulation after non-task-specific training respectively and 0.13 ± 0.13, 0.13 ± 0.26, 0.21 ± 0.21, 0.21 ± 0.14 mV (Z = 1.010, p = .3125, Z = .5791, p = .5625, Z = 2.1532, p = .0313, Z =1.6757, p = .0938) without stimulation prior training. (Fig. 7E).

Mean arm angular velocity increased to 0.26 ± 0.05 °/s with stimulation after training as compared to 0.20 ± 0.06 °/s without stimulation prior to training (Z = 1.8627, p = .0625); Mean COP anteroposterior displacement decreased to 34.46 ± 13.68 mm with stimulation after training as compared to 44.91 ± 15.81 mm (Z = -1.2297, p = .2188) without stimulation before training. The resultant mean change was an increase in angular arm velocity by .07 ± .05 °/s and a decrease in COP anteroposterior displacement decreased by 10.22 ± 16.33 mm with stimulation after training (Fig. 7F).

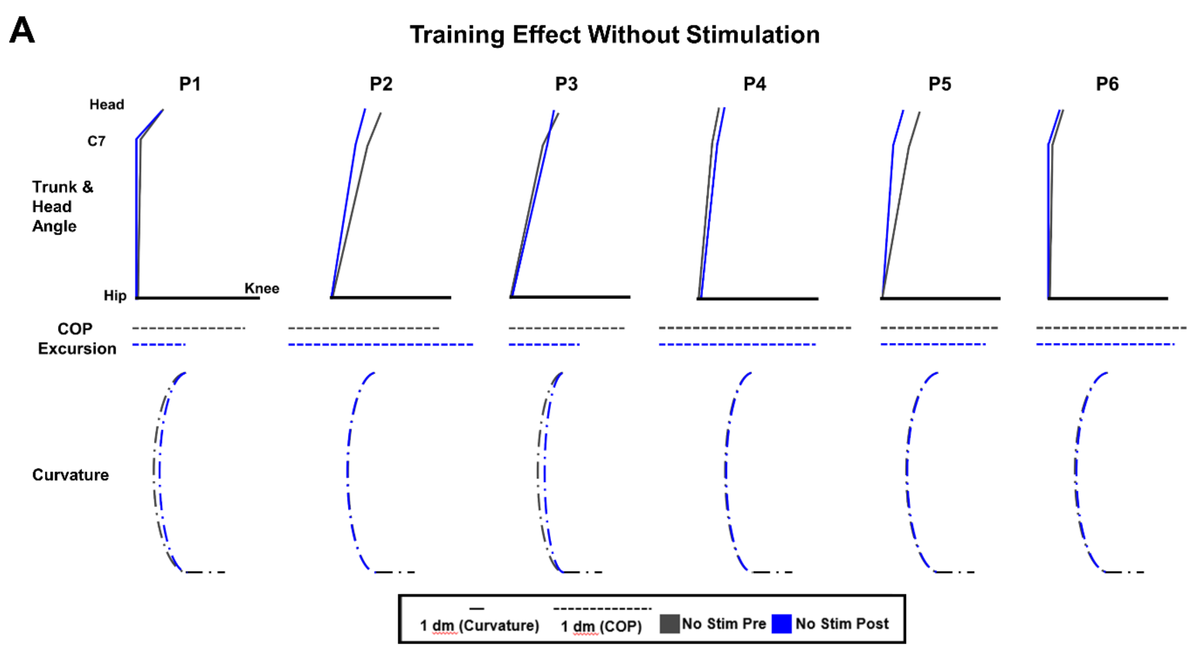


Figure 8. *Supplementary Figure 1*. Effects of sub-motor threshold spinal stimulation on quiet sitting characteristics for six participants. Three-dimensional (3D) joint kinematics showing head and trunk angles (top), center of pressure excursion (dashed line) and trunk curvature during quiet sitting A) without the presence of stimulation before (grey) and after (blue) training, Key joint landmarks are indicated.

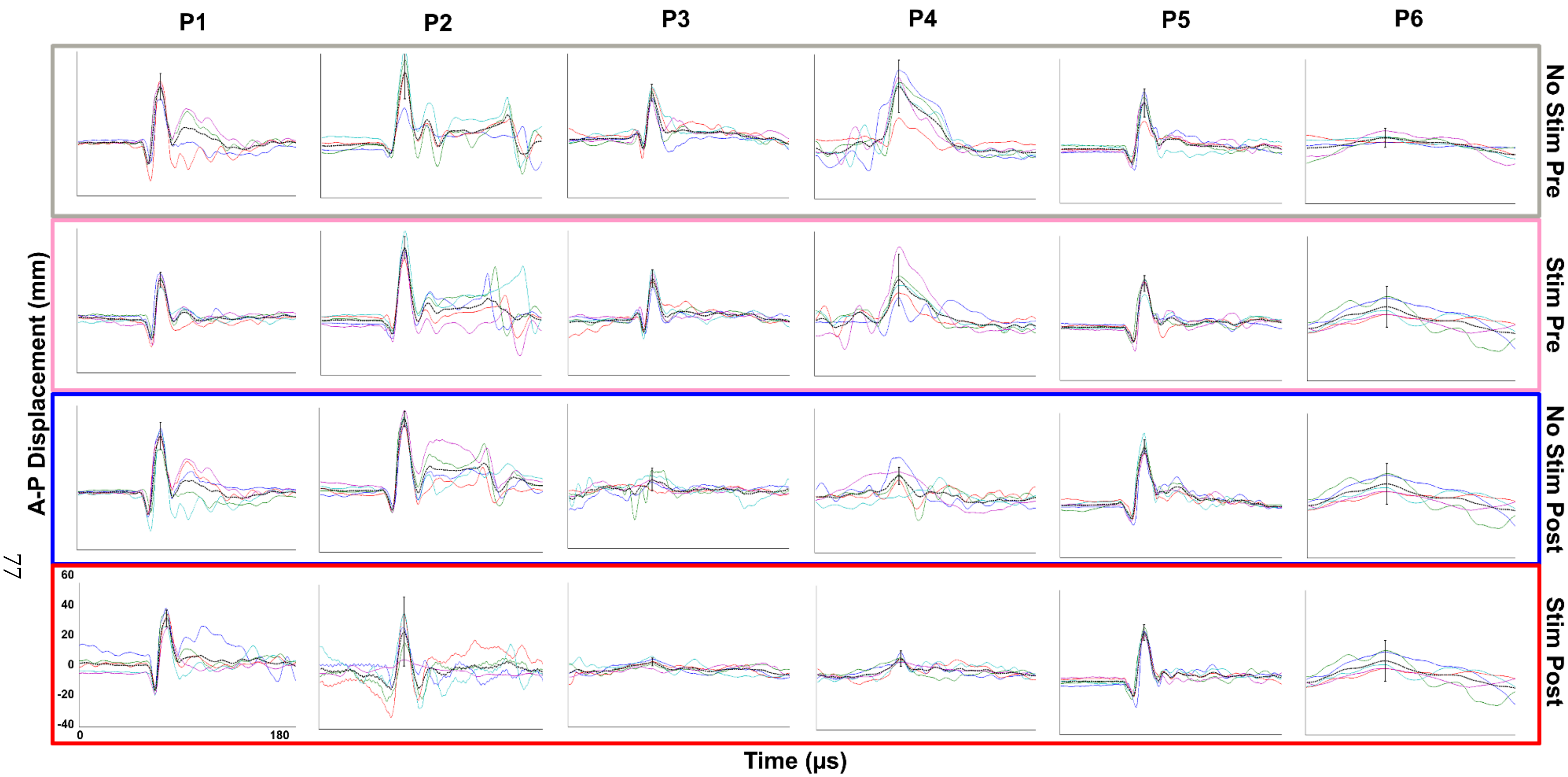


Figure 9. *Supplementary Figure 2.* Effects of transcutaneous spinal stimulation on anteroposterior center of pressure (COP) excursion during the self-initiated perturbation (SiP) test. The anteroposterior (A-P) COP displacement of all six participants without training or stimulation (grey), without stimulation after training (blue), with stimulation prior to training (pink), and with training and stimulation (red) are shown. Individual (colored traces) as well as the average COP displacements (black trace) are shown.

5.3 Discussion

Our results demonstrate the feasibility and effectiveness of transcutaneous electrical spinal cord stimulation combined with stand training in improving trunk and postural control in a long-term setting with the presence of non-task-specific training after chronic SCI. These improvements in quiet sitting and dynamic task ability were characterized by kinematics, kinetics, and neuromuscular activity patterns which were modified in the presence of tSCS. Despite non-task-specific training we saw functional improvements in a range of movements/tasks. The data indicates that tSCS and training shift the control strategies depending on the task (quiet sitting vs multidirectional leaning vs rapid arm movement).

Postural stability strategies during quiet sitting

During quiet sitting, decreased COP excursion, mean frequency and mean velocity was observed. COP excursion is often cited as a measure of stability achieved by the postural control system[168, 169] indicating that training and stimulation both improve postural stability. These results are expected and were observed behavioral as well. The mean frequency more interestingly decreased from medium frequency (0.3 - 1 Hz) to a low frequency (0 - 0.3 Hz) band.[168-170] It is suggested that medium frequency trajectories are associated with vestibular and somatosensory regulation whereas low frequency trajectories are associated with visual based postural regulation. high frequencies with proprioceptive regulation.[170-173] Therefore, participants with SCI before training or stimulation rely on more vestibular and somatosensory regulation to maintain balance without the presence of stimulation. Without and with stimulation after training a visual-vestibular-somatosensory regulation or only visual based strategy is used.[169-172] Without training and in the presence of stimulation, i.e. the acute effect of stimulation, resulted in a solely visual based balance strategy. Patients reported that they could feel the stimulation via increased perception of muscle tone, trunk rigidity, and the feeling of being pulled backward, and it could be hypothesized that the addition of stimulation resulted in additional sensory input making the vestibular and somatosensory system less reliable due to increasing the noise forcing the system to rely on the visual based postural control system. This shift in postural strategy from vestibular-somatosensory to visual-vestibular-somatosensory is further supported by significant decrease in COP velocity. Decreased COP velocity indicates lower level of regulatory activity required to maintain stability.[139, 174] Maki et al. suggested that high COP velocity, i.e. frequent postural corrections, maybe be an indicator of neural or sensorimotor dysfunction and indicative of compensation such that the higher COP velocity may be necessary to achieve and maintain stability.[139] This notion is supported by Prieto et al. who found com-pared the elderly to young able-bodied individuals and found that the elderly may have required significantly more postural control activity to achieve the same postural stability as compared to the younger population.[140]

Multidirectional leaning postural strategy

During multidirectional leaning, increases in COP excursion, mean frequency and mean velocity was observed with training and stimulation. Increase in COP excursion occurred in all directions indicating higher level of postural control. The improvement in postural control is supported by increased mean velocity indicating faster movement profiles of the COP. The underlying strategy to perform dynamic leaning is predominately visual based due to a low COP mean frequency (0 - 0.3 Hz).[168-170] Furthermore, a different leaning direction utilized a different biomechanical strategy all resulting in the functional improvement of leaning. Forward leaning employed a decreased trunk curvature, more erect upper body alignment during leaning, strategy; the head and trunk angle were maintained allowing to support the participants gaze. During backward leaning, upward gaze, i.e. increased head angle strategy, was used during directional leaning; the trunk angle and curvature were kept relatively constant indicating the use of a more hip based inverted pendulum type motion with the presence of training after stimulation as compared to a slouching kyphotic sitting strategy used without stimulation before training. During right and left leaning a combination of increased trunk angle and decreased trunk curvature, more upright posture, was used while the head angle remained relatively constant. Similar to backward leaning, leaning in the mediolateral direction used a more the rigid spinal alignment that acts as a lever arm resulting in a more inverted pendulum hip-based strategy during leaning.

Self-initiated perturbation postural strategy

During the SiP assessment, increased trunk angle and decrease trunk curvature were observed with stimulation after training indicating a more rigid spinal alignment. This change in postural alignment coupled with increased Obl and RA activity resulted in decreased COP integral both during the rapid arm raises as well as the "recovery" phase after the arm movement indicating better control despite faster arm movements.

Limitations and methodological considerations

A balanced, within-subject cross-over study design has been used, wherein each participant received an equal number of stimulation and no stimulation conditions within an experimental session. Each participant served as a self-control. The blinded design was intended, however, even participants with complete paralysis could perceive facilitatory effects of spinal stimulation on upright posture due to in-creased tone in the trunk musculature. In addition to the balanced. Further research with larger sample sizes is warranted to test, using a multi-factorial ANOVA design, the effects of factors such as the participants' body composition, level and duration of injury, presence of hardware in the spine, as well as training or practice. Paired comparisons of individual variables between no stimulation and stimulation conditions, not multiple comparisons, were utilized in this exploratory study

Multisite tSCS facilitates seated postural control

The spinal network is highly susceptible to the stimulation location,[59, 60, 175] intensity and frequency.[176] For instance, rhythmic stepping can be generated with stimulation over the T11-12 vertebral levels at a stimulation frequency of 30 Hz.[64, 133, 177] and standing and extension over the L1-L2 vertebral level at a stimulation frequency of 15 Hz.[88, 131, 137] Support for multisite stimulation for postural regulation has been suggested and here we show that the application does improve trunk control and postural stability in both quiet and dynamic seated postural tasks. We observed considerably increases in trunk muscle activity as compared to without stimulation in all directions. The critical relationship, however, is in the effect of stimulation on the integration of visual, vestibular, and somatosensory systems during postural regulation.

We suggest that multisite spinal stimulation can effectively modulate postural networks and enhance motor patterns appropriate for maintaining quiet sitting and performing dynamic tasks.

Chapter 6: Neuromusculoskeletal Model

6.1 Background

Dynamic Neuromusculoskeletal simulations allow one to study neuromuscular activation, coordination and estimate internal loading of the neuromusculoskeletal system. Modeling allows for the simulation of personalized gait to estimate the dynamics and kinematics for an individual and explore the biomechanical effects of treatment and various rehabilitation programs. 'Synthesizing detailed descriptions of the elements of the neuromusculoskeletal system with measurements of movement to create an integrated understanding of normal movement and to establish a scientific basis for correcting abnormal movement remains a major challenge.[178]

6.2 Introduction

Thoracic spinal cord injury often results in mobility impairments and altered postural alignment in movement patterns.[12, 101, 179] These impairments significantly impact an individual's quality of life.[5, 21] Consequently, development of effective treatments to restore or replace lost voluntary motor function can significantly impact a patient's quality of life and independence. Currently, clinical treatment is often selected from a few standard non-patient specific rehabilitation programs such as pressure relief movements, a regimen of stretching, strengthening, gait training, and prescription of appropriate assistive devices to compensate for motor deficits.[2] These treatments are generic as opposed to patient specific based on the characteristics and deficits of the individual with the injury. Furthermore, the treatment selection process is typically based on subjective scales and experience as opposed to objective and screening with a focus on functional recovery.[180] There is a need for the use of personalized neuromusculoskeletal modeling (NMS). NMS can serve to provide custom and objective treatment for functional motor deficits thereby improving the rehabilitation effectiveness. Since each spinal cord injury is unique, NMS allows for subject specific anatomical (e.g., skeletal structure and muscle lines of action), physiological (e.g., muscle force-generating properties), and/or neurological (e.g., constraints on achievable muscle excitation patterns) characteristics.[180] The development and use of NMS models inherently depends on the specific scientific questions as well as the experimental kinematic, kinetic, and physiological data and measurements to validate model-based estimates.[181]

Experimentally, there are two major limitations commonly present. First, muscle forces and muscle activation are not directly measurable. Second, cause-effect relationships are complex and difficult to isolate in dynamic systems from experimental data alone. Tools can facilitate the process but can be non-specific. For example, EMG is commonly used to experimentally determine muscle activity, but the EMG recordings alone are insufficient to determine overall kinematics and motion of the neuromusculoskeletal system. Determining how individual muscles contribute to observed motions is challenging.[182]

Clinically, a framework, in combination with human movement data (e.g. force plate, motion capture, electromyographic, goniometric etc.) is needed for assessment, identification and prediction.[182] The frame work allows for the assessment of movement patterns and the underlying coordination of muscles during normal and impaired movement. One can discern the altered gait patterns and trajectories as well as the underlying muscle activity resulting in such abnormalities.[183] These data can then be used to predict the functional consequences of various rehabilitative techniques, programs, and treatment.

Treatment design using patient specific neuromusculoskeletal modeling has been proposed as a three-step process: preparation, construction, and utilization[184] with best practices suggested by *Hicks et al.* 2014.[89]

6.2.1 Challenges

Numerous challenges exist in the ability to personalize and model, predict, and measure functional improvements post-intervention in motor disorder individuals. A primary challenge faced by this personalized modeling process is each custom NMS model is time intensive and currently impractical for regular clinical use. To remedy this issue, scaling standard models and calibrating them with training data has been gaining popularity. Calibration and scaling of NMS model involves using model geometry and muscle, ligament, tendon parameter values obtained from cadaver studies as well as anthropometric measurements of the participants.[184, 185] Since each muscle and bone geometry can be scaled to the participants measurements, scaling of a standard model is sufficient to estimate muscle and bone loads which currently cannot be validated experimentally.[180] One primary issue with scaling with regards to spinal cord injury, is there are limitations in patient movement depending on the level and severity of the injury as well as any surgically interventions such as implanted hardware and spinal fusion making the standard method inapplicable to much of the SCI community.

6.2.2 Solution

This thesis includes the development of a simplified software tool package and model sets to facilitate custom model development for SCI with the intended use on identifying asymmetries and global inefficiencies during stereotyped seated movement to aid rehabilitation and development of training programs. Using the Xbox One Kinect and the OpenSim platform the tool set captures and 3D kinematic data and converts it to marker joint location data to model movement in the OpenSim environment.

First the kinematic data captured from participants performing the stereotyped movements is used to calibrate the NMS model in OpenSim. Using inertial and visual based motion capture data (from the Kinect), generic models and custom models I created for each participant based on each specific injury, is scaled. Next, joint locations, body orientations, and individual body segment lengths are calibrated using the extracted marker locations. Ground reaction forces from force plate data are then mapped to model via inverse kinematics along with musculo-tendon properties from literature.

6.2.3 OpenSim

In the early 1990s, Delp and Loan introduced a musculoskeletal modeling environment, called SIMM that allows for the creation, modification and evaluation of neuromusculoskeletal models. SIMM was then established into an open-source simulation environment and called OpenSim.[93, 178, 186, 187] OpenSim is a user extensible software system developed for neuromusculoskeletal modeling. Users can collaboratively develop models of musculoskeletal structures and create dynamic simulations of movement. OpenSim software is ANSI C++ based and the graphical user interface (GUI) is written in Java. OpenSim technology makes it possible to develop customized controllers, analyses, contact models, and muscle models without the need to alter or compile source code. Users can analyze existing models and simulations and develop new models and simulations from within the GUI as shown in Fig. 1 Delp *et al.* 2007).[178] OpenSim includes a tool kit called SimTrack; SimTrack, enables researchers to generate dynamic simulations of movement from motion capture data but is currently limited to select motion capture devices.[178]

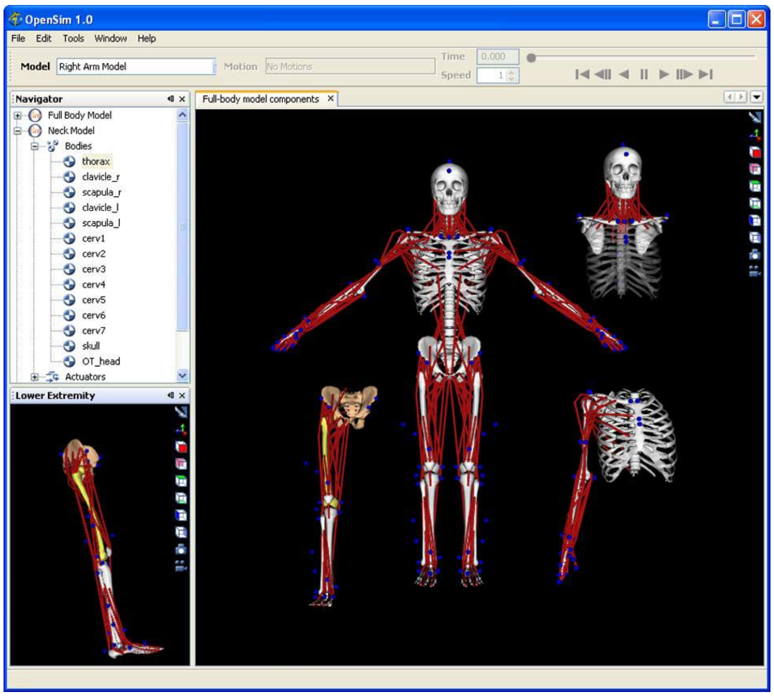


Figure 1. Screenshot from OpenSim. Models of many different musculoskeletal structures, including the lower extremity, upper extremity, and neck, can be loaded, viewed and analyzed. Muscles are shown as red lines; virtual markers are shown as blue spheres. (From Delp *et al.* 2007)[178]

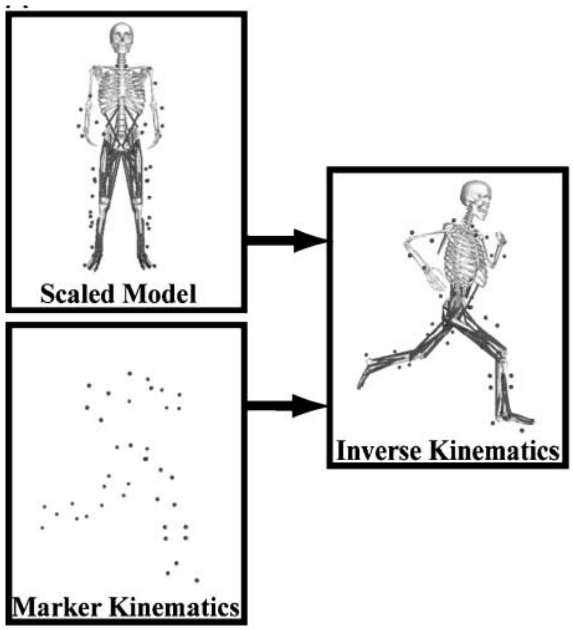


Figure 2. Visual for performing inverse kinematics. A. Subject-specific models were obtained by scaling segment lengths of a generic musculoskeletal model based on anatomical marker positions recorded of a subject in a standing posture (Image from Thelen *et al.* 2006)[181]

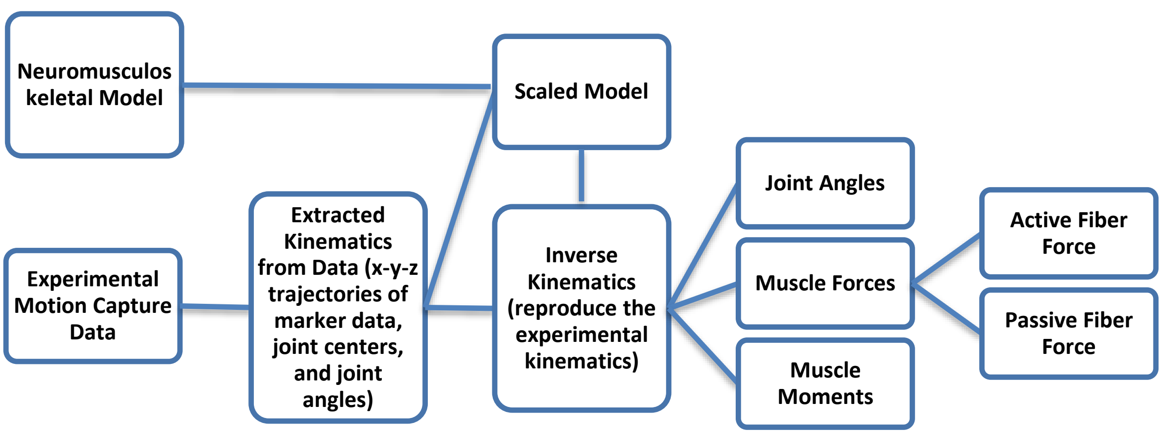


Figure 3. Detailed outline for generating a muscle-driven simulation of a subject's motion and performing inverse kinematics (modified from Delp *et al.* 2007 and Thelen *et al.* 2006)[178, 181]

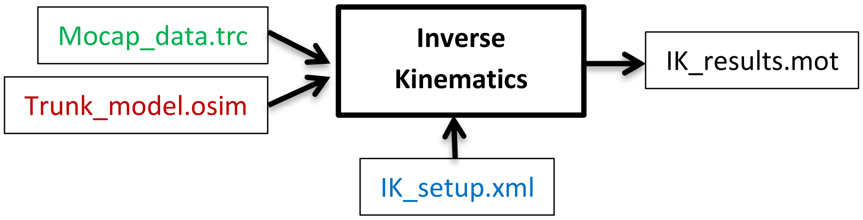


Figure 4. Inputs and Outputs of the IK Tool. Experimental data in green, OpenSim files in red, and settings files are in blue. (modified from OpenSim website: http://opensim.stanford.edu/)

3D motion capture data (Mocap_data.trc) is the experimental joint trajectories acquired from the motion capture system converted into the custom marker set. This data is obtained from either the inertial or visual-based motion capture system, in this case Xbox One Kinect, and listed frame by frame for a set time range, the duration of the assessment. The Trunk_model.osim is the subject-specific OpenSim model generated by scaling the custom neuromusculoskeletal model of the trunk, including model parameters and restrictions such as a patient with plates or hardware limiting range of motion, during sitting with ground reaction forces acquired by the force-plate actuated sitting apparatus. The IK_setup.xml is a file containing all the settings information for the IK tool built into OpenSim. This XML file includes the marker set (generalized spatial representation and labels of the makers used to scale and map the joint excursions), marker weightings, ground reaction forces and other forces acting on the system. The Scale Tool, marker weights are relative and determine how "well" the virtual markers track experimental markers; a larger weight for a given marker will mean less error–the distance between the virtual and experimental representations of a marker–for that marker (simtk-confluence.stanford.edu). The output (IK_results.mot) is the computed solution to the inverse kinematic problem where the resultant motion file contains joint excursions and trajectories (joint angles and displacements).

6.2.4 Neuromusculoskeletal Model Procedure (Simplified)

Step 1

A musculoskeletal framework and system needs to be created. The framework is defined by the musculoskeletal geometry, anthropometric body data, body segment dynamics, muscle contraction dynamics etc. The model needs to be simplified via supported assumptions to provide insight into the cause and effect relationship between internal muscle properties and dynamics and overall global effects during movement.

Step 2

The resultant simplified dynamic musculoskeletal model from step 1 needs to be scaled to the anthropometric data from each individual subject. The model is scaled from relative distances between markers obtained from motion-capture data and a 'marker set.' XML coding is used to initialize and customize the model from step 1 for each participant. The corresponding virtual marker locations in the model are proportionally scaled to match the total measured mass of the individual subject and the subject's physical body measurements. The total actuator length is proportionally scaled, and the resultant muscle fiber lengths and tendon slack lengths of the muscle-tendon actuators are scaled to retain the same percentages as the original model.[178]

Step 3

Experimental data captured by the motion capture system is used to solve the inverse kinematics problem. The model uses the marker set established in step 2 to best reproduce the raw marker data from the experimental data, i.e. the model uses the marker location data to best reproduce the joint angles and joint excursions from the experimental data when applied to the subject specific model. The fitting occurs frame-by-frame by solving the least-squares equation that minimizes differences between measured marker locations and the model's locations subject to joint constraints.[188] The inverse kinematics problem is to minimize the weighted squared error to determine the joint parameters that provide a desired movement and position of specific joints. The resultant solution is the pose that minimizes a sum of weighted squared errors of markers and/or coordinates. Kinematic analysis of a constrained system of rigid bodies, or kinematic chains, is performed using:

$$\boldsymbol{Squared\ Error} = \sum_{i=1}^{markers} w_i \left(\bar{x}_i^{subject} - \bar{x}_i^{model}\right)^2 + \sum_{j=1}^{joint\ angles} w_j \left(\Theta_i^{subject} - \Theta_i^{model}\right)^2$$

where $\bar{x}_i^{subject}$ and $\bar{x}_i^{model}$ are the three-dimensional positions of the *i*th marker or joint center for the subject and model, $\Theta_i^{subject}$ and Θ_i^{model} are the values of the *j*th joint angle for the subject and model, and w_i and w_j are factors that allow markers and joint angles to be weighted differently.[178]

6.2.5 Trunk Model Parameters

Muscle and musculotendon force generation can be approximated as a spring and damper system. Although the force generation can be characterized and modeled in numerous ways, OpenSim estimates muscle and tendon force as a Hill-type musculotendon model.[182, 189] The weighting factors of the spring and damper system were modified to more accurately represented muscle activation and force generation capabilities in spinal cord injury. The Hill-type model inherently assumes a uniform mechanical strain distribution along the muscle fiber, which may not be the case when injury occurs.[181] For example, it has been suggested that strain injury may be preceded by disruption of individual sarcomeres, leading to large local mechanical strains, which propagate to the musculotendon junction.[190] Therefore, the trunk model employs the musculotendon model described in Thelen *et al.* and implemented by Christophy *et al.* [92, 191]

In characterizing the joint kinematics, spinal segments were simplified to three degrees of freedom detailed in Christophy et al.[191] and used to globalize the individual segment motions into functionally relevant trunk movement: flexion-extension, lateral bending, and trunk rotation. An example of a patient's actual trunk flexion and extension, as captured by the motion capture system, was mapped to his NMS model and the poses and resultant muscle parameters prior to the inverse kinematics is shown in Fig. 5.

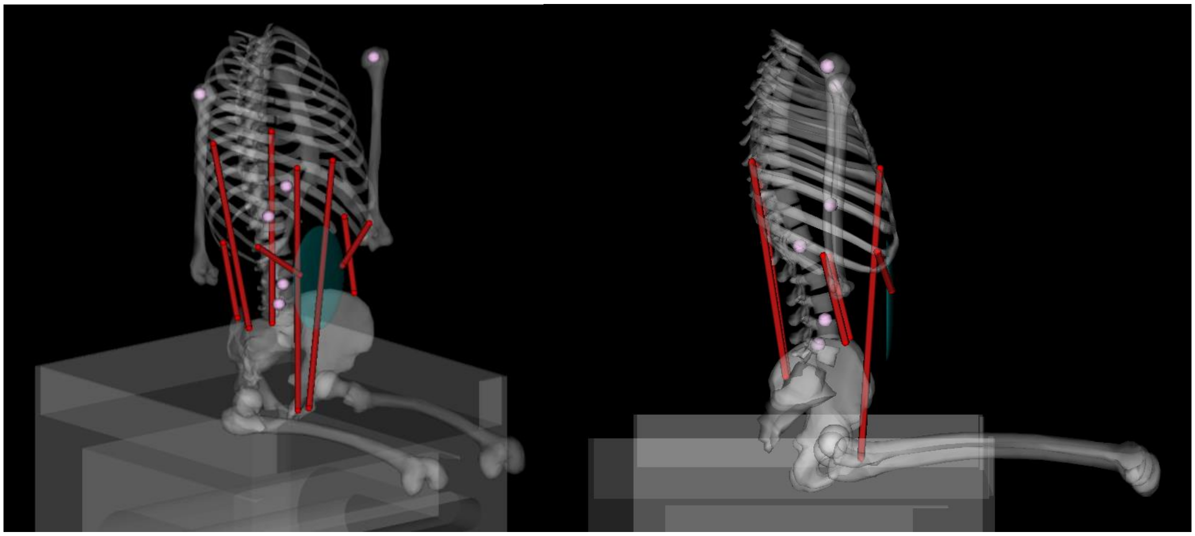


Figure 5. Representative neuromusculoskeletal model of a spinal cord injured participant, T2 AIS A, in an isometric and sagittal view. Red lines indicate muscle lines of action starting and ending at the insertion points. Pink dots represent joint location markers. Bone structures and the sitting apparatus are also shown.

NMS models have been gaining in popularity in their use especially with regards to locomotion and upper limb function.[91, 181, 184, 192] In the context of the trunk, focus has mainly been directed towards understanding characteristics of external perturbation, intrinsic spinal segments, bending, loading and the effects of functional electrical stimulation and epidural stimulation.[191, 193-196] A more global understanding of practical applications and in the development of rehabilitation protocols in sitting, however, has not been demonstrated.[90, 197, 198] Furthermore, taking it one step further with validating the subject-specific models on a continual basis to assess functional improvement during seated stability has not been shown.

6.2.6 Neuromusculoskeletal Model of Spinal Cord Injury – Case Example

A custom neuromusculoskeletal model for each participant with spinal cord injury was developed to examine the causes of their limitation to perform trunk flexion and extension in a seated posture. In this case example, it was hypothesized that asymmetric muscle activity of the erector spinae and external oblique limited flexion and extension. This case study demonstrates how simulations can provide insight into the causes of trunk instability and a means design and test training programs. Each theranostic model was modified from a trunk model developed by Christophy et al. and Lambrecht et al. with an implemented sitting apparatus.[90, 191] The model was scaled to the patient's body measurements and the vertebral movement characteristics were modified to the neurological level of injury. The sitting apparatus was designed in Autodesk Inventor (Autodesk, Inc., San Rafael, CA) and imported into OpenSim. Muscle lines of action and constraints as well as marker locations were custom developed to match those acquired by the motion capture system. The muscles were simplified to those that were clinically tested during the experimental protocols detailed in Chapters 4 and 5, i.e. external obliques, rectus abdominus, erector spinae. A representative model (T2 AIS A) is shown in Fig 5. The muscles were chosen because the erector spinae and the abdominal muscles, specifically the rectus abdominis, are the primary extensors and flexors of the spine respectively. The external oblique functions as a trunk flexor and axial rotator. The model is based on detailed descriptions from literature and previously developed models.[7, 53, 90, 135, 145, 191, 194, 195, 199]

The participant was instructed to maximally lean his torso, i.e. flex the trunk forward, as far as possible without use of his hands or head and while maintaining balance. The participant was then asked to maximally extend his torso, i.e. extend the trunk to lean backward, as far as possible. The movement was captured by the 3D motion capture system (KinectOne). The data was subsequently discretized, processed, and the joint location data, on a per frame basis, were mapped to the NMS model. Then inverse kinematics, based on the methods previously described, were performed using the mapped data.

The maximal flexion and extension are show in Fig 6. A. The active fiber force and flexion-extension moment arm were calculated throughout the range of motion performed. During flexion-extension, asymmetry between the left and right erector spinae (LT_ErS and RT_ErS) active fiber force, i.e. muscle activity, were identified (Fig 6. B). Decreased active force in rectus abdominus activity was also observed but muscle activity was more symmetric, i.e. bilateral muscle activity was of similar magnitude and activity throughout the flexion-extension. When looking at the flexion-extension moment arm on the right half of the body, the activity of the right external oblique (RT_EO_1 & RT_EO_2), the right erector spinae

(RT_ErS) and the right rectus abdominus (RT_RA) was heavily dependent on the trunk angle (Fig6. XX C).

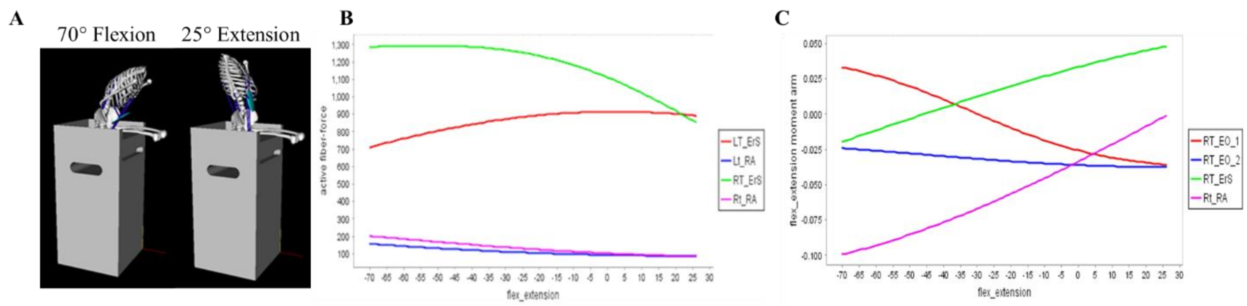


Figure 6. Modeling flexion and extension of a representative participant with thoracic spinal cord injury. A) Neuromusculoskeletal model during 70° Flexion and 25° Extension. B) Active fiber force of the left erector spinae (red), left rectus abdominus (blue), right erector spinae (green), and right rectus abdominus (magenta) during flexion and extension. C) Flexion-extension moment arm of the right external obliques (red and blue), right erector spinae (green), and right rectus abdominus (magenta) during flexion and extension.

The muscle moment arm indicated the mechanical advantage of the muscle. It is related to the joint's center of rotation and used in determining the torque which indicates the movement characteristics of limbs i.e. the movement produced under force of muscle action. From flexion to extension trunk movement, the simulation indicates increasing muscle moment arm from the erector spinae and rectus abdominus and decreasing muscle moment arm from the external obliques. Lastly, with increasing extension, the rectus abdominus muscle moment arm increased.

6.3 Discussion

In this chapter I have presented a patient- specific model of the trunk during sitting using the open-source simulation platform OpenSim. The model is intended as an analytic tool for researchers to analyze quiet and dynamic postural tasks and spinal kinematics of patient motion acquired from motion capture systems.

The presented data serves as a proof of concept of decision driven analytics, i.e. mapping patient movement to model and identify muscle parameters during flexion, extension, lateral bending, rotation and their combinations. The custom software to 1) extract joint locations from the Kinect sensor, 2) scale and map the motion capture data to the model, and 3) the custom model itself can be accessed at https://github.com/mrinalrath2. The distribution of the software is intended to further improve our understanding of movement after spinal cord injury and to serve as a tool to help design better training programs and improve methodologies for optimizing spinal stimulation parameters. Furthermore, the intention of this work was to develop and show proof of concept of a low cost easily accessible means to capture, model, and analyze patient motion with the goal to improve access and effectiveness to rehabilitation and therapy.

Motion capture data from patients performing quiet and dynamic postural tasks, such as quiet sitting and multidirectional leaning, coupled with EMG data from trunk muscles could serve as means to analyze muscle recruitment strategies, postural stability, muscle activation dysfunction after injuries, not limited to spinal cord injury but also other motor dysfunction from stroke, multiple sclerosis, low back strain, accidents, etc. This methodology can also be coupled with transcutaneous electrical stimulation and other methods of neuromodulation to optimize stimulation parameters and their potential effect on trunk control, range of motion, and dynamic stability digitally to maximize training sessions in a clinical setting with the patient.

In the case example, these results during the flexion and extension of a T2 AIS A SCI injury in a seated posture suggest asymmetric loading and that the right side is the patient's dominant side as compared to the left side. This is indicated by the higher magnitude of erector spinae activity on the right side of the body throughout the flexion-extension movement.

The simulation additionally indicated increasing muscle moment arm from the erector spinae and rectus abdominus and decreasing muscle moment arm from the external obliques. During extension the erector spinae's, a primary trunk extensor, line of action, i.e. lever arm, shortens with the muscle contraction, increasing force of muscle action resulting in an increase in the muscle moment arm and the resultant muscle force. The modeling of the trunk muscles is in line with previous studies in an able-bodied individual during symmetric trunk flexion;[193, 200] note however the study was conducted in standing without and with external loading and had different magnitude of responses. Contrastingly, however, during peak flexion, a maximal muscle moment arm of the erector spinae was observed due to the suggested monotonic increase in passive muscle and ligament contributions of the spine.[193, 200] Contrary to our findings, the model by Arjmand et al. found global extensors to become inactive during sagittal trunk flexion between 50 and 70°;[193] this result is likely due to the assumptions that muscle elongation and optimal length were estimated from a standing posture as opposed to a sitting posture and passive elongation properties from Davis et al. were utilized.[193, 201] Lastly, when considering the rectus abdominus, the muscle moment arm expectedly increased as the degree of extension increased; this is likely due to increased passive stretch and the length-tension relationship.

The practical further implications of these results suggest 1) targeted rehabilitation focusing on the left side half of the trunk muscles is needed to produce symmetric activity and 2) increased symmetry and cocontractions of the trunk extensors and flexors can improve flexion and extension ability. Observations in chronic low back pain patients in seated postures performing flexion and extension patterns by O'Sullivan indicate that in end-range flexion, higher co-contraction of the lumbo-pelvic stabilizing muscles were observed by pain-free able-bodied individuals.[202, 203] Although not directly tested in spinal cord injury, a transferable argument can be made that targeted training to improve erector spinae activity can not only facilitate seated flexion and extension[202, 203] but erector spinae-external oblique training can also improve upright-sitting ability.[203] Lastly, the simple simulation case example highlights the importance of implementing postural training specific rehabilitation programs personalized for each patient. Mapping of clinically observed movements via 3D kinematics applied to a theranostic neuromusculoskeletal model can elucidate asymmetry of muscle activity and altered muscle activity and can be used to design patient specific training programs. These training programs can be further enhanced by stimulation protocols that facilitate activation of the trunk muscles specifically the erector spinae, external obliques, and rectus abdominus. This work is intended to outline the methodology and show a proof of concept on the implementation of a theranostic neuromusculoskeletal model and warrants further investigation and application.

Chapter 7: Related Work

This chapter contains work published with collaborators and where I made significant contributions to data collection, analysis, writing and editing. Included works are with consent of all authors and contributors and include a brief summary of the study, the results, and discussions. These works are relevant towards the breadth of application and future directions which will be addressed in Chapter 8.

7.1 Challenging the Postural System and the effects of tSCS on Postural Control

7.1.1 Abstract

Neuromodulation of spinal networks can improve motor control after spinal cord injury (SCI). We sought to (1) determine whether individuals with chronic paralysis can stand with their knees and hips extended without additional support with the aid of non-invasive electrical spinal stimulation, and (2) investigate whether postural control can be further improved following repeated sessions of stand training. Using a double-blind, balanced, within-subject cross-over, and "sham"-controlled study design, 15 individuals with SCI, of varying severity, received transcutaneous electrical spinal stimulation to regain self-assisted standing. The primary outcomes included qualitative comparison of need of assistance on each knee and the hips during standing without and in the presence of stimulation in the same participants, as well as quantitative measures, such as the level of each knee assistance and amount of time spent standing independently, without trainer assistance. None of the participants could stand unassisted without stimulation or in the presence of "sham" stimulation. With stimulation all participants could maintain upright standing with minimum and some (n=7) without any assistance applied to the knees or hips using their hands for the upper body balance as needed. Quality of balance control was practice-dependent and improved with subsequent training. Electrophysiological properties of self-initiated postural adjustments during spinal stimulation enabled standing, revealed responses that facilitated equilibrium. Our findings indicate that the lumbosacral spinal networks can be modulated transcutaneously using electrical spinal

stimulation to facilitate self-assisted upright standing even after chronic motor and sensory complete paralysis.

7.1.2 Discussion

The present results qualitatively and quantitatively demonstrate the feasibility and effectiveness of non-invasive spinal stimulation in regaining self-assisted standing, without or with minimum assistance provided to the knees or hips, following chronic SCI. We identified specific stimulation characteristics that enabled effective standing equilibrium in paralyzed individuals. We demonstrated that postural spinal neuronal networks which are relatively non-responsive after SCI, become reactive to somatosensory information in the presence of tSCS. These networks can generate and sustain independent knee and hip extension with the aid of tSCS within a single treatment session. “Sham” stimulation, which was utilized by altering the stimulating pulse configuration or location of delivery, did not induce enabling effects, despite being perceived by the participants as helping them to maintain their trunk extension, similar to the effective tSCS. Postural control was further improved following repeated sessions of stand training both without and in the presence of tSCS, suggesting learning effects and indicating that sublesional reorganization of the postural networks may occur concurrently and synergistically with reorganization of the networks above the lesion.

In the present study, we observed phenomena consistent to other means of neuromodulation. Specifically, we observed periodic modulation of repetitively evoked motor potentials,[65] unique modulatory effects of different stimulation frequencies,[88] and the adjustment of the muscle responses to the changes in the body position.[4] The data indicate that that the proprioceptive inputs were processed by the spinal networks, which resulted in specific motor pools’ activation depending on the task or sensory environment. Stimulation frequencies that result in functional improvements in both sitting and standing not only had more robust COP behavior, but also allowed some postural control of balance, as evident by generated muscle activity during standing. As such, although facilitated standing cannot be achieved after motor complete paralysis without spinally induced leg motor output, interneuronal spinal mechanisms must be also involved, contributing to multisegmental intraspinal interplay, which results in complex behavioral regulation below the lesion. tSCS delivered in these participants resulted in re-appearance of the motor output and generated force responses contained both static and dynamic components. As such, our observations indicate that human spinal networks feature the critical level of posture-specific automaticity which can be exploited by utilizing non-invasive spinal neurostimulation, and function effectively even in the lack of supraspinal excitatory drive to facilitate standing posture and some balance control. The rapid effects occurred in the present study, may be due at least in part to the ability of tSCS to neuromodulate broader components of the neural networks that are necessary to engage for successful standing, including multisegmental projections to the trunk and lower limb musculature, due to wider current field, as compared with epidural stimulation.

It is plausible that changes in the geometry of the thoracolumbar spine and the relative position of the stimulating electrodes can influence the flow of current[204] and thus can contribute to the observed difference in the neuromodulation of the induced muscle responses during the sitting and standing positions. For instance, it has been shown that depending on the body position, different neural structures can be involved in the response during spinal stimulation.[161] It is critical to note that in the present study, without tSCS, very low levels of the leg muscle activity were observed even during self-initiated postural adjustments, and, therefore, it was impossible for the individuals with SCI to maintain upright posture without external assistance. During tSCS, once its intensity reached a critical threshold during sitting, the transition to standing increased the excitability of the postural-specific interneuronal networks to the level adequate to generate and maintain the body-weight-bearing. It appears that in the initial stages of neuromodulation, higher levels of tSCS intensity are needed to engage the networks to a physiological state necessary to process an effective level and range of somatosensory inputs required for generation of the upright posture. With subsequent sessions of neuromodulation, the level of stimulation could be reduced and still achieve a similar level of engagement of the spinal networks, as it was initially, as such the external assistance required to maintain standing proportionally reduced or was no longer required.

Early experiments with animals demonstrated that repetitive, long-term application of pharmacological agents or epidural spinal stimulation can cause plastic changes in the sublesional spinal postural networks, leading to restoration of postural limb reflexes and to substantial recovery of postural functions.[72, 75, 176] Such restored intrinsic spinal automaticity and, presumably, an increase in quality and quantity of supraspinal descending motor control after clinically complete, but anatomically discomplete[205] SCI in the presence of spinal stimulation, can facilitate functional recovery through the regaining of movement strategies.[206] Presumably, an increase in quality and quantity of supraspinal descending motor control after discomplete [205] SCI in the presence of spinal stimulation, [207-209] can facilitate functional recovery through the regaining of movement strategies.[206] Given the extensive functional reorganization of cortico-brainstem-spinal, corticospinal and spinal networks after SCI,[210] the level of functionality demonstrated during stand training is likely to be reflected in the level of synergism within and between the brain and spinal cord. The fact that improved motor strategies and sensorimotor responses occurred within a few sessions after years following SCI, indicates the potential of supraspinal-spinal plasticity.

Multisite tSCS delivered at different frequencies can concomitantly facilitate balance control and enhance weight-bearing during stepping tasks. These findings together indicate the functional continuum and important locomotor and postural networks' interactions, even though that may seem counterintuitive given the highly repetitive and rather predictable features of stepping compared to the more variable and subtle features of balance control during standing.[211, 212] The critical relationship, however, is in the tight interaction of sensory interplay with the multisegmental spinal networks, which seems to have the remarkable ability to readily associate a specific sensory ensemble with a particular motor outcome. We suggest that multisite spinal stimulation, can effectively engage and synergistically modulate postural and locomotor networks, and concurrently enhance generation of motor patterns appropriate for both standing and stepping.

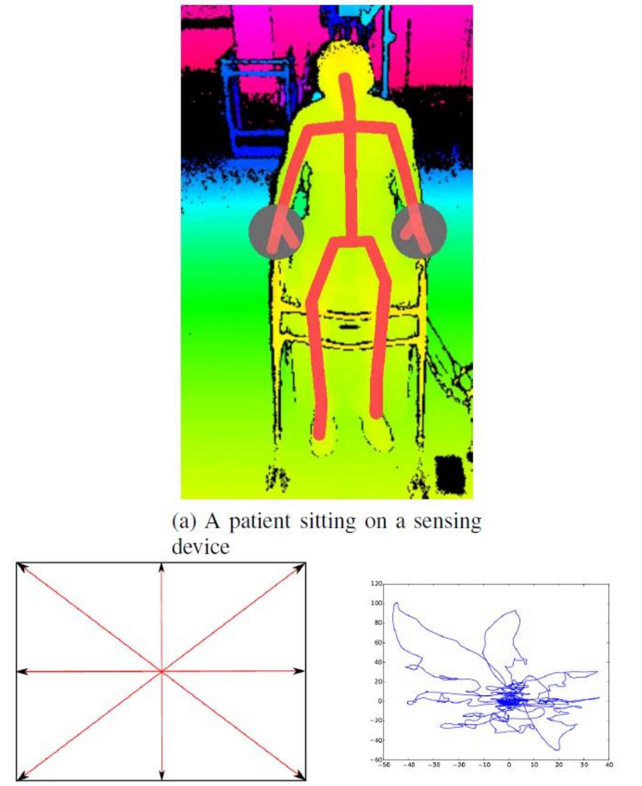
7.2 Seated Reward Function: Methods to Characterize and Quantify Postural Control

7.2.1 Abstract

This work introduces a new method for inverse reinforcement learning in large state spaces, i.e. movement of the human trunk during seated maneuvers, where the learned reward function can be used to analyze seated movement and quantify rehabilitation progress. Inverse kinematics and reinforcement learning can be computationally expensive due to the number of degrees of freedom and high volume of data. To avoid solving such learning problems in reward learning, we propose and evaluate a function approximation method that estimates a function to maximize the likelihood of the observed motion. We test the proposed method in a simulated environment on reward learning and show that it is more accurate than existing methods and significantly better in scalability. We also show that the proposed method can extend many existing methods to large state spaces. We then apply the method to participants with spinal cord injury wherein a patient was seated on a force plate and leaned their trunk in an indicated direction presented on a screen with biofeedback from the force plate. We evaluated the effect of training and stimulation on the observed patient trajectories.

7.2.2 Background

Recently, multi-electrode epidural and transcutaneous spinal cord stimulation have proven to be promising methods for a motor complete SCI patient to regain seated voluntary motor.[40, 50, 160, 167] To determine optimal spinal stimulation parameters, location, frequency, intensity etc. it is necessary to quantitatively measure the effects of different stimulations on a patient and its effects on voluntary motor control.[3, 4, 84, 95, 213-215] Patient motion was represented by a sequence of poses captured by 3D motion capture. In an experiment, a patient is seated of a force plate and is instructed to shift poses to follow instructions displayed on a monitor. The force plate continuously records the patient's center of pressure (COP) and is synchronized with the 3D visual motion analysis system. An aim of this study is to assist in the design of optimizing stimulation parameters as well as advancing the understanding of voluntary movement in individuals with spinal cord injury during seated postural tasks, both quiet and dynamic.



(a) A patient sitting on a sensing device

(b) Instructions on movement directions

(c) The patient's COP trajectories during the movement

Figure 1. Rehabilitative game and observed trajectory in a participant with spinal cord injury. (a) Depth field and overlaid digital skeletal structure of representative patient seated on a force plate implemented in the sitting platform. (b) directional indicators instructing the patient on the goal direction of movement. (c) representative patient's COP excursion during the overall multi-directional leaning task.

We assume the stimulation will alter the patient's inherent motor control system by affecting the patient's cost to switch between poses, as determined by body weight distribution, spinal alignment, gravity, ground reaction force etc. This cost minimization criterion has been tested and reported for standing and locomotion and herein applied to posture.[216-219] An accurate cost estimation will reveal the effect of spinal stimulation parameters on the ability to perform voluntary movement tasks, assuming all other factors to be invariant.

Human movement can be simplified to reward maximization and effort minimization. Reward maximizations serve to perform a task and effort minimization, i.e. cost minimization, implies the most effective mean to do so. Learning challenges this system as initially the weighting of cost optimization needs to be forgone to facilitate long term reward maximization. That is, to ensure a global minima of cost while maximizing reward, in this case poses and trajectory, without being bound in a local minima, needs to occur.

To estimate the patient's costs over different poses, the most straightforward approach is counting the pose visiting frequencies from the observed motion. Assuming the cost of a pose is linearly proportional to its visiting frequency, the patient may visit a high-cost pose, to follow instructions or to transition into a subsequent low-cost pose, which will make cost estimation inaccurate without regarding the context. In this work, we formulate the patient's COP trajectory as a Markov Decision Process, where each state represents a pose and is given a reward value. If the COP trajectory represented as a vector is perfectly in line with the instruction, i.e. perfectly correlated, then a reward of 1 is provided. If the COP vector is perfectly uncorrelated with the instruction, i.e. perpendicular, a negative reward is encoded. The overall reward then can be determined and assessed during different instructions and under different states or stimulation parameters. With this formulation, we adopt inverse reinforcement learning algorithms to estimate the reward value of each state from the observed motion of the patient.

Most of these methods are not practical for large-scale applications as they need to solve a reinforcement learning problem in each step of reward learning and are computationally infeasible. Only a few methods are applicable to large-scale applications. We propose an approximation method that guarantees the optimality of the learned functions as well as the scalability to large state spaces.

7.2.3 Results

During rehabilitation, a patient with spinal cord injury sits on support frame with a mounted force plate system and performs a series of dynamic stability movement tests. Each experiment is composed of two sessions, one without transcutaneous stimulation and one with stimulation. The electrodes configuration and stimulation signal pattern are manually selected by the clinician. In each session, COP position registered by a force plate and was visualized on the monitor to provide feedback on body displacement. Eight targets, presented at 45-degree angle increments around the center, starting in the forward right direction, or four targets, presented at 90-degree increments, starting in the forward direction), delineate the instruction for the patient to follow. The participant was asked to move the COP indicator to each target, which was present for 5 seconds, hold the position during that time, and return back to the starting position.

The COP sensory data from each session is discretized on a 100 x 100 grid, which is sufficient to capture the patient's small movements. The problem is formulated into a Markov decision process which is a discrete time stochastic control process. The Markov decision process establishes a mathematical framework for modeling decisions where each state captures the patient's discretized location and COP velocity and formulates the data into eight possible change vectors, the velocity is represented with a two-dimensional vector, corresponding to the cardinal and intercardinal directions (i.e. north, northeast, east etc.) and a value indicating the magnitude of the change. Under this process the problem has 80000 states (8 directions x 100 x 100 grid) and 8 actions (8 cardinal and intercardinal directions), and each action is assumed to lead to a deterministic state.

The metric for improvement is based on: 1) the limits of stability (maximum displacement towards a target a patient was able to perform while maintaining balance) and 2) how accurately they can shift their COP (or poses) in the target direction. Given the learned reward function, we score the patient's improvement with the correlation coefficient between the recovered rewards and the ideal rewards based on target states visited by the patient. The ideal reward for each state is the cosine similarity between the state's velocity vector and the instructed direction i.e. an ideal movement is when the state velocity vector matches the indicated direction and is perfectly correlated. Cosine similarity characterizes the orientation and not the magnitude of vectors: two vectors with the same orientation have a cosine similarity of 1. The result is shown in Table 1. It shows that a representative participant’s ability to follow the instructions is affected by the spinal stimulation, but whether it is improved dynamic postural control and voluntary movement varied depending on the indicated direction. The result also is limited and heavily dependent on the automated trajectory segmentation method which segmented the COP trajectory and instruction based on duration. A manual segmentation method may result in increased accuracy. The significance of the data indicates that the results support the development of a tool based on the reward function that will help physicians optimize stimulation intensities and parameters to improve postural control and stability in a quantifiable systematic method.

	forward	backward	left	right	top left	top right	bottom left	bottom right	origin
1u	-0.352172	-0.981877	-0.511908	-0.399777					-0.0365778
1s	-0.36437	-0.999993	-0.14757	-0.321745					0.154132
2u	-0.459214	-0.154868	0.134229	0.181629	0.123853	0.677538	-0.398259	0.264739	-0.206476
2s	-0.115516	-0.127179	0.569024	0.164638	0.360013	0.341521	0.0817681	0.134049	-0.00986036
3u	0.533031	0.0364088	0.128325	-0.729293	0.397182	0.155565	-0.48818	-0.293617	-0.176923
3s	-0.340902	-0.091139	0.344993	0.0557266	0.162783	0.740827	-0.0897398	-0.00674047	-0.414462
4u	0.099563	-0.0965766	0.145509	-0.912844	0.250434	-0.299531	0.577489	0.134106	-0.151334
4s	-0.258762	-0.019275	-0.263354	0.549305	0.0910128	0.755755	-0.225137	0.289126	-0.216737
5u	0.287442	0.0859648	-0.368503	0.504589	-0.297166	0.401829	0.0583192	-0.23662	-0.0762139
5s	-0.350374	-0.0969275	0.538291	-0.617767	-0.00442265	0.0923481	0.115864	-0.576655	-0.0108339
6u	0.205348	0.302459	0.550447	0.0549231	-0.348898	0.420478	0.378317	0.56191	0.145699
6s	0.105335	-0.155296	0.0193898	-0.283895	-0.0577008	0.220243	-0.31611	-0.296682	-0.0753326

Table 1. Correlation coefficients between the ideal reward and the actual reward using the inverse reinforcement learning function without and with the presence of stimulation. Columns indicate the direction of movement. Rows indicate participant number (1-6) and whether the trial was without (u) or with (s) the presence of stimulation. The numbers range from -1 to 1 where 1 represents perfect correlation and an ideal motion performed by the participant.

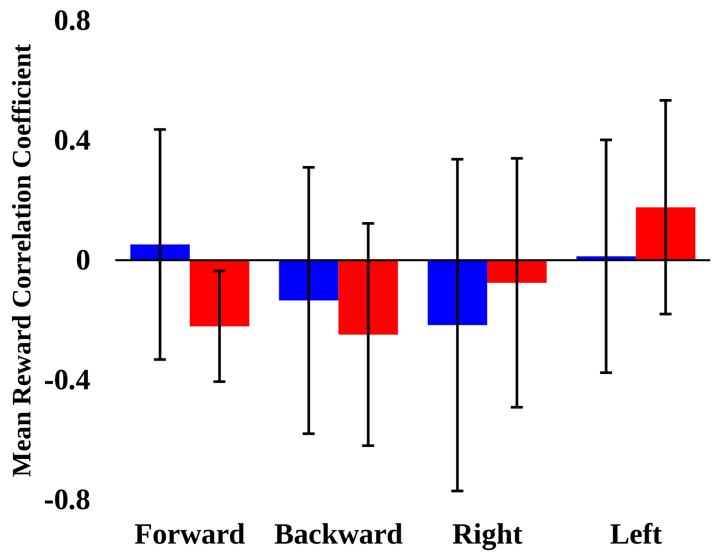


Figure 2. Acute effects of sub-motor threshold spinal stimulation on mean reward function correlation coefficient of ideal vs actual reward. Mean correlation coefficient and standard deviation without (blue) and with (red) stimulation during leaning in the indicated direction, n=6, Note the decreased variability with the presence of stimulation and the direction dependent effect on the reward function.

7.2.4 Discussion

This work deals with the problem of inverse reinforcement learning in large state spaces and solves the problem with a function approximation method that avoids solving reinforcement learning problems during reward learning. The simulated experiment shows that the proposed method is more accurate and scalable than existing methods and can extend existing methods to large state spaces as well as be applied to optimize stimulation parameters and training interventions in spinal cord injury rehabilitation.

Kinematically and kinetically, voluntary movement can be generalized as a goal-oriented task optimization constrained by physical limitations, such as range of motion and degrees of freedom, and coupled with an effort minimization function. Employing the use of an optimization-based controller provides the added benefits of generalizability and is a means to characterize task-oriented goals, i.e. rather than having to define a set number of means to perform a motion, an optimization occurs based on the functional result such as did: the COP trajectory travel in the instructed direction? In other words, the controller assess performance

In future work, we will remove the requirement of a-priori transition function by combining an environment model learning process into the function approximation framework. Furthermore, we can implement a weighted markov decision process to account for short-term costs versus long-term costs which could allow for a more accurate representation and further our understanding of the effect of training.[220] The weighted criterion can be used to discount short term costs for long term optimization of balance and would allow for a more flexible controller.[220] From a clinical perspective, future work should focus on relaying the weighted markov decision process to quantify the reward, i.e. accuracy of COP displacement, to the participant and 1) assess the impact on the effectiveness of seated training, 2) be extended in application to standing and other postural stabilization tasks, and 3) used intra-session to evaluate different stimulation parameters to determine optimal parameters to improve trunk control and postural stability.

Chapter 8: Conclusion

8.1 Scientific Contributions

8.1.1 Acute Effects of tSCS on Trunk Stability

The results demonstrate that, after more than two years following the onset of complete or partial paralysis, stimulation over the lumbosacral enlargement improved self-governing control of upright sitting. Spinal stimulation targeted similar networks to those that control rhythmic movements and upright standing, suggesting important functional and anatomical overlap between these systems. From a functional perspective, any strategy that can improve or regain sitting and postural control represents a substantial advancement for individuals with paralysis in their daily life activity.[95] The physiological implications of our findings are consistent with qualities that reflect independence, enhanced function of sensorimotor and autonomic systems, and improved quality of life of individuals with SCI. From a clinical perspective, our approach provides further evidence of the acute neuroplastic capacity of spinal and potentially supraspinal networks and provides a conceptional rationale for the development of a longer-term seated postural control protocol enabled by non-invasive spinal stimulation. The present results are indicative for planning an activity-based rehabilitation program for improving balance. Finally, this study highlights the importance of including assessments of postural-specific networks while seated, as outcomes that might be extrapolated to the potential to control standing.

8.1.2 Chronic Effects of tSCS on Trunk Stability

After chronic paralysis, self-regulated upright sitting can be recovered in the presence of non-invasive transcutaneous spinal cord stimulation over the lumbosacral enlargement. We observed changes in postural strategy from a visual-vestibular-somatosensory regulation to a more visual based strategy with stimulation before and after non-task specific training. We suggest that multisite spinal stimulation, can effectively engage and synergistically modulate postural networks and enhance motor pattern generation for quiet and dynamic sitting. From a functional perspective, the impact of these findings encompasses multiple functional systems that may contribute to the independence and quality of life and independence in individuals with SCI. From a clinical perspective, the data supports activity-dependent and non-invasive neuromodulatory interventions for rehabilitation and warrants further investigation on other potential benefits such as in standing, seated transfer, and locomotion.

8.1.3 Neuromusculoskeletal Model

The present work: 1) outlines a protocol for capturing 3D kinematic data and implementing neuromusculoskeletal models, 2) tool sets to capture the 3D kinematics using a low-cost sensor, the Xbox KinectOne sensor, 3) includes an open-source model for assessing human trunk and posture, and 4) includes a case example, a proof of concept, on how a global perspective of the model with mapped movements from the patient can aide training development and rehabilitation protocol. A custom theranostic neuromusculoskeletal model can be rapidly generated and used to evaluate a patient's seated performance as well as track improvement and identify asymmetries and suggest underlying muscle activity. Immediate next steps would include three main avenues: 1) synchronization of a two Kinect system for more accurate 3D kinematics, 2) long term study with seated training and its effects of training progress, and 3) modeling a patient's movements without and with spinal stimulation or other interventional therapies to characterize the effects. Form a long-term perspective, integration of the two-Kinect system, long-term assessment with training without and with interventional therapies will need to be combined into a database and using machine learning algorithms and principle component analysis, develop an automated approach to developing training protocols focused on progression and user-defined improvement parameters.

8.1.4 Challenging the Postural System and the effects of tSCS on Postural Control

After years following complete paralysis, self-assisted or minimally assisted standing was recovered by the enabling effect of non-invasive electrical neuromodulatory approach and improved using repeated training sessions. The observed functional and electrophysiological effects were similar qualitatively and quantitatively to those seen in experiments with epidural stimulation. The similarities between the non-invasive and invasive approaches are of critical importance in further exploration of the mechanisms of functional recovery following spinal cord stimulation therapies. The physiological impact of these findings encompasses multiple functional systems that may contribute to the independence and quality of life in a broad population of individuals with SCI. The present data demonstrate that extensive neuroplastic changes of spinal and potentially supraspinal networks can occur using the non-invasive neurostimulation intervention while engaging sensory inputs associated with a motor task. These data are consistent with a growing body of evidence of the potential for functional recovery of multiple physiological systems years after the onset of severe paralysis when treated with a combination of activity-dependent and neuromodulatory interventions.

8.1.4 Seated Reward Function

This work deals with the problem of inverse reinforcement learning in large state spaces and solves the problem with a function approximation method that avoids solving reinforcement learning problems during reward learning. The simulated experiment shows that the proposed method is more accurate and scalable than existing methods and can extends existing methods to large state spaces. A clinical application of the proposed method is in characterizing dynamic seated trunk movement during multi-directional leaning and has functionality beyond the directed task as a means for assessing long term functional improvement and help optimize intervention methods. In future work, we will remove the requirement of a-priori transition function by combining an environment model learning process into the function approximation framework.

8.2 Future Directions

The long-term objective for the next steps outlined in each scientific contribution is to develop an automated tool set that can optimize stimulation parameters and intervention methods, suggest training protocols based on limitations identified in the neuromusculoskeletal model, and quantify patient's ability during quiet and dynamic seated tasks thereby tracking patient rehabilitation progress. The resultant end technology and software are novel in that they end-to-end software can be distributed to any clinic and serve as an assistive device for training, including, but not limited to, individuals with spinal cord injury or motor disorders, or able-bodied individuals seeking improved trunk and postural control.

Noninvasive Enabling Strategies

The immediate next steps are to extend the study design to include additional participants as well as an able-body control group. This will allow for a multifactorial ANOVA design with task specificity necessary to quantify the training effect. Furthermore, a blinded cross over study design implemented with and without training and with and without the presence of stimulation can elucidate the effects of each and provide insight into developing more optimal rehabilitation therapies and intervention methods.

Neuromusculoskeletal Modeling

The immediate next steps are to provide the digitized patient performance data and custom neuromusculoskeletal models to OpenSim community/ Biomechanics modeling lab for further model implementation and development. These developments include, but are not limited to, using the computed muscle control protocol and comparing the results obtained from the studies detailed above to the kinematic data to the obtained experimental EMG data. This serves three functions: first it serves as a validation method to test model accuracy and can be used to update the settings to identify excitation parameters; second, the validated model can be used to then design, implement and test trunk stiffness estimation parameters and other relevant parameters by using experimental vs stimulated data; third, a refined NMS model can be then used to perform forward dynamic stimulations to quantify and assess how changing parameters such as force generation capabilities, stiffness, range of motion, and more can effect kinematic output. This allows for a forward predictive patient specific model to identify kinematic limitations in the participant population, design and test rehabilitation programs (training, stimulation, and other intervention methods that affect movement can be incorporated) that will result in the most functional movement related to a task and general movement ability.

Chapter 9: Appendix

9.1 Supplementary Tables

9.1.1 Supplementary Table 1. Clinical characteristics

Participant	AIS					
	NLI	Grade	UEMS	LEMS	LT	PP
P1	T4	A	50	0	44	44
P2	T2	A	50	0	36	36
P3	T9	A	50	2	66	66
P4	T2	A	50	0	36	36
P5	C4	C	28	0	84	84
P6	T3	A	50	0	42	42
P7	C5	C	42	13	80	70
P8	T3	A	50	0	42	40

NLI – Neurological level of injury; AIS – American spinal injury association scale (AIS) classification; UEMS – upper extremity motor score; LEMS – lower extremity motor score; LT – light touch; PP – pin prick.

9.1.2 Supplementary Table 2. Mean EMG activity during multi-directional leaning

EMG (mV) – FORWARD

PARTICIPANT	No Stimulation					Stimulation				
	E-T7	**E-L3**	**Obl**	**RA**	**RF**	**E-T7**	**E-L3**	**Obl**	**RA**	**RF**
P1	0.0828	0.1158	0.1938	0.1214	0.1835	0.1716	0.2198	0.1049	0.0807	0.1491
P2	0.0700	0.0445	0.0602	0.5919	0.2053	0.0358	1.9557	0.3930	0.0552	0.2366
P4	0.1026	0.0166	0.0218	0.0512	0.0844	0.0473	0.3598	0.1384	0.1168	0.1035
P5	0.0323	0.0401	0.0180	0.1242	0.0728	0.2038	0.1118	0.1114	0.2171	0.1047
P6	0.1080	0.0621	0.1290	0.1203	0.0728	0.2038	0.1118	0.1114	0.2171	0.1047
P7	0.0557	0.0256	0.0292	0.0364	0.0706	0.2107	0.4081	0.2105	0.0979	0.0753
P8	0.0646	0.0152	0.0120	0.0328	0.0234	0.0892	0.8149	0.0907	0.1399	0.0471

EMG (mV) – BACKWARD

PARTICIPANT	No Stimulation					Stimulation				
	E-T7	**E-L3**	**Obl**	**RA**	**RF**	**E-T7**	**E-L3**	**Obl**	**RA**	**RF**
P1	0.0591	0.0812	0.1588	0.1019	0.1541	0.1759	0.2237	0.1202	0.0863	0.1372
P2	0.0362	0.0388	0.0193	0.0645	0.1821	0.0405	1.9902	0.4814	0.0245	0.2113
P4	0.0595	0.0128	0.0173	0.0379	0.1183	0.0590	0.4147	0.1716	0.1466	0.1405
P5	0.0880	0.0446	0.0163	0.1904	0.0721	0.2304	0.1326	0.1414	0.2073	0.0953
P6	0.0543	0.0476	0.0951	0.0446	0.0721	0.2304	0.1326	0.1414	0.2073	0.0953
P7	0.0484	0.0190	0.0276	0.0540	0.0445	0.1848	0.4133	0.2095	0.0989	0.0662
P8	0.0436	0.0060	0.0053	0.0091	0.0108	0.0790	0.8046	0.0988	0.1964	0.0463

EMG (mV) – RIGHT										
PARTICIPANT	**No Stimulation**					**Stimulation**				
	E-T7	**E-L3**	**Obl**	**RA**	**RF**	**E-T7**	**E-L3**	**Obl**	**RA**	**RF**
P1	0.0793	0.0875	0.1519	0.1000	0.1465	0.1682	0.2127	0.1092	0.0785	0.1388
P2	0.0680	0.0376	0.0141	0.0716	0.1895	0.0375	1.8866	0.5125	0.0258	0.1686
P4	0.0687	0.0114	0.0140	0.0313	0.1138	0.0339	0.2541	0.0875	0.0852	0.1357
P5	0.0697	0.0320	0.0158	0.1343	0.0921	0.0780	0.1264	0.0520	0.1908	0.1096
P6	0.0527	0.0336	0.0656	0.0639	0.0033	0.1903	0.1264	0.0520	0.1908	0.0241
P7	0.0298	0.0184	0.0216	0.0296	0.0494	0.1932	0.4605	0.2129	0.1130	0.0762
P8	0.1835	0.0931	0.1129	0.1879	0.0763	0.0701	0.6897	0.1141	0.1340	0.0449

EMG (mV) – LEFT										
PARTICIPANT	**No Stimulation**					**Stimulation**				
	E-T7	**E-L3**	**Obl**	**RA**	**RF**	**E-T7**	**E-L3**	**Obl**	**RA**	**RF**
P1	0.0859	0.0843	0.1571	0.1042	0.1539	0.1702	0.2142	0.1043	0.0783	0.1346
P2	0.0534	0.0397	0.0217	0.0700	0.2063	0.0349	1.7669	0.4001	0.0606	0.2564
P4	0.0754	0.0138	0.0185	0.0391	0.1152	0.0424	0.2996	0.1272	0.1027	0.1472
P5	0.0857	0.0349	0.0212	0.1651	0.0831	0.1923	0.1236	0.0519	0.1664	0.0800
P6	0.1058	0.0413	0.1189	0.0698	0.0831	0.1923	0.1236	0.0519	0.1664	0.0800
P7	0.0816	0.0270	0.0199	0.0306	0.0484	0.2152	0.4426	0.2438	0.1081	0.0682
P8	0.0145	0.0027	0.0030	0.0046	0.0061	0.0218	0.0199	0.0241	0.0388	0.0107

E-T7 – erector spinae level T7; E-L3 – erector spinae level L3; Obl – external obliques; RA – rectus abdominis; RF – rectus femoris

Note: P3 was omitted due to a neurological level of injury of T9 and was not included in the EMG calculations.

9.1.3 Supplementary Table 3. EMG activity during multi-directional leaning Wilcoxon Signed Rank Test Statistics

		E-T7	**E-L3**	**Obl**	**RA**	**RF**
Forward	Z	1.4176	2.4181	1.6009	0.8872	1.0774
	P	0.1560	0.0156	0.1094	0.3750	0.2813
	rank	23	28	24	20	21
Back	Z	2.1532	2.4181	2.1532	1.6009	2.1532
	p	0.0313	0.0156	0.0313	0.1094	0.0313
	rank	27	28	27	24	27
Right	Z	0.5562	2.4181	2.4181	2.1532	2.4181
	p	0.5781	0.0156	0.0156	0.0313	0.0156
	rank	18	28	28	27	28
Left	Z	1.4176	2.4181	1.0431	1.4176	1.0774
	p	0.1563	0.0156	0.2969	0.1563	0.2813
	rank	23	28	21	23	21

9.1.4 Supplementary Table 4. Clinical characteristics and anthropometrics of chronic study participants

Participant ID	Sex	NLI	AIS Grade	Age (yrs)	Height (cm)	Body Mass (kg)	Post-SCI (yrs)	Stimulation Intensity Threshold (mA)		Stimulation Intensity Used (mA)	
								T11 30 Hz	L1 15 Hz	T11 30 Hz	L1 15 Hz
P1	M	T4	A	25	180	91	8	50	60	40	50
P2	M	T2	A	23	169	80	6	140	120	100	80
P3	M	T9	A	26	156	50	3	110	80	100	60
P4	M	T2	A	26	157	57	9	40	15	25	5
P5	M	T3	A	30	188	84	11	70	70	60	65
P6	M	T6	A	26	188	59	5	85	125	80	120

NLI – Neurological level of injury; AIS – American spinal injury association scale (AIS) classification

9.1.5 Supplementary Table 5. Clinical characteristics of chronic participants

Participant	AIS					
	NLI	**Grade**	**UEMS**	**LEMS**	**LT**	**PP**
P1	T4	A	50	0	44	44
P2	T2	A	50	0	36	36
P3	T9	A	50	2	66	66
P4	T2	A	50	0	36	36
P5	T3	A	50	0	42	42
P6	T6	A	45	0	30	56

NLI – Neurological level of injury; AIS – American spinal injury association scale (AIS) classification; UEMS – upper extremity motor score; LEMS – lower extremity motor score; LT – light touch; PP – pin prick.

9.1.6 Supplementary Table 6. Mean EMG activity during multi-directional leaning

		EMG (mV) – MEAN							
		No Stimulation					**Stimulation**		
		E-T7	**E-L3**	**Obl**	**RA**	**RF**	**E-T7**	**E-L3**	**Obl**
RIGHT	Pre	0.17	0.08	0.09	0.21	0.06	0.19	0.73	0.45
	Post	0.10	0.04	0.06	0.19	0.06	0.12	0.73	0.34
LEFT	Pre	0.18	0.06	0.12	0.18	0.06	0.19	0.59	0.44
	Post	0.11	0.04	0.08	0.29	0.06	0.12	0.69	0.28
FORWARD	Pre	0.18	0.07	0.07	0.26	0.06	0.19	0.70	0.46
	Post	0.10	0.04	0.08	0.24	0.06	0.11	0.70	0.31
BACKWARD	Pre	0.13	0.08	0.09	0.33	0.06	0.20	0.72	0.44
	Post	0.13	0.04	0.08	0.34	0.06	0.12	0.73	0.28

E-T7 – erector spinae level T7; E-L3 – erector spinae level L3; Obl – external obliques; RA – rectus abdominis; RF – rectus femoris

Note: P3 was omitted due to a neurological level of injury of T9 and was not included in the EMG calculations.

9.2 Supplementary Videos

Videos are synchronized with the center of pressure (COP) recordings.

9.2.1 Supplementary Video 1. Video exemplifying stimulation intensity adjustment in participant P5 (AIS C, C4, 7 years post-injury) during the preliminary experiment. (https://www.liebertpub.com/doi/suppl/10.1089/neu.2017.5584/suppl_file/Supp_Video1.mov) The participant was instructed to sit quietly with eyes open, and to minimize the use of his arms to maintain sitting posture. Note "slouching" seated posture without spinal stimulation, followed by trunk extension during stimulation starting at an intensity of 55 mA (motor threshold) at approximately 14 seconds into the video. The sub-motor threshold stimulation intensity of 50 mA was used in the subsequent main experiments. The center of pressure (COP) time series in the anteroposterior (blue trace) and mediolateral (red trace) directions are presented in the top right panel. The resultant COP trajectory is presented in the bottom right panel.

9.2.2 Supplementary Video 2. The dynamic stability test in participant P6 (AIS A, T3, 10 years post-injury). (https://www.liebertpub.com/doi/suppl/10.1089/neu.2017.5584/suppl_file/Supp_Video2.mov) Eight targets were presented, separately, for 5 seconds on the monitor placed in front of the participant. The participant was asked to move the COP indicator as close to each target as possible without losing balance, hold the position unassisted during that time, and return back to the starting position. The task was performed without (left panel) and in the presence (right panel) of spinal stimulation delivered at the sub-motor threshold intensity. The COP trajectories are presented in the bottom panels. Note improved trunk control and an increase in the limits of stability in all directions in the presence of sub-motor threshold stimulation.

9.2.3 Supplementary Video 3. Self-initiated perturbations in participant P8 (AIS A, T3, 6 years post-injury). (https://www.liebertpub.com/doi/suppl/10.1089/neu.2017.5584/suppl_file/Supp_Video3.mov) The participant was instructed to rapidly extend the right arm forward from his side to a fully extended position, then return the arm back to the initial position based on verbal cues. The task was performed without external assistance without (first 25 seconds) and in the presence (last 23 seconds) of spinal stimulation delivered at the sub-motor threshold intensity. The COP time series in the anteroposterior (green trace) and mediolateral (blue trace) directions are presented in the bottom panel. Note that, without spinal stimulation, all attempts resulted in falls, whereas, in the presence of sub-motor threshold stimulation, the same task was performed without losing balance.

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