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Case Report

Short-term Cortical Plasticity Associated With Feedback-Error Learning After Locomotor Training in an Individual With Incomplete Spinal Cord Injury

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Abstract

Background and Purpose: For rehabilitation strategies to be effective, training should be based on principles of motor learning, such as feedback-error learning, that facilitate adaptive processes in the nervous system by inducing errors and recalibration of sensory and motor systems. This case report suggests that locomotor-resistance training can enhance somatosensory and corticospinal excitability, and modulate resting-state brain functional connectivity in a person with motor-incomplete spinal cord injury (iSCI).

Case Description: Short-term cortical plasticity of a 31-year old man who had sustained an iSCI 9.5 years ago was examined in response to body-weight support treadmill training with a velocity-dependent resistance applied by the Lokomat robotic gait orthosis. The following neurophysiologic and neuroimaging measures were recorded before and after training. Sensory-evoked potentials were elicited by electrical stimulation of the tibial nerve, and recorded from the somatosensory cortex. Motor-evoked potentials were generated using transcranial magnetic stimulation applied over the tibialis anterior representation within the primary motor cortex. Resting-state functional magnetic resonance imaging (fMRI) was collected to evaluate short-term changes in patterns of brain activity associated with locomotor training.

Outcomes: Somatosensory and corticospinal excitability were observed to increase following the locomotor-resistance training. Motor-evoked potentials were increased (particularly at higher stimulation intensities), and seed-based resting-state fMRI analyses revealed increased functional connectivity strength within the motor cortex associated with the less affected side following training.

Discussion: Our observations suggest evidence of short-term cortical plasticity after one session of locomotor-resistance training in three complementary neurophysiologic measures. Future

investigation in a sample of individuals with iSCI will enhance our understanding of potential neural mechanisms underlying behavioral response to locomotor-resistance training.

Background

Gait retraining strategies after neurological injury have been focused on body-weight support treadmill training (BWSTT) approaches that provide repetitive movement of the legs through the gait cycle, which is enabled by the treadmill and assisted by therapists or robotic devices.[1, 2] These approaches support motor learning theory underpinnings, such as task-specific practice, by providing locomotor-related sensory cues through feedback pathways to facilitate the production of appropriate muscle activation patterns.[3, 4] Loading through the legs during stance provides sensory input facilitating the production of extensor muscle activity, [4-6] while hip flexor stretch at late-stance facilitates the initiation of the swing phase.[7] However, guiding the limbs through the 'correct' gait movements may not adequately challenge the motor control system for neurological adaptation to enable better functional ambulation.[8]

Feedback-error learning is based on the evidence that sensory and motor neural networks can adapt in response to performance errors during training. Afferent feedback pathways provide information to the central nervous system (CNS) for error detection and adaptation of motor programs.[9] Short-term locomotor adaptations have been observed after repeated exposure to an altered movement environment, and as a result persistent changes in afferent input are thought to be mediated by feedback-error learning.[9] BWSTT can be combined with feedback-error learning by applying resistance to lower limb flexion movements. The addition of resistance would enhance activation of length- and load-sensitive receptors in the flexor muscles.[10] Similar to the effect of load on extensor motor neurons, this may produce sustained excitatory drive to flexor motor neurons through afferent feedback pathways.

Short-term locomotor adaptations to a robot-applied resistance has produced high stepping or longer stride after-effects in people with motor incomplete spinal cord injury (iSCI).[11-13] After 3 months of training, these after-effects were transferred to over-ground stepping when examined immediately after a training session.[14] Other indices of over-ground ambulatory capacity (e.g. 10 Meter Walk Test; 10MWT) and more complex walking tasks (e.g. obstacle crossing, stair climbing, etc) also improved after training.[14]

Feedback-error learning from training with resistive-force fields has been proposed to adapt functionally-specific sensory and motor areas of the brain. Real-time changes in motor cortex excitability in response to different task demands (e.g. locomotor resistance or assistance) reveal the adaptive nature of muscle-specific pathways.[15, 16] Motor learning following upper limb resistance training also involves adaptations in somatosensory function, as evidenced by changes in the response amplitude to a sensory-evoked potential (SEP).[17] These findings of adapted pathways are complemented by evidence of more specific changes in sensory and motor cortical regions associated with motor learning. Parietal, frontal, and cerebellar networks have demonstrated greater functional connectivity during resting-state functional magnetic resonance imaging (fMRI) after 1-hour of upper limb resistance training. The connectivity strength of these neuronal networks was related to improved behavioral measures of motor learning.[18] Thus, neurophysiologic and resting-state fMRI measures can be used to determine how locomotor-resistance training adapts sensory and motor networks through feedback-error learning. This case report explored whether locomotor-resistance training could enhance somatosensory and corticospinal excitability along with resting-state functional connectivity as indices of short-term adaptations following feedback-error learning in a person with motor-iSCI.

Case Description: Patient History and Review of Systems

The patient was a 31-year old man (height = 170 cm, weight = 60 kg) who sustained a traumatic motor-incomplete SCI at C5 (American Spinal Injury Association Impairment Scale; ASIA C) following a fall 9.5 years ago. His ASIA lower extremity motor score (LEMS) was 5/25 (right) and 18/25 (left), light touch was 34/56 (right) and 34/56 (left), and pin prick was 34/56 (right) and 36/56 (left). The Walking Index for Spinal Cord Injury Scale (WISCI II) was scored at 9. He was completely independent with activities of daily living, primarily using a power wheelchair for indoor and outdoor mobility, but was able to stand and walk indoors for short distances with a walker and Dictus brace (provides dorsiflexion assist; Dictus®, Henderson, NV) on the right. His self-selected comfortable walking speed was 0.18 m/s, as measured using the 10MWT. He had no significant medical history and was not taking prescription medications. The individual's goals are to improve ambulatory capacity and more complex walking skills. He was practicing walking short distances on a daily basis using parallel bars or a wheeled-walker.

This individual's limited ambulatory capacity combined with his residual motor function made him an ideal candidate for this approach. He also had previous experience with BWSTT on the Lokomat robotic gait orthosis (Hocoma AG, Volketswil, Switzerland) 2 months prior to our testing. This demonstrates his ability to physically tolerate locomotor training. We performed a session of unassisted BWSTT and quantitatively measured his lower limb flexor muscle strength to further determine the appropriateness of this approach. The individual in this study provided written informed consent. All procedures were approved by the University (Blinded) Ethics Board.

Examination

We measured the participant's maximum voluntary contraction (MVC) for hip and knee flexor muscles, bilaterally, using isometric strength testing with the Lokomat L-Force feature.[19] Three trials were repeated to calculate an average MVC per joint. Positive force values were recorded from all joints (left hip: 15.7 N; left knee: 20.8 N; right hip: 7.9 N; right knee: 1.3 N). The individual also performed 20 minutes of unassisted BWSTT at 1.1 km/hr with 10 kg of body-weight support so that we could record his baseline hip and knee kinematic trajectories during treadmill walking. These data **were** subsequently used to calculate the amount of resistance applied by the Lokomat; see approach. The individual reported a score of 5, indicating 'hard', on the Borg CR-10 Scale measuring rate of perceived exertion after the session.

Based on this examination, it was determined that the individual had sufficient lower-limb strength and was able to physically tolerate 20 minutes of unassisted BWSTT, confirming his capability to undergo this approach.

Clinical Impression

Given the individual's goal of improving functional ambulation and results from the examination data, he is an appropriate candidate to apply feedback-error learning through locomotor-resistance training. We evaluated changes in sensory and motor neural pathways in response to feedback-error learning using neurophysiologic (SEPs and motor-evoked potentials; MEPs) and fMRI measures. If locomotor-resistance training is a successful approach of feedback-error learning, we propose that SEPs and MEPs will show facilitation of neural pathways, and greater resting-state functional connectivity will be observed in sensory and motor cortical areas.

Approach

Locomotor Training

Our study examined the effect of a single bout of locomotor resistance training on neurophysiological outcomes. Due to the time demands of conducting our evaluations, we obtained SEP and fMRI recordings before and after session #1, and MEPs recording before and after session #2. Each session was 30-minutes of BWSTT with the Lokomat; scheduled 25 days apart.

The BWSTT was implemented using customized software control of the Lokomat robotic gait trainer. The drives were programmed to apply a velocity-dependent moment against both hip and knee sagittal-plane movements throughout the step cycle. The instantaneous torques (M) applied to hip (h) and knee (k) joints were calculated as:

$$\begin{bmatrix} M\mathrm{h} \\ Mk \end{bmatrix} = -\begin{bmatrix} Bh & 0 \\ 0 & Bk \end{bmatrix}\begin{bmatrix} \theta\mathrm{h} \\ \theta k \end{bmatrix}$$

where B_h and B_k are the corresponding viscous coefficients (N·m·s/rad) and θ_h and θ_k are the angular velocities (rad/s) of the hip and knee, respectively.[14] Data from the unassisted BWSTT session were used to determine the hip and knee angular velocity during swing from the time between the onsets of hip flexion and extension using a custom Matlab program. The average angular velocities of the hip and knee (θ_h and θ_k) during swing were used to determine the desired B values. The amount of resistance (M_h and M_k) was defined as 10% of MVC. Because the resistance is velocity-dependent, its effect will be greatest during the swing phase, leading to error detection via afferent feedback pathways to the CNS, and modification of the locomotor commands to enhance flexor muscle activity to overcome the resistance.[9, 10]

Locomotor-resistance training was conducted at 1.1 km/h, the fastest speed tolerated by the participant, with 10 kg body-weight support. During the training, the subject was allowed to use his upper extremity on the hand-rails for balance and light support, if needed. The individual reported his rate of perceived exertion on the Borg CR-10 Scale after training. We monitored heart rate and blood pressure response to training.

Neurophysiological Measurement

SEPs were conducted before and after the first training session with 2.5 hours between training and post-testing. SEPs were derived from square wave pulses (0.5ms duration) delivered through surface electrodes to the tibial nerve in the popliteal fossa (GRASS SD9 Stimulator with SIU-V Isolation Unit, West Warwick, RI.) with the participant seated. Stimuli were delivered at 2 Hz for a total of 300 stimulations for 3 different conditions: sensory-, motor- and 150% motor-threshold. Intensity was set to the minimum stimulator output required to 1) produce sensation distal to the stimulation site, 2) produce a small muscle twitch (motor threshold), and 3) 150% of the motor threshold, respectively. Electroencephalographic (EEG) data were recorded from the Cz, CPz, AFz, C1-C4, and CP1-CP4 electrode sites (64-channel NeuroConn GmbH, Neuro Prax® MR DC-EEG, Germany) in accordance with the international 10–20 system for electrode placement, and referenced to the right mastoid. Impedance was kept below 5 kΩ. EEG data were amplified (20,000), notch filtered at 50 Hz and digitized (2000 Hz) before being stored for off-line analysis. SEPs were extracted using the EEGLab toolbox (Institute for Neural Computation, University of California – San Diego, CA) for MATLAB (Matlab V2009, The MathWorks, Natick, MA) by averaging baseline corrected epochs time locked to stimulation (within -100 to 200ms) after rejecting trials with any visually identified artifact. SEP amplitude was measured as the difference between the negative 50 component and mean baseline activity.

Resting-state fMRI was conducted before and after the first training session with 1.5 hours between training and post-testing. A single resting-state fMRI scan shot EPI sequence (TR = 2000ms, TE: 30ms, flip angle θ = 90°, voxel dimension = $3mm^3$ with 1mm gap, 36 slices, FOV 240 x 240mm, scan time= 8.2min/scan) was recorded with the subject lying supine and eyes fixed on a visual stimulus. The subject was instructed to think of nothing in particular and not to fall asleep. Scanning during rest allowed examination of functional connectivity between the motor cortex and other CNS areas without the influence of a specific task. Resting-state fMRI data processing and analysis was carried out using the Data Processing Assistant for Resting State fMRI (DPARSF v2.3, http://www.restfmri.net/forum/DPARSF),[20] a Matlab plug-in based on Statistical Parametric Mapping (http://www.fil.ion.ucl.ac.uk/spm),[21] and Resting-state fMRI Data Analysis Toolkit (http://www.restfmri.net).[22] For data processing, the first 10 time points were discarded and slice timing and head motion correction were performed. Functional data were then co-registered to the T1 anatomical image (TR= 7.7ms , TE: 3.5ms, flip angle θ = 8° , voxel dimension = $1mm^3$, 170 slices, FOV: 256mm , scan time= 191sec), and resampled to a 3mm isotropic voxel resolution before normalization into Montreal Neurological Institute (MNI) template space. These data were smoothed using a 4mm FWHM Gaussian kernel, the linear trend of the time courses was removed and temporally bandpass filtered (0.01-0.08Hz). Nuisance covariates (six head motion parameters, global signal, white matter signal and cerebrospinal signal) were regressed from the processed data prior to functional connectivity analysis. A spherical region of interest (ROI) seed was placed within the right (MNI coordinates: x=8, y=-42, z=66; radius: 6mm) and left (MNI coordinates: x=-8, y=-42, z=66; radius: 6mm) motor cortex associated with the motor representation of the contralateral lower extremity. Functional connectivity was quantified for each seed ROI as the linear correlation of the time course between the seed ROI and each voxel within the brain.

MEPs were conducted immediately before and after the second training session. MEPs were elicited while the participant was seated. Surface electromyography (EMG) was recorded bilaterally from the tibialis anterior. EMG recordings were amplified (2000) and band-pass filtered (1–200 Hz) before being digitized (1000 Hz). Transcranial magnetic stimulation (TMS) was delivered with a 70-mm double cone coil (Magstim Super Rapid², Magstim Company, Ltd) to the leg motor cortex. The optimum site to elicit a MEP was determined and marked on the individual's head with a washable marker. The participant was asked to maintain a background activity of approximately 10% of his maximum voluntary contraction (determined by manual muscle testing with a physical therapist). The background EMG was measured as the mean of the rectified EMG signal at 50ms prior to the TMS pulse to verify no changes occurred from pre- to post-training. A recruitment curve was generated by applying stimuli in 10% increments of stimulator output in sequential order, starting from below motor threshold to maximum MEP amplitude.[16] Five stimuli were delivered at each intensity with a 5-sec inter-stimulus interval, and rest period between intensity levels. Average peak-to-peak MEP amplitudes were calculated for each intensity level.

Outcomes

The participant was able to physically tolerate locomotor training with resistance. His rating of perceived exertion was 7 ("very hard") after both training sessions. Average resting heart rate and blood pressure was 76 bpm and 130/70 mmHg, respectively. Locomotor training increased heart rate and blood pressure to 92 bpm and 147/83 mmHg in the last five minutes, respectively. Heart rate and blood pressure returned to 82 bpm and 124/80 mmHg at five minutes post-training respectively.

Figure 1 shows the average hip and knee joint angles during the gait cycle for with and without resistance (also see the video clip).

Session #1 Results

Prior to training, the sensory threshold for the right leg was at the maximum stimulator output. At this intensity, a palpable muscle twitch distal to the stimulator indicated the motor threshold had also been reached; therefore no further stimulation intensities could be tested. We observed a negative response at Cz approximately 50 ms after stimulation (Figure 2a). During the post-training assessment, SEPs for both sensory and motor thresholds were reduced in the right leg and we could test stimulation intensities at up to 150% motor-threshold. SEPs demonstrated changes at Cz with visualization of a negative component at 50 ms for each condition. The amplitude of the N50 component was greater at the SEP motor- and 150% motor-thresholds (Figure 2b). The participant did not show any observable changes in SEP response on the left leg for sensory and motor thresholds.

Before training, resting-state fMRI-based correlation analyses showed greater intrahemispheric and interhemispheric homotopic functional connectivity for the left compared to right leg representation in the motor cortex. Following training, increased local intrahemispheric and decreased interhemispheric homotopic functional connectivity strength was observed for the right motor cortex seed. The functional connectivity topography and strength for the left cortex seed region was largely unchanged following training (Figure 3).

Session #2 Results

Average peak-to-peak MEP amplitudes increased with higher stimulator intensities for the left leg. Post-training peak-to-peak MEP amplitudes were higher than pre-training for most stimulator intensities, in particular at the highest level (Figure 4). Before and after training, no MEPs could be elicited from the right leg.

Discussion

This case report demonstrates how feedback-error learning can be implemented with BWSTT in persons with iSCI to challenge locomotor control and adapt CNS mechanisms. Feedback-error learning has been applied by locomotor-resistance training in healthy adults and individuals with iSCI,[12, 14, 15] however, our case study is the first to examine how this approach supports neurophysiological underpinnings of motor learning theory after CNS injury. We observed short-term changes in cortical activity after a session of Lokomat training with resistance, suggesting sensorimotor adaptations in response to activation of afferent feedback pathways. This approach suggests that exposure to walking in an altered movement environment, such as resistive forces, changes sensory and motor representations of the lower limb to recalibrate an appropriate motor program.[9]

Prior to training, it was difficult to elicit SEPs from the participant, whereas both sensory and motor responses demonstrated larger amplitudes in the leg motor cortex area after training. A possible explanation for this finding is increased transmission in spinal feedback pathways from proprioceptive muscle afferents leading to facilitation of sensorimotor pathways.[23] A change in somatosensory function after feedback-error learning seems possible due to direct connections between somatosensory areas and the primary motor cortex,[24-26] along with other motor areas in the brain.[27] SEP changes on the right side may possibly reflect the sparing of sensory tracks, even though no MEPs could be produced. Recent evidence shows that motor learning produces changes in sensory function, in terms of a larger SEP magnitude and enhanced sensorimotor connectivity, following resistance training of an upper limb motor task in healthy adults.[17, 18] Importantly, these changes were not observed among subjects practicing the motor task without resistance or during passive movements (without motor activation).[17, 18] It seems probable that the increased SEPs detected in our study may be specific to the effect of resistance, thus aligned with the theory that resistance drives error feedback along sensory pathways to the CNS.

An important finding demonstrated by our study participant was larger MEP amplitudes after performance of resistance training, indicating enhanced excitability of the corticospinal tract to the leg muscles. These findings are consistent with role of the primary motor cortex and corticospinal tract in modulating locomotor adaptations.[16] Barthelemy et al showed that MEPs in the tibialis anterior muscle could be modulated by locomotor adaptations to forces around the ankle in able-bodied adults.[15] Application of a force that assisted ankle dorsiflexion resulted in MEP suppression, while resistive forces resulted in MEP facilitation during walking. As well, locomotor adaptations to walking with the Lokomat (compared to regular treadmill walking) include increased amplitude of MEPs elicited in the knee flexors.[16] We also observed increased MEPs (recorded while the participant was seated) after only one training session. Such enhanced corticospinal excitability could underlie the retention of motor adaptations that we have previously observed after months of Lokomat-resistance training.[28] Facilitation of the corticospinal pathway from the primary motor cortex provides evidence of successful application of feedback-error learning.

While primary motor cortex projections through the corticospinal tract could be accessed by TMS, resting state fMRI provides the opportunity to characterize changes in the functional connectivity of motor cortex with other CNS areas related to motor learning and walking function. Resting-state fMRI activity patterns revealed alterations in functional connectivity after training between the leg motor cortical representations and adjacent cortical regions, and homotopic regions in the contralateral hemisphere, primarily for the right motor cortex. These changes may be linked to underlying short-term neural modulation, such as improved synaptic efficiency, from exposure to the resistive forces during training. Our findings are similar to a previous study showing functional connectivity changes in the cerebellar cortex, parietal and frontal motor areas following exposure to resistive forces during an upper limb motor task.[18] Specifically, they reported that changes in connectivity between the cerebellar cortex and frontal motor areas (primary motor cortex and supplementary motor area) were dependent on motor learning.[18] Adapted sensorimotor relationships through learning to correct for resistive forces can be retained after training. Our measures of short-term cortical plasticity may reflect modulation of both sensory and motor pathways in response to locomotor adaptations derived from feedback-error learning. We also observed greater changes for the right motor cortex seed (associated with the less affected side) compared to the left motor cortex, suggesting that functional connectivity may depend on the integrity of preserved corticospinal tracks (our participant had more severe motor impairments in the right lower limb**.** It is also interesting to speculate if the observed increase in local connectivity strength in the right sensorimotor regions may be related to the observed increases in both motor and sensory-evoked potentials following training. It may be possible that increasing local connection strength could have a summative effect that contributes to the observed increases in evoked potentials. A future direction for this work will be to examine whether resting-state functional connectivity is correlated with measures of sensorimotor excitability, and how these measures may relate to behavioral assessments of sensorimotor impairment in SCI.

It has been proposed that adaptation through feedback-error learning depends on both sensory and motor systems. Motor learning can stem from changes in motor commands, sensory feedback, or both in combination. One possibility is that motor learning involves adjustments to motor commands that recalibrate the central contribution with subsequent downstream effects that augment proprioceptive feedback. Another possibility is that feedback-error learning involves a recalibration of both sensory and motor systems.[18, 29] Previous evidence shows that active involvement in the production of movement is required to properly engage the feedback-error pathways.[29]

Due to the nature of a case report, it is impossible to determine whether BWSTT alone (without resistance) would have the same result as locomotor training with resistance. Because this locomotor resistance paradigm is a relatively novel activity for our study participant, it is possible that any type of extended or intense locomotor training compared to his usual daily routine may enhance sensorimotor pathways. It is important to note that previous studies have reported differences in behavioral and neural indices of motor adaptation between subjects training with and without resistance for a novel upper limb motor task.[18, 29] While adaptations to locomotor behavior have been reported for this paradigm in able-bodied adults and CNS injury populations,[12, 14, 30] future research should focus on understanding neural mechanisms after long-term training in combination with observations on functional improvements to confirm how feedback-error learning theory is applied through locomotor-resistance training.

Although this case report provides important information about how locomotor-resistance training supports feedback-error learning, there are several limitations that need to be addressed. Due to time constraints we did not perform repeated baseline assessments to ensure stability in the neurophysiological measures before the intervention. While there is inherent variability in these outcomes, we took precautions to reduce variability from the environment and investigators. However, changes in the individual’s arousal state may influence the findings. Future controlled studies are warranted to determine the benefit of locomotor-resistance training with blinded assessors and a sham condition. During data collection, resistance may have changed between reapplication of the electrodes for the SEPs, and may explain the reduced sensory and motor stimulation thresholds at post-training. We were unable to match M-wave amplitudes between pre- and post-training evaluations, thus changes in current delivery may have influenced SEP amplitude. Although, we attempted to control for this potential confound by re-establishing stimulation thresholds prior to SEP recording at each session. We used manual palpation to determine the appropriate level of background EMG while eliciting MEPs. When interpreting changes in MEP amplitudes during post-training we cannot discount the possibility that the slight increase in background EMG at 80% maximum stimulator output may have impacted the resultant MEP amplitude. However, a previous study has reported similar maximum MEP amplitudes for background contractions of 10–40% of maximum voluntary effort.[31] It is also possible that we may have generated different recruitment curves had we employed a random rather than a serial stimulation approach. However, we used the same approach both before and after the intervention thus it is unlikely that order effects impacted the results. In addition, the subject used his upper extremity to provide light support during the swing phase, mostly with the more affected side, similar his compensatory strategies for overground walking. Use of the upper extremity for support may have reduced the load on the extensor muscles during training. However, it is unlikely to impact activation of the flexor muscles and the response to the added resistance.[2, 10]

In summary, this case report has shown that locomotor-resistance training may be a successful approach to implement feedback-error learning theory for gait rehabilitation strategies after iSCI. These data suggest that changes in resting state functional connectivity, SEPs, and MEPs can be detected after one training session and may be sensitive to the sensorimotor adaptations underlying feedback-error learning associated with locomotor-resistance training. However, the findings of this report should be interpreted with caution given some of the methodological limitations and that only a single subject was tested. Nevertheless, these measures together provide a complementary and integrative view of possible neural mechanisms underlying the response to locomotor-resistance training that has been shown to enhance recovery of functional ambulation following iSCI.[14] These findings raise interesting possibilities for the design and evaluation of gait rehabilitation strategies for people with iSCI.

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Figure 1: Illustrative graph demonstrating the added resistance during training. Hip and knee joint angles during the gait cycle for the left (L; grey lines) and right (R; black lines) sides are plotted to show non-resistance (NR; solid lines) and Lokomat-resistance (LR; dash lines) walking. Average joint angle curves were calculated from 25 steps and normalized to the percentage of gait cycle time (0% - heel strike to 100% - subsequent ipsilateral heel strike). Upward deflections represent flexion.

Figure 2: Average sensory-evoked potentials (SEPs) for sensory threshold (ST), motor threshold (MT) and 150% motor threshold (MT150) for A) pre-training, and B) post-training on the left hemisphere over the Cz electrode (right leg). During pre-training, ST and MT were at the maximum stimulator output; therefore no further conditions were tested. At post-training, all conditions could be collected. The negative 50 (N50) component (vertical grey dotted line) can be visualized and shows larger negativity with MT and MT150 at post-training.

Figure 3: Functional connectivity (FC) results projected onto inflated medial and superior cortical surfaces in standard Montreal Neurological Institute (MNI) space. At baseline, greater FC strength was observed when seeding the left motor cortex leg representation compared to the right motor cortex. Following training, increased FC was observed between the leg area of both primary motor cortices and multiple cortical regions. When seeding the right motor cortex, connectivity strength appeared to show an increased lateralization following training that was not apparent for the left motor cortex. Warmer colors represent larger positive correlation values between seed activity and voxelwise brain resting activity. The right anterior cingulate cortex (MNI coordinates: x=5, y=34, z=28) was examined as a control site to examine changes in non-

motor cortical regions. This region was shown with resting-state fMRI to be functionally connected to non-motor prefrontal cortical regions related to attentional processing and executive function[32]. The spatial pattern of connectivity was largely unchanged after training. CS: central sulcus.

Figure 4: Average peak-to-peak motor evoked potential (MEPs) amplitudes from the left tibialis anterior muscle (less affected side) pre- (white circle) and post-training (black square) following session #2 of treadmill walking with Lokomat-resistance are displayed. MEPs were higher for most of the stimulus intensities tested after training, particularly at the highest stimulator intensity. Stimulator intensity is expressed as a percentage of maximum stimulator output (% MSO). The mean background rectified EMG activity 50 ms prior to the stimulus for each stimulation intensity is plotted. Error bars denote standard deviation. Note: we were not able to elicit MEPs for the right limb, which has more severe sensorimotor impairments.

Video: The video shows our subject walking on the Lokomat with and without resistance.

Figure 1

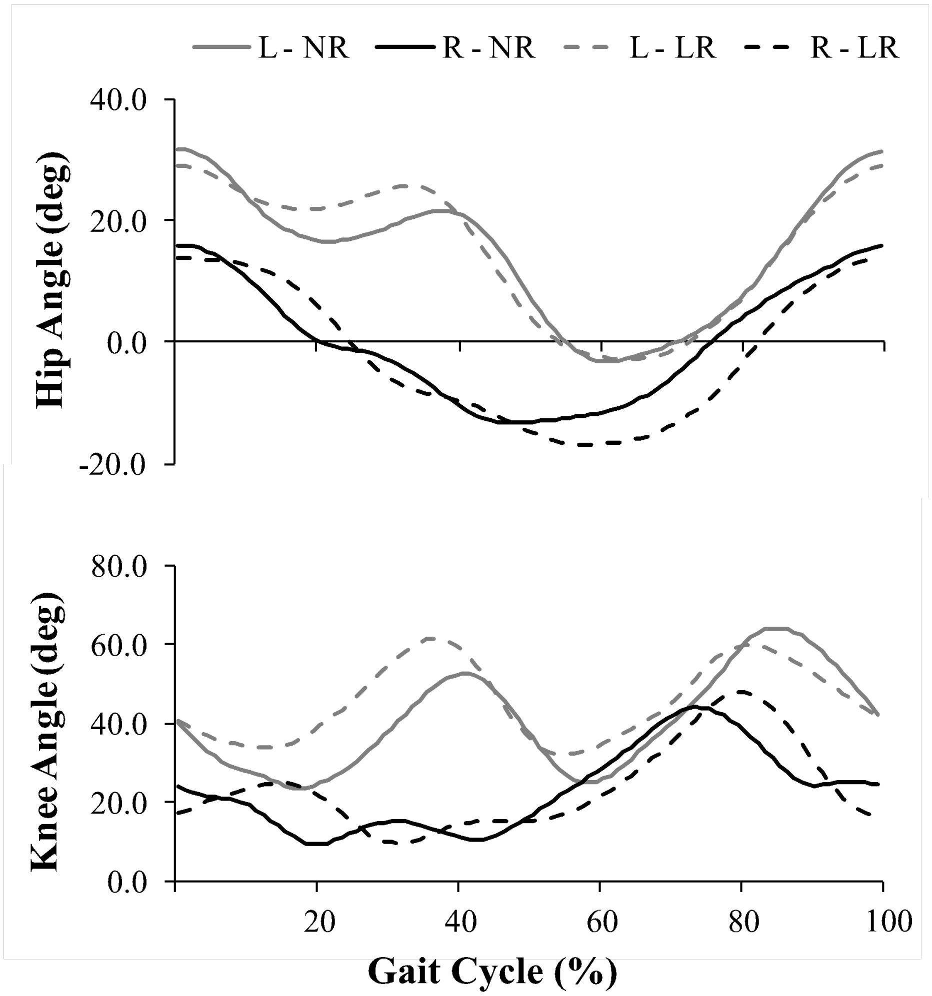

L - NR
R - NR
L - LR
R - LR
Hip Angle (deg)
40.0
20.0
0.0
-20.0
Knee Angle (deg)
80.0
60.0
40.0
20.0
0.0
20
40
60
80
100
Gait Cycle (%)

Figure 2

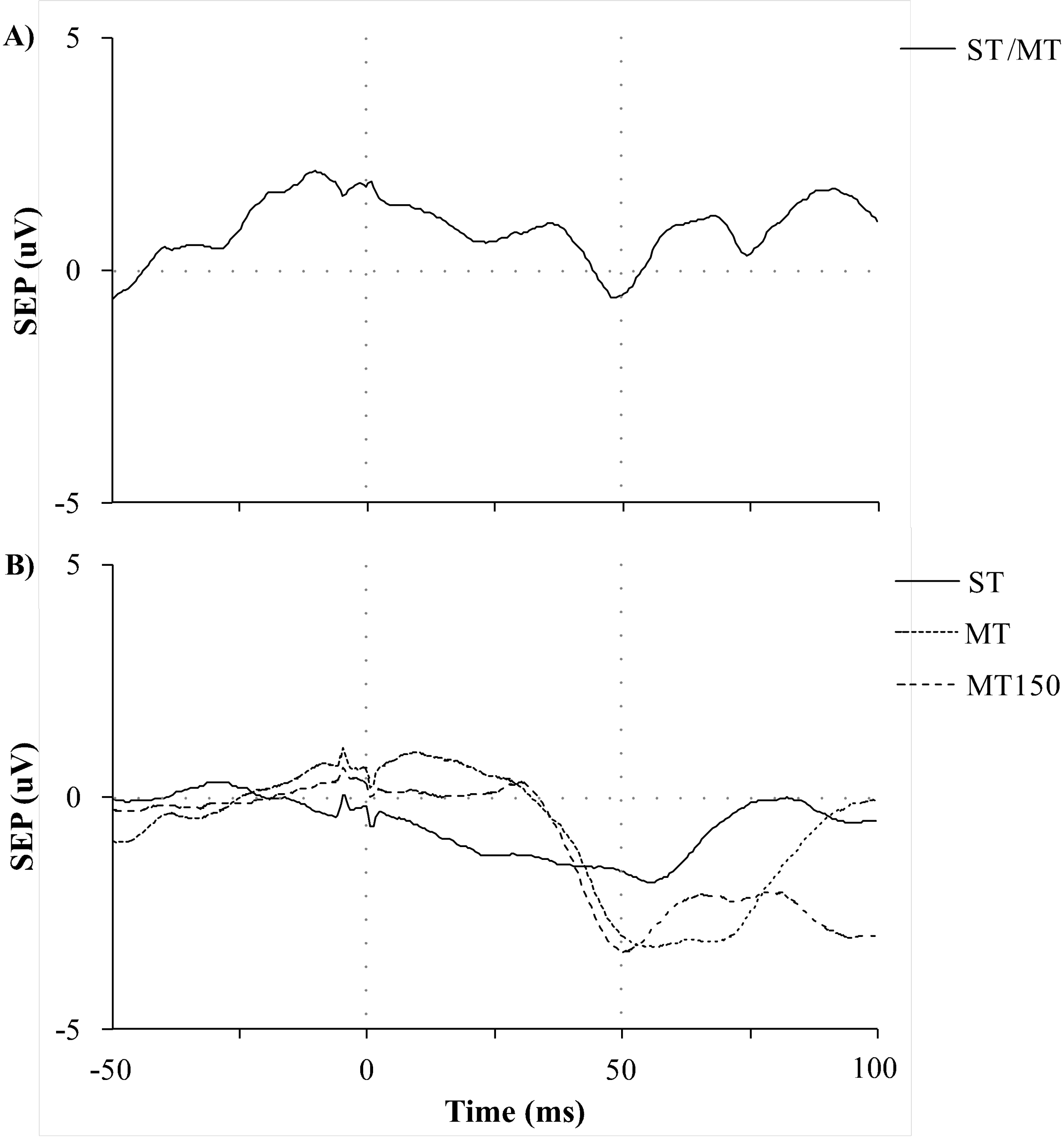


Figure 3

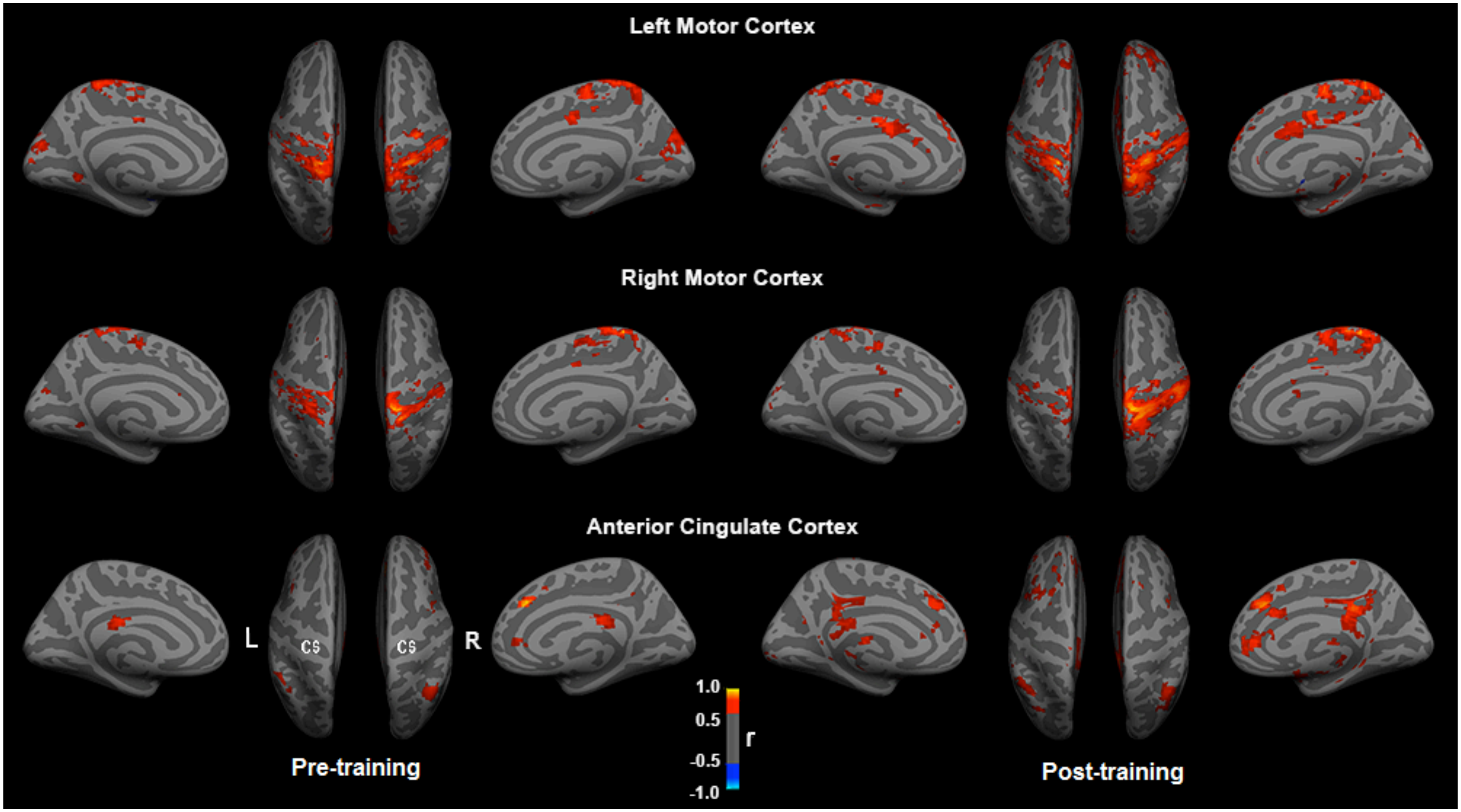
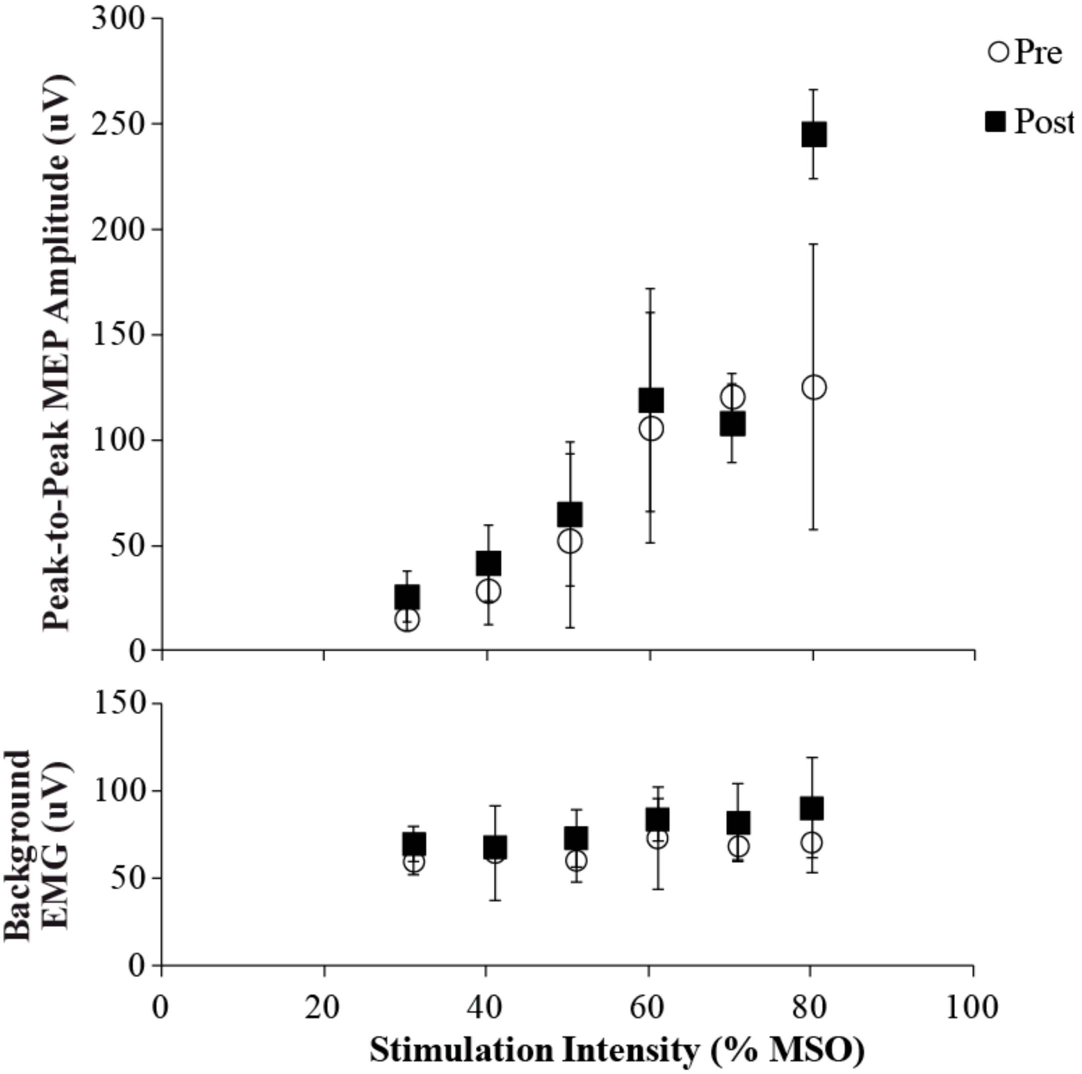

Left Motor Cortex
Right Motor Cortex
Anterior Cingulate Cortex
L
CS
CS
R
1.0
0.5
-0.5
-1.0
r
Pre-training
Post-training

Figure 4


○ Pre
■ Post
Peak-to-Peak MEP Amplitude (uV)
300
250
200
150
100
50
0
Background EMG (uV)
150
100
50
0
0
20
40
60
80
100
Stimulation Intensity (% MSO)