

Official Title of the Study: Locomotor Function Following Transcutaneous Electrical Spinal Cord Stimulation in Individuals With Hemiplegic Stroke

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Statistical analysis

Spatiotemporal gait symmetry

- Participants walked at their self-selected velocity along the 8 m GAITRite electronic walkway (CIR System Inc., NJ, USA) placed in the middle of a 14 m walkway. Each participant completed three trials to account for trial-to-trial variance, and the results were averaged. For each trial, spatiotemporal gait measurements of step length and swing time were extracted. Gait symmetry, the difference between a subject's paretic (P) and non-paretic (NP) side, was calculated by the following Symmetry Index equation:

$$\text{Symmetry Index} = \left(1 - \left| 1 - \frac{NP}{P} \right| \right) \times 100\%.$$

- This calculation results in a maximum value of 100% irrespective of which limb demonstrates greater values, with improvements observed as positive values. The symmetry indices of three trials for each participant were averaged.
- ***Bootstrapping for spatiotemporal symmetry and RMTs.*** For gait symmetry, bootstrap methods were performed to statistically verify changes in the outcomes Post and at 3FU relative to Pre, and 3FU relative to Post (SPSS v27.0, IBM, Inc., Chicago, IL). Additionally, bootstrap methods were performed to evaluate the changes in RMTs from Pre to Post. Bootstrapping is a nonparametric statistical analysis that employs resampling techniques and has been effectively used in studies with small sample size. Specifically, bootstrapping resamples each original data set with replacement, and recombines it to create bootstrap sets, from which the means and 95% confidence intervals (CIs) were obtained. We constructed 1,000 bootstrap samples for each outcome and calculated the Pre-Post, Pre-3FU, and 3FU-Post mean raw symmetry index differences, and the Pre-Post means differences of the RMTs of the resampled data to create statistical results. Then, 95% CIs of the differences were constructed to test the null hypothesis of no difference in the mean. Since we hypothesized that the outcomes would improve in subsequent timepoints, we used a one-tailed paired t-test. The raw changes in spatiotemporal symmetry

indexes and RMT changes are presented in the results with 95% CIs and the P -value from the bootstrap. The level of significance was set at $P<0.05$.

Fast gait speed and 6 min walk test (6MWT)

- Fast gait speed. To measure gait speed, participants performed the 10 m walk test (10MWT) at fast velocity. The test was repeated over 3 trials and the average speed of the three trials was calculated.
- 6 min walk test (6MWT). The 6MWT was conducted to examine gait endurance. Participants were instructed to complete 6 min of overground walking, covering as much distance as possible.
- ***Minimum clinical important differences (MCID) for gait speed and 6MWT:*** For gait speed and 6MWT, MCID was used to assess for meaningfulness of improvements (gait speed MCID=0.14m/s; 6MWT distance MCID=34.4m). These thresholds are defined as the smallest changes in health-related measures that patients perceive as meaningful improvements in rehabilitation. This approach was chosen over relying solely on statistical significance since a statistically significant change may not always translate into a meaningful improvement in rehabilitation outcomes.

Neurophysiological outcomes

- Electromyography (EMG) acquisition during walking. Surface EMG (Trigno, Delsys, Inc.) was recorded at Pre and Post in five muscles (rectus femoris, RF; vastus lateralis, VL; medial hamstring, MH; tibialis anterior, TA; and medial gastrocnemius, MG) as participants walked at their self-selected speed for 10 m. All EMG data was collected at 2000 Hz. The selected EMG signals from each participant were band-pass filtered from 40 to 500 Hz with a zero-lag fourth-order Butterworth filter, demeaned, rectified, and low-pass filtered with a zero-lag fourth-order Butterworth filter at 4 Hz. To facilitate comparison between subjects, the filtered signal was normalized to its peak value and resampled into 100% of the gait cycle from heel strike to heel strike.

- **Muscle synergy analysis.** The concept of muscle synergies indicates synchronous neural commands to execute each phase of gait cycle and the group of muscles that are activated together in response to a neural command. We conducted non-negative matrix factorization to obtain the EMG-based muscle synergy analysis during walking. Muscle activity during walking can be grouped into sets of co-excited muscles, termed as muscle modules or synergies. Studies have identified well-coordinated gait in healthy individuals can be produced by four or five groups of synergies. Recent evidence suggests that disinhibition and/or hyperexcitation of the brainstem descending pathways and intraspinal motor network diffuse spastic synergistic activation post-stroke. As a result, simplified or merged muscle synergies compared to non-impaired individuals are typically observed and have been found to predict their degree of impairment. Furthermore, previous studies suggest that muscle synergies are encoded in the spinal cord, therefore we hypothesized that modulating spinal networks with tSCS may lead to positive changes in motor control of stroke survivors that could translate to sustained functional gait changes. Previous research suggested that the increase in number of muscle synergies indicates improvement in neuromodular complexity. To determine the number of muscle synergies necessary to reconstruct the original EMG signal, the variability accounted for (VAF) was calculated and used as the reconstruction quality criterion given by

$$VAF = \frac{1 - (EMG_o - EMG_r)^2}{EMG_o^2} \geq 90\%,$$

where EMGo is the original EMG signals, EMGr is the reconstructed EMG signals calculated by multiplying muscle group weightings and activation timing patterns. The number of motor synergies of each walking trial was chosen such that the VAFs exceeded 90%.