

Study Protocol

Official Title: Effects of Transcutaneous Cervical Spinal Cord Stimulation on Upper Limb Motor Function After Traumatic Brain Injury

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1. Scientific Background

Traumatic Brain Injury (TBI) is estimated to result in permanent disabilities for approximately 5.3 million people in the United States, including over 500,000 individuals living in Pennsylvania alone. Among the most common chronic disabilities following brain injuries are upper limb impairments, which significantly compromise independence in daily activities and social inclusion. Currently, the standard clinical approach for rehabilitation of these individuals with chronic motor impairments is physical training administered at low doses, which has limited effects in improving functional movements. Therefore, alternative rehabilitation approaches are needed to leverage upper limb motor recovery after TBI. As a promising approach, spinal cord stimulation (SCS) has shown substantial motor improvements in patients with brain lesions caused by stroke. However, the effects of SCS in improving upper limb motor function in individuals with chronic TBI remain unexplored.

Cervical SCS has emerged as a potential approach for motor rehabilitation after brain injury. Our research group has pioneered the use of cervical SCS as an effective rehabilitative approach for upper limb motor impairments caused by brain lesions after stroke. In this approach, electrical stimulation is delivered using invasive electrodes implanted along the epidural space of the cervical spinal cord, which preferentially depolarizes proprioception sensory fibers in the dorsal roots. In turn, the activation of proprioception sensory neurons is used to modulate the excitability of motoneurons via indirect spinal pathways, thereby enabling assistive effects that facilitate volitional movements and reduce spasticity immediately as SCS is delivered. Importantly, our data show that SCS can immediately improve all (1 - 4) motor impairment components in participants with brain lesions caused by hemorrhagic stroke. Given the similar pathophysiological features between hemorrhagic stroke and TBI, these findings strongly support the potential applicability of SCS as a therapeutic intervention for motor rehabilitation following TBI.

Cervical transcutaneous SCS (tSCS), applied using electrode pads placed on the skin, is a non-invasive alternative to invasive epidural SCS for motor rehabilitation. Mirroring the mechanisms of invasive SCS delivered with implanted electrodes. Experimental and computational studies have previously demonstrated that cervical tSCS also preferentially activate proprioception sensory fibers, thereby enabling immediate assistive effects. As a safe, cost-effective and accessible approach, tSCS is therefore well suited for investigating the rehabilitative potential of both invasive and non-invasive SCS in improving chronic motor impairments following TBI.

2. Study Objectives

Our hypothesis is that tSCS can immediately facilitate voluntary motor output of upper limb muscles in individuals with TBI by modulating residual descending inputs to spinal motoneurons. Specifically, we propose that this neuromodulatory approach may produce immediate effects on arm and hand strength, joint synergies, spasticity and arm motor control in individuals with chronic motor deficits after TBI. To test my hypothesis, I propose the following three aims:

Aim 1: Test the immediate efficacy of tSCS in amplifying voluntary motor output. Specifically, we posit that tSCS can immediately increase the maximum voluntary contraction (MVC) strength

produced during elbow, shoulder and hand movements. The immediate effects of tSCS will be measured by comparing the MVC force across tSCS ON and OFF conditions.

Aim 2: Test the immediate efficacy of tSCS in reducing abnormal joint synergies and spasticity in individuals with chronic post-TBI motor impairments. To test this, we will assess joint synergies using subcomponents of the Fugl-Meyer Assessment (FMA) for upper extremity motor function (i.e., movement combining synergies and movement out-of-synergies) and spasticity using the Modified Ashworth Scale. The immediate effects of tSCS will be measured by comparing these metrics across tSCS ON and OFF conditions.

Aim 3: Identify optimal tSCS frequencies to improve fine motor control. We hypothesize that low-frequency tSCS ($\leq 60\text{Hz}$) improves fine motor control by preserving, whereas high-frequency tSCS ($>60\text{Hz}$) disturbs fine motor control by blocking proprioception inputs from upper limb muscles. We will compare arm kinematics during a planar reach task, while tSCS is delivered at 30Hz, 60Hz and 100Hz. The effect of tSCS frequencies on arm reaching kinematics will be assessed in both neurologically intact and individuals with chronic post-TBI motor impairments. Neurologically intact participants will be a control group to isolate effects of high-frequency tSCS.

Upon completion of these aims, I expect to build evidence supporting the use of SCS to improve upper limb chronic motor impairments in individuals with TBI. These results will lay the groundwork for future studies aimed at developing invasive and non-invasive SCS neuroprosthetic devices.

3. Study Design & Methods

The proposed study is a prospective, non-randomized, open-label, descriptive, experimental study. The following outcomes were assessed only when the corresponding motor deficit was identified in the participant during the baseline clinical evaluation. When the associated deficit was not present, the outcome measure was not administered and no data were collected.

The primary outcome of this study is to evaluate the immediate effects of transcutaneous spinal cord stimulation (tSCS) on amplifying voluntary motor output in individuals with traumatic brain injury (TBI):

- **Arm and Hand Strength:** Strength will be measured during isometric maximum voluntary contraction (MVC) of shoulder flexion, shoulder extension, elbow flexion, elbow extension, and grip, under tSCS ON and OFF conditions.

The secondary outcome is to evaluate the immediate effects of tSCS on reducing spasticity and abnormal joint synergies, as well as on improving arm motor control in individuals with TBI:

- **Movement smoothness:** An exoskeleton robot (KINARM) will be used to assess arm movement smoothness during two-dimensional (2D) reaching tasks under transcutaneous spinal cord stimulation ON and OFF conditions. Movement smoothness will be quantified

using log-dimensionless jerk of the hand velocity. Log-dimensionless jerk will be compared across transcutaneous spinal cord stimulation ON and OFF conditions within the same experimental session.

- **Joint Velocity:** An exoskeleton robot (KINARM) will be used to assess arm joint velocity during two-dimensional (2D) reaching tasks under transcutaneous spinal cord stimulation ON and OFF conditions. Arm joint velocity will be quantified as the ratio between the time required to move the arm from an initial position to a final target and the distance between the positions (m/s). Arm joint velocity will be compared across transcutaneous spinal cord stimulation ON and OFF conditions within the same experimental session.
- **Discomfort/Pain:** Discomfort and/or pain experienced by participants during transcutaneous spinal cord stimulation will be assessed using a self-reported 0–10 scale, where low values indicate low discomfort/pain, and high values indicate high discomfort/pain.
- **Joint Synergies:** The "movement combining synergies" and "movement out-of-synergies" subcomponents of the Fugl-Meyer Assessment (FMA) for upper extremity motor function will be used to quantify joint synergies under transcutaneous spinal cord stimulation ON and OFF conditions. The Fugl-Meyer Assessment (FMA) is a performance-based impairment index designed to evaluate upper extremity motor function in individuals with post-stroke hemiparesis. The FMA for upper extremity motor function consists of 33 items, each scored with 0–2 points (0 = cannot perform task, 2 = fully performs task), resulting a maximum score of 66 points. For this study, the subscores from the 'movement combining synergies' and 'movement out-of-synergies' components will be summed to quantify changes in joint synergies. FMA subscores will be compared across transcutaneous spinal cord stimulation ON and OFF conditions within the same experimental session.
- **Spasticity:** Spasticity will be measured using the Modified Ashworth Scale (MAS) for the following muscle groups under transcutaneous spinal cord stimulation ON and OFF conditions: shoulder flexors, shoulder extensors, shoulder abductors, shoulder adductors, elbow flexors, elbow extensors, wrist pronators, wrist supinators, wrist flexors, wrist extensors, and finger flexors/extensors. The MAS is a 0–4 ordinal scale that quantifies resistance to passive stretch as a measure of spasticity, with lower scores indicating minimal spasticity and higher scores indicating marked spasticity. The MAS scores will be summed across all muscle groups to create an overall metric quantifying spasticity. MAS scores will be compared across transcutaneous spinal cord stimulation ON and OFF conditions within the same experimental session.

4. Eligibility Criteria

Inclusion Criteria:

TRAUMATIC BRAIN INJURY (TBI) SUBJECTS:

- Participants must have suffered a traumatic brain injury resulting in impairments in arm and hand motor function at least one year prior to enrollment.
- Participants must be between the ages of 21 and 70 years old.

HEALTHY CONTROL SUBJECTS:

- Participants must have full range of motion in their upper limbs;
- Participants must be between the ages of 21 and 70 years old.

Exclusion Criteria:

TRAUMATIC BRAIN INJURY (TBI) SUBJECTS:

- Participants with severe behavioral or cognitive impairments (e.g., aphasia, apraxia, visual neglect) that could preclude their ability to participate in the study.
- Participants diagnosed with Paroxysmal Sympathetic Hyperactivity (PSH);
- Participants with post-TBI heterotopic ossification or tendon contractures that restricts passive range of motion of upper limb joints;
- Participants with uncontrolled epilepsy or untreated seizure disorders;
- Participants with implanted electronic devices, such as pacemakers and spinal cord stimulators;
- Participants taking benzodiazepine for spasticity;
- Participants with serious disease or disorder (ex. neurological condition other than TBI, cancer, severe cardiac or respiratory disease, renal failure, etc.) that could affect their ability to participate in this study.
- Female participants must not be pregnant or breast feeding.
- Evaluation to sign consent form score <12.

HEALTHY CONTROL SUBJECTS:

- Participants who have any serious disease or disorder (e.g. cancer, severe cardiac or respiratory disease, neurological conditions, etc.) or cognitive impairments that could affect their ability to participate in this study.

5. Statistical Considerations

This study is a prospective, non-randomized, open-label, descriptive experimental study designed to evaluate the immediate effects of transcutaneous spinal cord stimulation (tSCS) on upper-limb motor function in individuals with traumatic brain injury (TBI). Because all outcomes will be measured within the same participants under both **tSCS OFF** and **tSCS ON** conditions, each participant will serve as their own control. The primary analyses will therefore use within-subject comparisons between stimulation conditions:

$$\Delta = \text{Outcome}_{ON} - \text{Outcome}_{OFF}$$

For outcomes in which higher values indicate improvement, such as maximum voluntary contraction strength, positive values of Δ will indicate improvement with tSCS. For outcomes in which lower values indicate improvement, such as spasticity scores, negative values of Δ will indicate improvement with tSCS.

Because this is a descriptive experimental study and the expected sample size may be limited, statistical inference will be based primarily on non-parametric bootstrap procedures rather than assumptions of normally distributed data. For each outcome, paired bootstrap resampling will be used to estimate the distribution of the within-subject stimulation effect. The tSCS ON and OFF measurements from each participant will be kept paired during resampling to preserve the within-subject design.

Bootstrap analyses will use at least 10,000 resamples. Confidence intervals will be calculated using percentile-based bootstrap intervals or bias-corrected and accelerated intervals when appropriate. The primary interpretation will focus on the estimated effect size and confidence interval rather than statistical significance alone.

Primary Outcome Analysis

The primary outcome is the immediate effect of tSCS on voluntary motor output, assessed using arm and hand strength.

- **Strength**

For each strength measure, the maximum voluntary contraction value will be extracted for each condition. The primary analysis will compare MVC strength between tSCS ON and OFF conditions using paired bootstrap analysis.

Secondary Outcome Analyses

Secondary outcomes will evaluate the immediate effects of tSCS on movement smoothness, joint velocity, discomfort/pain, abnormal joint synergies, and spasticity:

- **Movement Smoothness**

Movement smoothness will be assessed during two-dimensional reaching tasks using the KINARM exoskeleton robot. Smoothness will be quantified using log-dimensionless jerk of the hand velocity. For each participant and condition, log-dimensionless jerk will be compared across valid reaching trials. The primary summary metric will be the participant-level mean or median log-dimensionless jerk under tSCS OFF and tSCS ON conditions.

- **Joint Velocity**

Joint velocity during two-dimensional reaching tasks will be assessed using the KINARM exoskeleton robot. Movement velocity will be calculated as the distance traveled divided by movement time and expressed in meters per second. For each participant and condition, joint or hand movement velocity will be compared across valid reaching trials.

- **Discomfort and Pain**

Discomfort and/or pain experienced during tSCS will be assessed using a self-reported 0–10 scale, with lower values indicating less discomfort or pain and higher values indicating greater discomfort or pain. Because discomfort/pain is primarily assessed during stimulation, this outcome will be compared descriptively using mean, standard deviation, median, interquartile range, minimum, and maximum values.

- **Joint Synergies**

Joint synergies will be assessed using the “movement combining synergies” and “movement out-of-synergies” subcomponents of the upper-extremity Fugl-Meyer Assessment. These subscores will be summed up to create a joint synergy score for each participant under tSCS OFF and tSCS ON conditions. Paired bootstrap analysis will be used to compare summed FMA scores between tSCS ON and OFF conditions.

- **Spasticity**

Spasticity will be assessed using the Modified Ashworth Scale. MAS scores will be summed across muscle groups to create an overall spasticity score for each participant under tSCS OFF and tSCS ON conditions. A negative value will indicate reduced spasticity during tSCS. Paired bootstrap analysis will be used to compare summed MAS scores between tSCS ON and OFF conditions.

Missing Data

All available data will be included in the analysis. Participants with both tSCS OFF and tSCS ON data for a given outcome will be included in the paired analysis for that outcome. Participants missing either the OFF or ON measurement for a given outcome will be excluded from that specific paired comparison but may remain eligible for other outcome analyses.

Outliers and Data Quality

Data will be inspected for technical artifacts, implausible values, and acquisition errors before statistical analysis. Outliers will not be removed solely on the basis of their magnitude. Values will only be excluded if they are determined to result from technical error, task noncompliance, or invalid data acquisition.