Official Title: High Definition Neuromuscular Stimulation in Tetraplegia

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STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

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High Definition Neuromuscular Stimulation in Tetraplegia

General Introduction

Overview of disorder studied, and current treatments

Spinal cord injury (SCI) is an insult to the spinal cord resulting in a change, either temporary or permanent, in its normal motor, sensory, and/or autonomic function. It is estimated that the annual incidence of spinal cord injury (SCI), not including those who die at the scene of the accident, is approximately 40 cases per million population in the U. S. or approximately 12,000 new cases each year.

SCI primarily affects young adults. As the average age of the population in the United States rises, the average age of the spinal cord injury increased from 28.7 years in the 1970's to 41 years as of 2005. In addition, advances in the chronic care of people with spinal cord injury have significantly increased their life expectancy. As a result, the number of people in the United States who are alive in 2012 who have SCI has increased to a 270,000 persons, with a range of 236,000 to 327,000 persons.

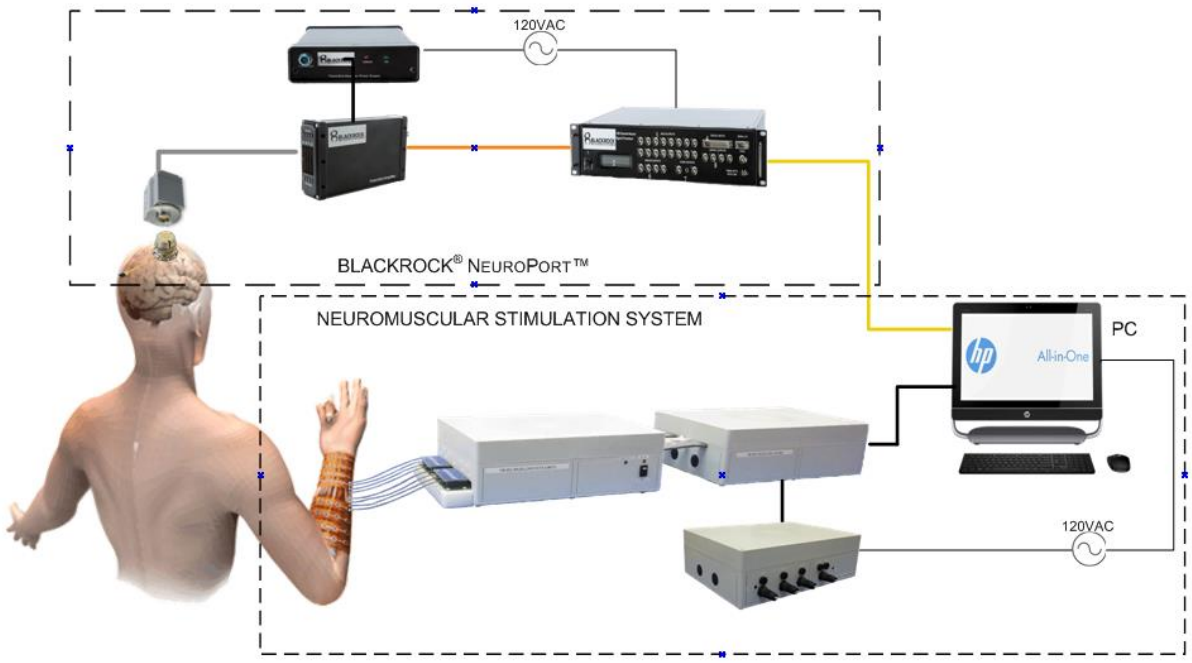
Persons with tetraplegia, also termed quadriplegia, have sustained injuries to one of the eight cervical segments of the spinal cord; those with paraplegia have lesions in the thoracic, lumbar, or sacral regions of the spinal cord. Since 2005, the most frequent neurologic category at discharge of persons reported to the database is incomplete tetraplegia (40.8%), followed by complete paraplegia (21.6%), incomplete paraplegia (21.4%) and complete tetraplegia (15.8%). Less than 1% of persons experienced complete neurologic recovery by hospital discharge (National Spinal Cord Injury Database, 2012).

Previous Work

Battelle (a private nonprofit applied science and technology development company headquartered in Columbus, Ohio) has developed a technology that provides high definition neurostimulation (Bouton et. al. 2012). This technology can target specific muscles in the forearm to allow wrist and hand/finger movements. The objective of the study proposed in this

submission is to demonstrate high definition neuromuscular stimulation of a paralyzed limb through computer-generated commands (or as triggered by a battery-operated EEG wireless headset). This will be an important step towards creating a neural bridge/bypass for patients with paralysis from spinal cord injury, stroke, or motor neuron disease. See Figure 1 for an overall system diagram and neuromuscular sleeve and glove components of the system..

The high definition Neuromuscular Stimulator is an investigational device developed by Battelle (Columbus, Ohio) that has been reviewed by a registered IRB (at Battelle) and has been used with human subjects with no adverse effects. The sleeve to be added in figure 1 (b,c) is a non-significant risk addition. The sleeve has been approved by the FDA in a significant risk study (see attached) that uses a chip implanted into the motor cortex. The sleeve itself is a non-significant risk device and does not elevate the present study to significant risk.



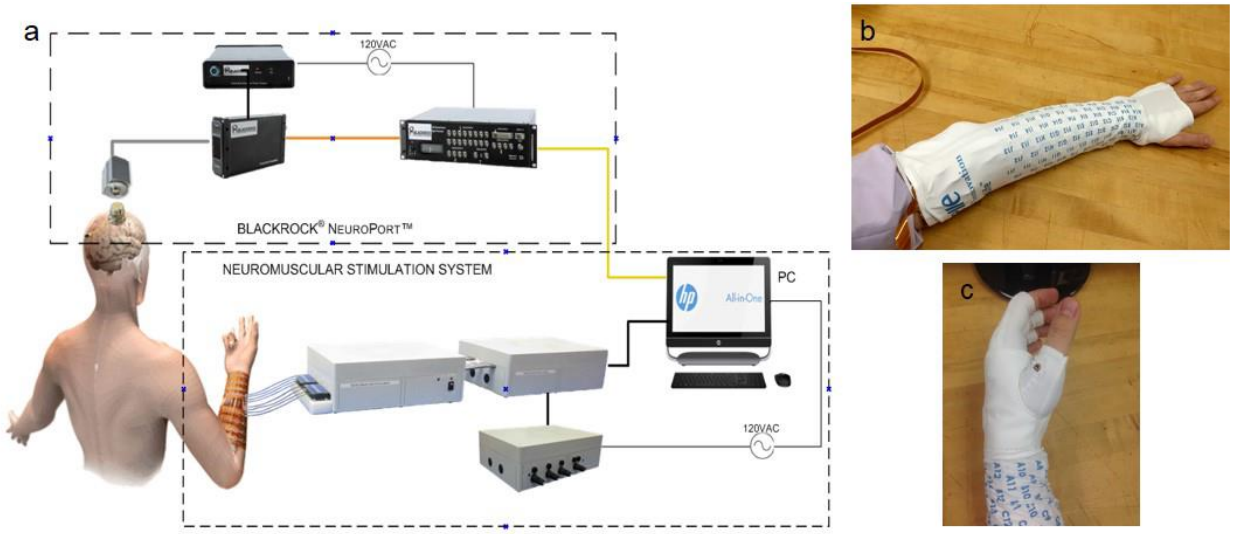


Figure 1. a) Overall Neural Bridging System Diagram.; b,c) Neuromuscular stimulation sleeve and glove

Study Rationale

Most neuromuscular stimulation systems have large area pads and only allow gross motion. The high definition technology developed by Battelle will allow finer movements, including individual finger movement. The objective of this study is to demonstrate high definition non-invasive neuromuscular stimulation of an upper extremity in tetraplegic, also termed quadriplegic, participants as an important step towards developing a neural bridge/bypass for spinal cord injury or motor neuron disease and rehabilitation in stroke patients. In initial sessions, the computer will generate pre-determined movements and create the corresponding stimulation patterns and isolate individual wrist and hand/finger movements (after a calibration period).

In later sessions, and with training, the participant may be able to imagine a small number (1-3) basic movements that are detected by the EEG headset and then be evoked by the Neuromuscular Stimulator. The stimulation NMES will be in the form of a cuff/array is comprised of 12mm circular or a sleeve consisting of a flexible circuit that has electrodes with custom of 12mm diameter. In the case of the sleeve, the cuff and electrodes will be housed in a spandex-type material. A non-toxic conductive enhancer (hydrogel discs applied, or conductive

lotion) lotion will form the interface between the electrodes and the skin allowing stimulation of small and large muscles and in the arm and hand to evoke a wide variety of spatial patterns and associated movements. The optional glove (Figure 1, b and c) connects to the sleeve and provides information back to the system about the position of the hand and arm in space, as well as the flexion and extension of the fingers and wrist. The glove does not provide stimulation and is for positional information gathering only.

Purpose

The purpose of this study is to demonstrate high definition non-invasive neuromuscular stimulation of an upper extremity in tetraplegic participants. This will be an important step towards developing a neural bridge/bypass for spinal cord injury or motor neuron disease and rehabilitation technology for stroke patients as well.

Protocol Overview and Design

The target population will be people with C4-6 ASIA A spinal cord injuries (motor and sensory complete neurologic injuries) who are more than 1 year post injury and who are neurologically stable.

Protocol Specifics

Participation Criteria

This study will plan to enroll up to 15 subjects who have been diagnosed with tetraplegia. Study participants will be persons of any race, ethnic group, or gender. Participants who enter will be free to withdraw from the study at any time without affecting their access to other treatments at OSU and affiliated hospitals. The first 5 eligible and consenting participants will be accepted into this study. No gender or minority will be excluded. However, since the sample size is small and participants will be accepted on a first come, first served basis, there may be inadequate representation of ethnicities, genders, and race in the study sample.

The total duration of the study is expected to be about 18 months, and each participant is expected to be on the study for about 6 months. Once the study is completed, participants will be discontinued from the study. Participants may also discontinue the study if they wish at any time.

Inclusion and Exclusion Criteria

Inclusion Criteria:

- Must be 21 years or older.
- Must be tetraplegic (C4-6 ASIA A)
- 12 months post injury and neurologically stable
- Participant is willing to comply with all follow-up evaluations at the specified times.
- Participant is able to provide informed consent prior to enrollment in the study.
- The participant is fluent in English.

Exclusion Criteria:

- No active wound healing or skin breakdown issues.
- No history of poorly controlled autonomic dysreflexia.
- Other implantable devices such as heart/brain pacemakers
- Subjects who rely on ventilators

Informed Consent

Informed consent will be obtained by the PI or their designee with documented specific knowledge of the study. The informed consent form will be reviewed with the participant and all questions will be addressed before the participant signs the consent form. The participant will also be given a copy of the signed consent, and a copy of the consent will be placed in the patient's medical record. Participants will be given the option to agree or not agree to be videotaped throughout the study. These videos will be used for educational purposes; including lectures and presentations. Participant's videotape decision will not affect his/her participation in the study.

Study Phases

The study design will consist of the following two (2) phases listed below.

I. Baseline assessment and calibration (approximately 1 month)
II. Testing motions: pre-sequenced and EEG-triggered motions; further calibration as needed (approximately 5 months)

Phase I - Baseline

- Medical history review
- Physical and neurological exam
- EMG
- Fit and calibrate external stimulator: The Battelle Neuromuscular Stimulator will be setup and calibrated to evoke wrist and hand/finger movements.

Phase II – Testing Motions

After the Battelle Neuromuscular Stimulator is setup and calibrated, various spatial and temporal stimulation patterns will be tested to evoke wrist/hand movements in various sequences of individual and combined movements.

Each subject will be asked to participate in test sessions, for up to 3 times a week for about 5 months. Each session will typically last less than 3 hours (including setup time). The first half hour, approximately, will be needed for setup of the stimulator system. Active stimulation time will be monitored to avoid fatigue. Once the stimulator is calibrated and tested, the patient may also be asked to imagine approximately 1-2 basic movements, thereby being detected by the EEG headset, which will trigger a wrist/hand movement. If successful this will be an important first step toward regaining volitional control of a paralyzed limb.

Outcomes and Data Analysis

Statistical analysis will be conducted with a biostatistician consultant. Continuous outcome variables will be summarized by the mean, median, standard deviation, minimum and maximum. Adverse effect data will be reported continuously, including all serious and non-serious adverse effects.

Primary and Secondary Outcomes

The primary outcome measure of this study is the achievement of individual wrist and hand/finger joint movement via high definition neuromuscular stimulation.
The targeted primary and secondary outcomes are therefore as follows:

- Primary outcome- consistent and repetitive voluntary movement in the targeted muscle groups
- Secondary outcome- consistent movement in the targeted muscle groups that is functional (manipulate or pick up an object)

Risk Analysis

Risks

Training and therapeutic sessions involving functional electrical stimulation will need to be monitored for autonomic dysreflexia signs and symptoms.

As with any muscle stimulator, there can be a risk of excessive current and skin irritation or burns. The Neuromuscular Stimulator, however, limits the average output current density to less than $2mA/cm^2$ at the skin and the average power density to less than $0.25W/cm^2$ to provide safe levels and avoid tissue damage However, despite these built-in safety limits, current and power density could exceed FDA guidelines if electrodes lift off of the skin. This has the potential to cause potentially causing minor irritation or first degree burns locally. The research investigator will monitor frequently during test sessions for any signs of electric shock, skin irritation, and/or burns. The sleeve material itself is spandex, with registration marks printed on it. The material itself has been tested for biocompatibility; the printing has not, nor has the sleeve after laundering. The investigators, who will already be monitoring frequently for signs of irritation from electric shock, will also monitor for signs of allergic skin reaction. The sleeve has been approved by the FDA in a significant risk study (see attached) that uses a chip implanted into the motor cortex. The sleeve itself is a non-significant risk device and does not elevate the present study to significant risk.

The study PI and co-investigators will be responsible for the evaluation, monitoring, and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE) as provided in this clinical investigation. The study participants will be evaluated for any possible AEs from the time written study informed consent is obtained until study closure or the subject exits the study.

- Any pre-existing condition unless a worsening of that condition in terms of nature, severity, or frequency develops.

- Medical or surgical procedure unrelated to the clinical protocol (i.e., dental or cosmetic procedure)
- Technical observation or a device events that does not result in a medically undesirable situation for the subject

Documentation of Adverse Events

All AEs from the time the study informed consent is signed through the final study visit will be recorded as AEs on the study event log; each event being documented separately. All AEs and SAEs will be followed until:

- AE is resolved and has returned to normal/baseline or has stabilized
- Subject has withdrawn from the study
- AE is judged by the investigator to be no longer clinically significant
- Study closure at which time, the responsibility for following any ongoing AEs will be transferred to the incoming clinical care team.

Dr. Mysiw will serve as Point of Contact to which the team will report adverse events. All non-serious adverse events will be reported to the Ohio State University Institutional Review Board (IRB) during the annual reporting period.

For those events that are determined to be related to stimulation therapy or device specific, the sponsor/investigator will report the strength of the relatedness using the following terms:

- **Definitely related:** The event is resolved by discontinuing stimulation
- **Probably related:** The event resolves upon discontinuing stimulation and cannot be reasonably explained by the subject's current clinical state
- **Possibly related:** The event may have been produced by the study subject's clinical state, however, the effect of stimulation cannot be ruled out
- **Unlikely related:** The event did not occur temporally to stimulation and can be explained by the subject's current clinical state or any other cause
- **Unrelated:** The event is explained by the subject's current clinical state or any other cause

For purposes of determination of a UADE the following categories will be considered related: "definitely related" and "probably related".

Reporting of Serious Adverse Events

SAEs reported during the protocol defined reporting period per section 4.1.4 will be:
• Evaluated for their relatedness per section 4.1.4
• Reported to the Data Safety Monitoring Committee

Procedures for Minimizing Risks

The risks associates with this study are minimal. Participants may terminate from the study if they wish at any time. Study participants may also wish to discontinue participation for any reason. Subjects who prematurely withdraw from the study due to an adverse event will be followed (e.g. telephone contact, and/or follow-up visits, etc.) until resolution of the event. Risks to confidentiality are negligible in this protocol, since participants will not be identified by name, or by any personal data, in any summary reports or publications. CRFs will be maintained in locked files and password-protected databases behind the Ohio State University Medical Center firewall. Data and safety monitoring activities for this study will continue until all subjects have completed their participation in the study.

Potential Benefits

Functional electrical stimulation (FES) systems have been created that stimulates muscle and restores functional movement in paralyzed limbs. This is one of the first studies in humans to combine high definition neuromuscular stimulation and EEG to produce real-time control of a paralyzed limb.

Study Justification

The target population will be people with C4-6 ASIA A spinal cord injuries (motor and sensory complete neurologic injuries) who are more than 1 year post injury and who are neurologically stable. This population is more likely to have reached a stable level of functional movement. People with this level of paralysis are totally dependent in all aspects of self-care. Restoration of functional movement in this population requires exploration of neuroprosthetic applications to increase functional movement that has quality of life implications. This BCI system is the first

attempt to utilize cortical sensors and a high definition stimulation system to bypass the injured spinal cord and produce volitional movement in humans.

Device Description

The Battelle System (as shown in Figure 2) is comprised of an Emotive (San Francisco, CA) EEG headset, a personal computer (PC) which runs the appropriate algorithms, and a non-invasive Neuromuscular Stimulator. The Neuromuscular Stimulator has been reviewed and approved for use in a non-significant risk study by a registered IRB. In this study both wrist and individual finger movement was demonstrated (Bouton and Annetta 2012) – see Figure 3.

The Emotive device is battery-operated and wireless and the Neuromuscular Stimulator is electrically isolated from mains power and earth ground and is compliant with the applicable patient and touch leakage currents in accordance with IEC60601-1:2005. Therefore, the two subsystems that are in contact with the patient are electrically isolated and do not provide an unsafe current leakage path through the patient. Furthermore, a hazard analysis was performed to identify and evaluate other potential risks associated with the use and operation of the system. Required risk controls were incorporated in the design of the system hardware.

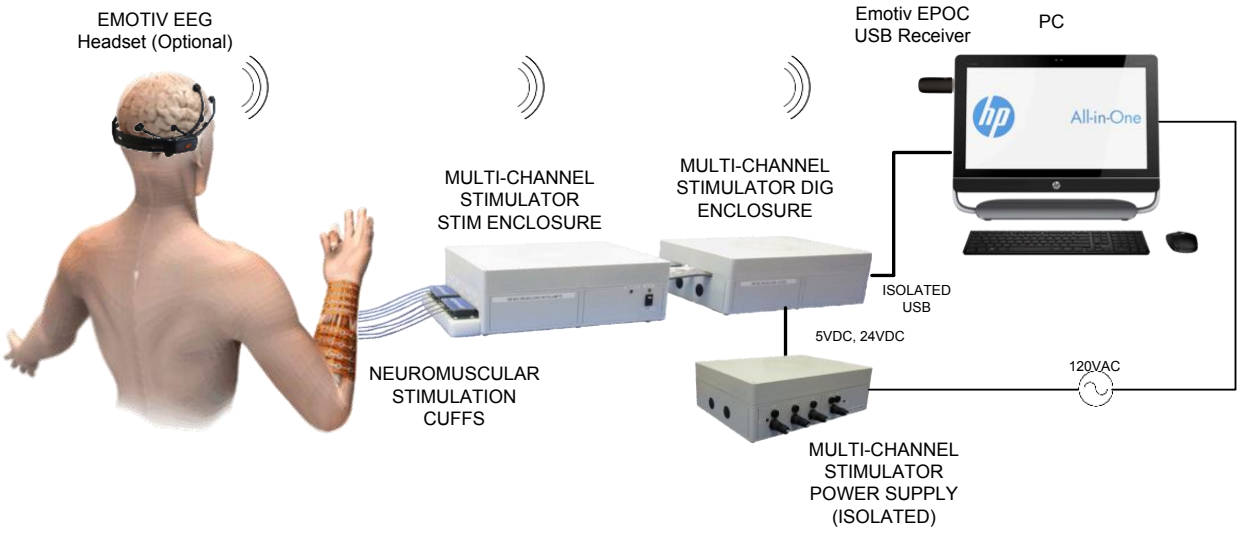


Figure 2. Overall System Diagram with Additional Details.

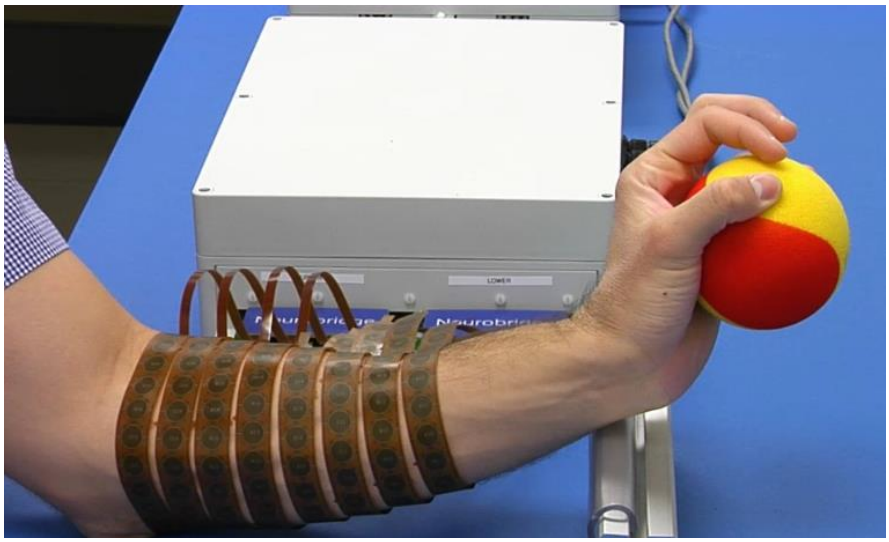


Figure 3. Neuromuscular Stimulator in Able-Bodied Study.

Stimulation Parameters

The stimulation parameters of the Neuromuscular Stimulator are as follows:

- Maximum peak current is 20mA with a maximum pulse width of 0.5ms.
- Maximum pulse frequency is 50 pulses per second.
- Maximum output voltage is 300 volts ± 10%.

- Maximum average current density is 2 mA/cm^2 at the Neuromuscular Stimulation Cuff electrode surface.
- Maximum average power density is 0.25 W/cm^2 at the Neuromuscular Stimulation Cuff electrode surface.

Monitoring Plan

Plan Description

The data management for this study will maintain a level of data integrity and confidentiality that will provide optimum adherence to all 21 CFR regulations, while providing a standardized method of data collection and recording to enable the investigators and regulatory agencies to accurately reconstruct the events of a study, confirm protocol compliance, and produce data that is accurate and appropriate in demonstrating study results.

REFERENCES

Bouton, C., "Fusing Neural Decoding and Neuromodulation Technologies and Associated Engineering Challenges," North American Neuromodulation Society, 15th Annual Meeting, Las Vegas, NV (8-11 Dec 2011).

Bouton C., Annetta A., Arora S., Buck V., Eubanks C., Friend J., Glenn B., Mack N., Masters M., Schimmoeller A., "High Definition Neuromuscular Stimulation and Encoding," IEEE Engineering in Medicine and Biology Conference Brain Machine Interface Workshop, San Diego, CA (Sep 2012).

Bouton, C. and Annetta, N., "Neural Bridging: Recoding Motor Cortex Activity and Linking to High Resolution Neuromuscular Stimulation," North American Neuromodulation Society, 16th Annual Meeting, Las Vegas, NV (6-9 Dec 2012).

Spinal Cord Injury Facts and Figures at a Glance, National Spinal Cord Injury Statistical Center, Birmingham, Alabama https://www.nscisc.uab.edu February 2012.