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FDA INVESTIGATIONAL DEVICE EXEMPTION
(IDE) APPLICATION

Reanimation in Tetraplegia
ORIGINAL SUBMISSION

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TABLE OF CONTENTS

PART III – Other Study Information

REFERENCES

APPENDICES

PART I – REPORT OF PRIOR INVESTIGATIONS

1. 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 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

In a study published in Nature by Hochberg, et al tetraplegic participants were implanted with a 96-channel microelectrode array in the cortex. Movement intentions from neural activity were decoded from the microelectrodes and used by tetraplegic participants to successfully operate a robotic arm by their thoughts. The microelectrode array is a multichannel, high-density, device that allows neural recordings from large populations of neurons. Over the past two decades, this patented microelectrode array technology has undergone numerous refinements and repeated validations in a variety of species (humans, monkeys, birds, rodents, felines, fish) and

preparations (in vitro and in vivo). This effort delivered a proven and well-documented method to obtain stable and long-term neural recordings of action potentials (spikes) and field potentials in brain and peripheral-nerve tissue. Because the array can be wired to various connector types, researchers can choose a connector that is optimal for chronic (long-term) or acute (short-term) recordings from small to large participants as well as from slice and cell culture preparations (Blackrock Microsystems).

Battelle, (a private nonprofit applied science and technology development company headquartered in Columbus, Ohio) was directly involved with the Hochberg study referenced, and specifically developed the decoding algorithms used in four of the participants (Bouton 2009), and has now developed a technology called "Neural Bridge" to link neural decoding to neurostimulation (Bouton 2011, Bouton et al, 2016, Sharma et al, 2016). Specifically, Battelle has developed a technology that decodes brain activity for imagined movements and then transforms the data into neuromuscular stimulation patterns to evoke the limb movement that was imagined. This technology in effect creates a 'neural bridge/bypass' or 'virtual spinal cord' to bypass injured or degenerated pathways. This technology can target specific muscles in the forearm, for example, to allow wrist and hand/finger movements based on the decoded brain activity in the participant's motor cortex. The objective of the study proposed in this submission is to allow reanimation of a paralyzed limb under complete voluntary control of the participant. This will be a significant step towards the artificial spinal cord / nervous system with potential applications beyond spinal cord injury, including stroke and motor neuron disease. See Figure 1 for an overall system diagram and neuromuscular sleeve and glove components of the system. The Neuroport device is a (510(k) K070272, K090957) cleared device manufactured by Blackrock Microsystems (Salt Lake, Utah) and the Neuromuscular Stimulator System is an investigational device developed by Battelle (Columbus, Ohio) that has been reviewed by a registered IRB and has been used with human participants with no related adverse effects reported. (See the Device Description section for further details.)

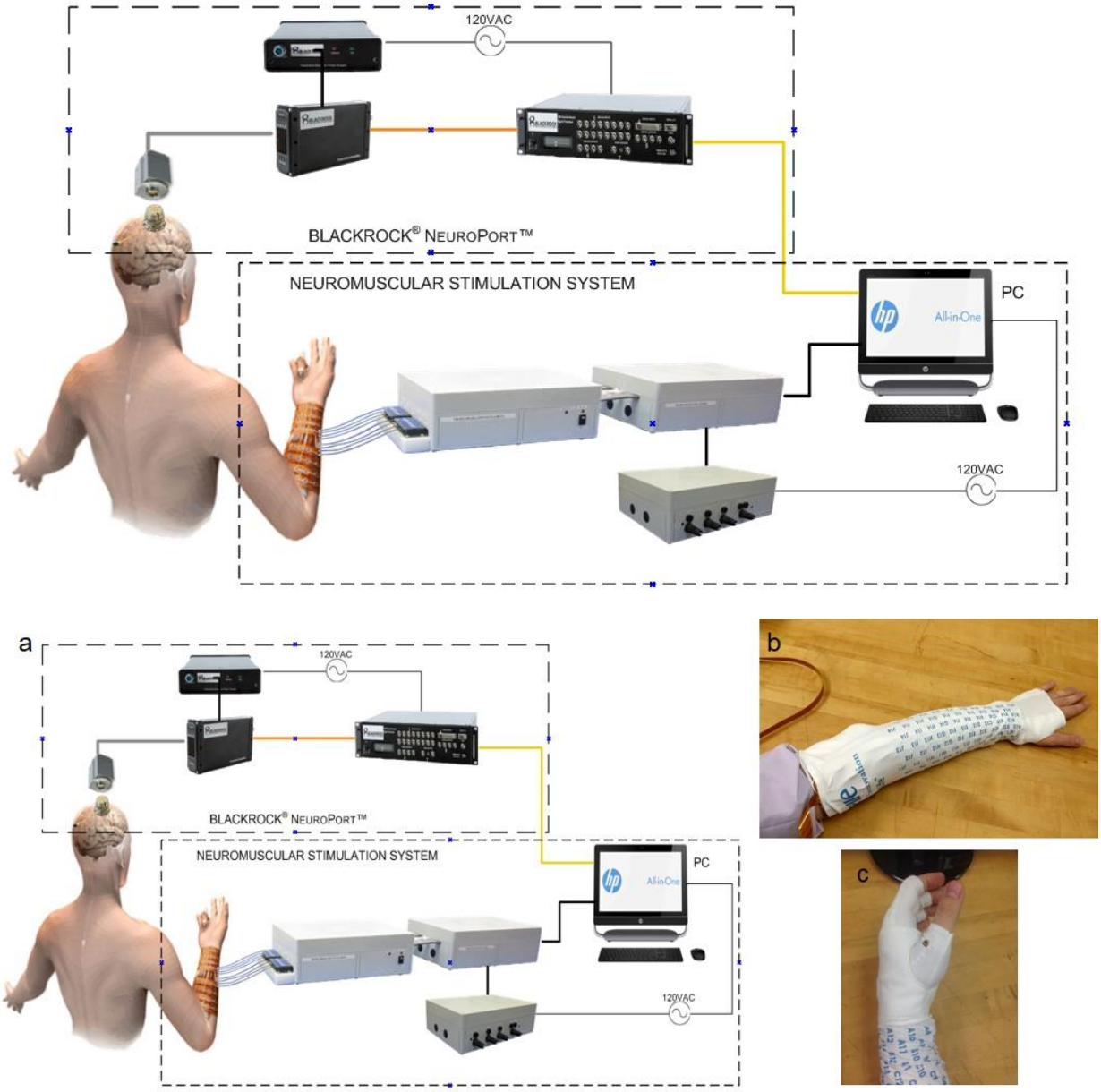

Figure 1. a) Overall Neural Bridging System Diagram; b,c) Neuromuscular stimulation sleeve and glove

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Study Rationale

This study will extend the previous work in neural decoding and allow the investigators to better understand how the human nervous system can be augmented or bridged when trauma or disease has occurred which decouples the nervous system from the voluntary control of muscles.

Previous work allowed participants to imagine various limb movements and control a computer cursor or other devices (Bouton 2009). The key extension in this study is to allow participants with tetraplegia to regain voluntary control of a paralyzed limb. The system will use re-coding algorithms to first decode brain activity in the motor cortex and then re-encode the signals for high definition stimulation of the selected muscles. "Neural bridging", as it is termed, involves signal monitoring (in the nervous system with a Neuroport microelectrode array), decoding of the information present, and then re-encoding appropriate stimulation signals for non-invasive insertion in another location in the nervous system, in this case directly to the muscles of interest. The insertion of signals back into the nervous system will be achieved through a non-invasive function neuromuscular stimulation system (NMES) (Bouton et al 2012). The NMES will be in the form of a cuff/array or a sleeve consisting of a flexible circuit that has electrodes of 12mm diameter. In the case of the sleeve, the cuff and electrodes are housed in a spandex fabric. A non-toxic FDA-approved conductive lotion forms the interface between the electrodes and the skin allowing stimulation of small and large muscles in the arm and hand to evoke a wide variety of 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.

Neurostimulation systems have been developed to restore functional movement in chronic paralysis population. The approach that provides the most functional multidimensional movement control utilizes a combination of a brain-computer interface (BCI) with implanted cortical sensors. However, to date, human applications of implanted BCI technology have been limited to assistive technologies such as power chairs or robotic arms. An implanted BCI neuroprosthetic system designed to produce functional upper limb movement was only recently tested in an animal.

The system described in this study is unique in that the BCI system translates intended action into human motion. Unlike the animal study previously referenced where the functional movement was generated through an implanted functional electrical stimulation system, this study will deliver surface stimulation through the NMES.

Team Expertise

This investigation will be conducted at the Neuromodulation Center at The Ohio State University. This Center represents a collaborative effort between faculty in the Departments of Neurological Surgery, Neurology and Physical Medicine and Rehabilitation. The OSU functional neurosurgery team led by the PI, Dr. Milind Deogaonkar is internationally renowned for expertise with functional and stereotactic neurosurgery, Dr. Deogaonkar's surgical team has performed over 2,500 neurological system implants in the past 16 years for various neurological, chronic pain and other applications.

The study participants will be recruited from the Spinal Cord Injury Rehabilitation Service, which is a CARF accredited spinal cord injury rehabilitation program within the Department of Physical Medicine and Rehabilitation (PM&R). The PM&R program at OSU is nationally recognized as a preeminent rehabilitation program. Dr. Jerry Mysiw is the Chair of PM&R and a study co-investigator.

Battelle has extensive experience in developing commercial medical products for human use and in neural decoding in paralyzed human participants (Bouton 2009). Battelle has also developed training methods to enhance the ability of participants to evoke targeted neural activity in the primary motor cortex for various imagined arm and hand movements. Battelle has also tested the study components (cuff, sleeve, conductive lotion and stimulator system) in a Battelle IRB-approved Study (Battelle IRB 0466) without adverse effects or complications.

PART II - INVESTIGATIONAL PLAN

1. Investigational Purpose

The purpose of this clinical study is to allow the investigation of the Neural Bridging System for participants with tetraplegia to assess if the investigational device can reanimate a paralyzed limb under voluntary control by the participant's thoughts.

2. Protocol Overview and Design

The target population will be people with C4-C6 ASIA A spinal cord injuries (motor and sensory complete neurologic injuries) who are more than 1 year post injury and who are neurologically stable.

3. Protocol Specifics

3.1 Participation Criteria

This study will plan to enroll up to 5 participants 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 is intended to be excluded. However, since the sample size is small, there may be inadequate representation of ethnicities, genders, and race in the study sample.

3.1.1 Inclusion and Exclusion Criteria

Inclusion Criteria:

- Must be 21 years or older.
- Must be tetraplegic (C4- C6 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.
- Participant must have a caregiver willing to participate in the study who will provide care for the surgical site.

Exclusion Criteria:

- No active wound healing or skin breakdown issues.
- No history of poorly controlled autonomic dysreflexia.
- Medical contraindications for general anesthesia, craniotomy, or surgery.
- Diagnosis of acute myocardial infarction or cardiac arrest within previous 6 months.

- Participants with any type of destruction and/or damage to the motor cortex region as determined by MRI.
- Dementia
- Psychiatric disturbances
- Other implantable devices such as heart/brain pacemakers
- Participants who rely on ventilators
- Co-morbid conditions that would interfere with study activities or response to treatment, which may include:
  - Life expectancy < 3 years
  - Severe chronic pulmonary disease
  - Confirmed seizure disorder that requires continued clinical care
  - Local, systemic acute or chronic infectious illness
  - Life threatening cardiac arrhythmias
  - Severe collagen vascular disorder
- Kidney failure or other major organ system failures History of a neurological ablation procedure.
- Labeled contraindication for MRI.
- History of hemorrhagic stroke.
- History of HIV infection or ongoing chronic infection (such as tuberculosis).
- Pregnant or of child-bearing potential and are not taking acceptable methods of contraception.

Participation in another investigational device or medication trial

3.1.2 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.

3.2 Study Phases

The study design will consist of the following four (4) phases listed below.

I. Baseline (approximately 8 weeks prior to surgery)
II. Surgery (approximately 1-2 weeks)
III. Decoding and stimulation (approximately 60 months)
IV. Follow-up (approximately 8 weeks post device explantation)

3.2.1 Phase I - Baseline

- Medical history review
- Physical and neurological exam, and neuropsychological tests (see Section 3.2.5)
- Functional Magnetic Resonance Imaging (fMRI)
- Transcranial Magnetic Stimulation (TMS)
- Neurophysiological recordings:
- Electromyography (EMG)/Nerve Conduction Studies (NCS), Electroencephalography (EEG), Quantitative EEG (QEEG), and evoked response assessments involving the Event-related Potential (ERPs) and steady state sensory evoked potentials (SSEP)
- Pre-test the external stimulator prior to implant

3.2.2 Phase II - Surgery

The patient will undergo a standard fronto-parietal image guided craniotomy to expose the sensory and motor cortex. Subsequently, one or two Blackrock Microsystems Neuroport arrays will be implanted into the motor cortex in the standard fashion using the Neuroport pneumatic wand.

The electrodes used in this study are manufactured by Blackrock Microsystems. The Blackrock Microsystems Neuroport array is a 4.4 by 4.2 mm, chronically implantable array containing 96 electrodes, with an electrode spacing of 400 μm, capable of recording from areas of the central and peripheral nervous system for extended periods. The electrodes are Parylene-coated, silicon shanks with platinum or iridium oxide tips. The wires connecting the electrode array to the Blackrock connector are 25 μm gold alloy insulated wires collectively sealed as a bundle with silicone elastomer. The electrode and wire bundle lengths are user-specified and, once constructed, are not variable. The array of electrodes is biologically inert and can function implanted in cortex for three or more years. The electrodes typically have impedances in the

range of 100-800 kΩ (at 1kHz) and are capable of recording single and multi-unit action potentials with signal-to-noise ratios of up to 10 and peak-to-peak amplitude of greater than 1 mV.

Postoperative Management and Monitoring

Post-operatively, participants will be taken to the neurosurgical step down unit and subsequently to the routine patient ward. Participants will also have a CT scan post operatively to evaluate the brain for intracranial air, hemorrhage and to assess the location of the electrodes.

Surgical recovery

Following surgery, participants will return to their home and enter into a postoperative recovery phase, which is normally expected to be 1-2 weeks from the initial implant, but may take longer depending on wound healing time. The pedestal site should be cleaned at least once every seven days or as required. This procedure will most likely require some assistance from a caregiver. To help reduce the risk of infection, it is important that all caregivers who touch the patient above the neck have clipped nails. The Pedestal Cap should remain on the Pedestal at all times and should only be removed by the physicians or trained investigators on the study. Caregivers should be careful not to touch the pedestal without first touching the patient elsewhere (skin to skin) to discharge any static electricity, and not to bump the Pedestal Connector.

3.2.3 Phase III - Decoding and Stimulation

Neural signals from the implant will be monitored and re-coded by the Neural Bridging System. Re-coding involves the process of decoding neural signals and then encoding the appropriate stimulation patterns for an intended movement. Decoding algorithms will decipher neural signals using pattern recognition methods to classify different movements imagined by the participant. The Battelle Neuromuscular stimulator will be setup and calibrated to evoke the imagined wrist and hand/finger movements. Encoding algorithms will use the calibration data and the decoded data to create the appropriate spatial and temporal stimulation patterns to evoke imagined movements.

Each subject will be asked to participate in test sessions, for up to 3 times a week for about 60 months. Each session will typically last less than 4 hours (including setup time). The first 30 minutes, approximately, will be needed for setup of the Blackrock and stimulator system. Once the stimulator is calibrated, the participant will be asked to imagine wrist and hand movements and the decoding algorithms will identify the desired movements. Once a select set of imagined movements have been identified, the stimulator system will apply the appropriate spatial stimulation patterns to the forearm to achieve motion in the paralyzed limb. This will give the patient voluntary control of the select movements in the paralyzed limb. Neurophysiological recordings and evaluations will also be conducted during these test sessions. Active stimulation time will be monitored to avoid fatigue. Trained study personnel will set up and perform the device during the study visits. At the conclusion of the study, the patients will have the cortical implant removed via a second procedure.

The participant(s) will receive haptic feedback above the level of their injury during motor tasks to enhance their motor performance. Haptic feedback simply provides a skin sensation (e.g. vibration), is well characterized in the literature (Shull & Damian, 2015), and is a well-studied and safe stimulus carrying no significant increase in risk. The apparatus will be electrically isolated from the participant. The participants currently receive electrical skin stimulation for feedback I the study. Haptic feedback is a non-electrical safer means of providing even more meaningful sensory information to enhance motor capability.

During this phase of the study a virtual reality headset may be used to provide visualizations of imagined movements. If the virtual reality headset is not used, the virtual environment will be displayed on a screen. On occasion, the virtual reality headset may show the participant incongruent movements, that is, movements different from reality, to study the participant's sense of agency. This reanimation study offers a unique opportunity to study the neural mechanisms of motor awareness, such as sense of agency or movement intentions. Agency is the sense that we control the actions of our own body (Gallagher, 2000; Jeannerod, 2003) and is a fundamental aspect of the experience of self. In this study, normal efferent and afferent sensorimotor information is replaced by the reanimation system and visual feedback, respectively. Congruent and incongruent visual feedback presented via virtual reality may

provide important information about the fundamental mechanisms of self-awareness. The importance of showing both congruent (the VR representation looks the same as the intended movement) and incongruent (the VR representation shows different movement than the participant's intended movement, is important in understanding whether or not the participant is self-aware of the movements he is making with his paralyzed limb. This type of VR experiment is currently being done with the participant (i.e. showing congruent and incongruent movements), but on a flat screen which is a less immersive and less engaging environment. The addition of the device may remove some bias of the participant being able to see his limb, which is typically covered to some degree, but is never completely out of view.

Use of VR will advance our current "screen-limited" understanding of the reasons that influence ownership or control a person with tetraplegia may have over a hand or limb they cannot feel. It is anticipated that improving visualization and subjective feeling of movement during training will enhance training efficiency and make it easier for participants to move their limbs. We will explore whether brain-computer interface training using virtual reality decreases training time compared to standard (non-VR) training protocols.

A brain machine interface is expected to function at all times, interpreting brain activity and producing movements. One way our brain limits the production of activity from neural activity in the motor cortex is by gaiting the signal emanating from motor cortex during various state of consciousness. Therefore the brain machine interface should be able to understand different brain states and adjust its function appropriately. Currently we have very limited knowledge about the activity of motor cortex during sleep in primates. Some have suggested that the activity of neurons during certain parts of the sleep cycle may be related to motor learning. EEG/EMG recordings and intracortical data from our participants will allows us to better understand the relationship between brain activity and motor output during various stages of sleep.

Additional to the weekly test sessions, the participant will be admitted to The Ohio State Wexner Medical Center for overnight sleep evaluations. We will ask the participant to perform a variety of motor tasks. Those will be similar to the ones that the participant performed during the recording sessions. While the participant is performing the motor tasks we will record EMG

from biceps, triceps, and deltoids along with recording the EEG and intracortical activity. We will continuously record this activity throughout the night in order to correlate it with various sleep stages.

3.2.4 Phase IV - Follow-up

The subject will have the device explanted when the study team and Principal Investigator have determined the subject is healthy enough to undergo explantation. After explantation surgery, participants will be ask to complete the same fMRI, neurophysiological recordings, neuropsychological tests, and TMS procedures as they did during the baseline phase.

3.2.5 Study Specific Procedures

Neuropsychological Tests

Neuropsychological tests are useful to us to help categorize whether there are minimum neuropsychological criteria for successful patient selection and to determine safety (i.e., whether the procedure carries risk of decline in neuropsychological function post-explant).
Neuropsychological tests will include but not limited to:

- Motor-Free Visual Perception Test (MVPT-3)
- Wechsler Adult Intelligence Scale (WAIS-III)
- Wechsler Memory Scale (WMS-III)
- Delis – Kaplan Executive Function System (DKEFS)

Neurophysiological Recordings

The neurophysiological recording and evaluations will include Electromyography (EMG)/Nerve Conduction Studies (NCS), Electroencephalography (EEG) EEG, Quantitative EEG (QEEG), and evoked response assessments involving the Event-related Potential (ERPs) and steady state sensory evoked potentials (SSEP). These studies are non-invasive and are routinely performed in the hospital and the clinic by the Ohio State Neurophysiology, PM&R and epilepsy teams. These studies will be performed at various times and will involve spontaneous recordings as well as recordings linked to decision making paradigms as well as auditory, tactile and visual non-

invasive stimuli. These evaluations may also be performed in conjunction with intraoperative microelectrode recording and stimulation.

Electroencephalography (EEG) is a routine physiological measure of cerebral function that has been used to evaluate TBI as well as to prognosticate survival and global outcome after TBI. Quantitative EEG (QEEG) methods evaluate brain functions and task specific EEG changes that can provide information about patterns of brain activity related to attention, learning and behavior. QEEG results in the same patient before and following cortical array implantation will allow changes in brain function to been quantified. Event-related potentials (ERPs) reflect processing that involves selective attention, memory, comprehension and other types of cognitive activity in the brain. ERP provides a non-invasive method of studying cognitive processes in both normal and pathological states. Comparing recordings before, during, and following cortical array implantation will allow changes in cognitive activity to be quantified. P300 is an ERP elicited by visual stimuli. The characteristics of the P300 have been used as metrics of cognitive function. Steady state evoked potentials to periodic stimuli and somatosensory evoked potentials can be used to quantify and characterize the strength of sensory signals that reach the brain for processing. This information is critical for phenotyping the degree of disruption of sensory tract inflow of spinal cord injured patients, evaluating the somatosensory contribution to motor ERPs and intracortical motor unit activity, and determining whether plasticity changes sensory tract inflow between pre- and post-implant conditions.

Electromyography (EMG) and nerve conduction studies (NCS) evaluate peripheral sensory and motor nerve pathway integrity, which can be lost to different degrees by patients with different levels and severity of spinal cord injury. EMG of the patient's limbs will be collected pre- and post-implant and during decoding/stimulation to quantify and characterize the strength of voluntary motor signals that reach limb muscles. This information is critical for phenotyping the degree of disruption of motor tract outflow of spinal cord injured patients, evaluating voluntary vs. brain-machine interface stimulated motor patterns that can be elicited, and determining whether study participation is associated with plasticity changes in motor tract outflow from brain through the spinal cord. Nerve conduction studies (NCS) will be collected pre and post-

implant to characterize the integrity of peripheral sensory and motor pathways, which further helps to phenotype patients with spinal cord injury.

Functional magnetic resonance imaging (fMRI)

We are collecting pre-implantation fMRI in order to localize the neural representations of movements of the upper limb, wrist, hand, and/or fingers. This information will be combined with anatomical information, clinical judgment, and intraoperative stimulation and recording to select the cortical implant placement site. After explantation surgery, we will be collecting fMRI to determine if training and use of the Neural Bridging System has resulted in any change in the locations of neural representations of movements of the upper limb, wrist, hand, and/or fingers. In both pre-implantation and post-explantation fMRI sessions, we will ask the participant to complete a task with visual and/or auditory stimuli designed to evoke neural representations of the movements of interest.

Transcranial magnetic stimulation (TMS)

To complement the fMRI motor mapping of the motor cortex that is being used for pre-surgical implant location planning and post-explant evaluation of motor cortex plasticity, we will also include transcranial magnetic stimulation (TMS) pre-implant and post-explant to map the hand and arm area of the motor cortex. TMS is a non-invasive brain stimulation method that delivers a magnetic pulse through the surface of the skull to the motor cortex. This induces a depolarization of neurons in the corticospinal tract, which results in a twitch of peripheral limb muscles innervated by that brain region. This modality is commonly used clinically as an alternative to fMRI for pre-surgical motor mapping to assist in planning prior to brain surgery. It is used experimentally to investigate corticospinal tract plasticity associated with motor recovery, e.g., after stroke. Potential risks include seizures (2%, mostly among patients who were previously known to have seizures) and headache. Mapping of the hand/arm area with MRI-navigated TMS in patients with spinal cord injury serves 3 purposes: 1) it validates the cortical motor maps obtained through fMRI; 2) it distinguishes the sectors of cortical motor maps that are capable of controlling voluntary motion through the corticospinal tract in the spinal cord from areas that have been rendered mute from cord injury; and 3) it allows for quantification of plasticity, or change in sectors of motor maps that are capable of controlling voluntary motion through the corticospinal tract after stimulator explant.

We will perform TMS pre-implant (baseline, phase I) and post-explant (follow-up, phase IV). We will deliver navigated TMS based on the patient's brain MRI scans to stereotactically identify and target near the "hand knob" of the primary motor cortex on the central sulcus. Recording EMG electrodes will be placed on the skin surface above the most distal upper limb motor groups under voluntary control by the patient, as defined by the pre-implant EMG study, as well as the extensor digitorum communis (EDC) and the abductor pollicis brevis (APB). We will find motor threshold, defined as the lowest stimulation intensity that produces a motor evoked potential, or EMG twitch response, of 100-500uV in the target voluntary muscle group on at least 50% of trials. We will start at an intensity of about 35% of stimulator output, adjust intensity up if needed until we are able to see twitch responses, then use a staircase method to adjust intensity up/down to find the motor threshold. The staircase will lower stimulation intensity 1-2% for trials with an EMG peak-to-peak response >500 uV or increase the intensity 1-2% for trials with EMG responses <100 uV.
Using the 110% of the MT intensity defined in the previous step, we will determine the spatial extent of the upper limb cortical motor map by stimulating over a grid overlaying the central sulcus, precentral gyrus, postcentral sulcus and precentral sulcus and reporting locations with motor evoked potentials (MEPs).

3.3 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, as well as effects related to the surgical procedure and device-related.

Primary and Secondary Outcomes

The primary outcome measure of this study is the achievement of voluntary movement of the upper extremity. Based on previous neural decoding that has been demonstrated in humans (Bouton 2009), it is expected that many of the following movements will be recognizable and classifiable in the motor cortex and can be achieved physically through the multichannel

stimulator: wrist flexion, extension, adduction, and abduction; forearm pronation/supination; flexion and extension of fingers.

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)

4. Risk Analysis

4.1 Risks

The surgical risks for implantation are the same as for any intracranial craniotomy, image guided procedures and implantable device such as a deep brain stimulator or a motor cortex stimulator procedure. This includes hemorrhages (intraparenchymal, subdural or epidural hematoma), paralysis, coma and/ or death, stroke, leaking of fluid surrounding the brain, seizures, infection, allergic reaction, temporary or permanent neurological complications, confusion or attention problems, pain at the surgery sites and headaches.

Training and therapeutic sessions involving BCI regulated 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 stimulator in the Neural Bridging System, 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. Despite these built-in safety limits, current and power density could exceed FDA guidelines if electrodes lift off the skin. This has the potential to cause causing minor irritation or first degree burns locally. The research investigator will monitor frequently during test sessions for wrinkles and misalignment of the sleeve, and 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 formally tested for biocompatibility, both in vitro and in vivo, prior to printing and laundering. The printed, laundered sleeve was tested in Battelle′s IRB-approved Able-bodied study for up to 8 hours, with and without similar nontoxic conductive lotion. No adverse skin

reactions were observed. The investigator, who will already be monitoring frequently for signs of irritation from electric shock, will also monitor for signs of allergic skin reaction.

When using virtual reality (VR) systems, there is the risk of feeling nauseous, disoriented or dizzy, similar to sensations of motion sickness. About 1 in 4,000 people using VR systems have a risk of seizures, similar to the risk of having a seizure while watching TV. Showing incongruent movements on the virtual reality headset may causeconfusion or frustration. The researchers will monitor participants closely for signs or symptoms of confusion that may occur.

The study Sponsor-investigator 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 normal expected postoperative complaints or symptoms, unless the event involves a clinically significant change in a patient's severity or duration of symptoms, or that requires clinical intervention other than the ordinary postoperative care. The following are some expected postoperative outcomes that *may* occur: headache, autonomic dysreflexia, incision pain, nausea, vomiting, low grade fever, dizziness, sleepiness, nervousness, insomnia, constipation, urinary retention, confusion, etc.
- 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

4.1.1 Safety Endpoints

The study safety endpoints will include a characterization of all adverse events (AE) for all participants, including those related to the implant surgical procedure, the implantable device,

and stimulation of patients with tetraplegia. In addition, these safety profile elements will be compared across the various phases of the study. Furthermore, patients with clinically significant complications related to surgery (hemorrhage, stroke, infection) will not undergo implantation or further participation in the study.

Participants may choose to withdraw from the study at any point, in addition, the study investigators may decide to conclude a patient's participation in the study for the following medical reasons:

- Onset of epilepsy;
- Significant decrement in neurological exam;
- Development of serious adverse events, physical or psychological, including negative behavioral symptoms, major depression, or suicidal ideation;
- Intra- or extra-cranial infection unresponsive to antibiotic treatment;
- Serious infection around the percutaneous connector unresponsive to antibiotic treatment;
- Development of intracranial hematoma requiring evacuation; and
- Need for urgent Magnetic Resonance Imaging (MRl) of any kind (brain or body).

4.1.2 Serious Adverse Events

A Serious Adverse Event (SAE) is an adverse event that is fatal or life-threatening, permanently disabling, requires or prolongs hospitalization, or results in significant disability, congenital anomaly, or birth defect (OSU IRB Policy v 12/19/16).

4.1.3 Unanticipated Adverse Device Effects

An unanticipated adverse device effect (UADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with the device [and/or stimulation therapy] if that effect, problem, or death that was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants (21 CFR 812.3(s)).

Any UADE will result in an evaluation of that effect as soon as is possible, and will then be reported to the IRB within 10 days (OSU IRB policy v 12/19/16) and to the FDA within 10

working days after the sponsor-investigator first receives notice of the effect(s). [21 CFR 812.46(b), 812.150(a)(1), 812.150(b)(1)]

Device Malfunction

A device malfunction is the failure of a device to meet its performance specifications or other performance as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed (21 CFR 803.3(k)).

4.1.4 Documentation of Adverse Events

All AEs from the time the study informed consent is signed through the time of device explantation will be recorded as AEs on the study adverse event log; each event being documented separately. Any adverse event occurring after this time and is considered related to the device or therapy by the Principal Investigator will be reported. 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.

The Principal Investigator will serve as point of contact to which the team will report adverse events. All non-serious adverse events will be reported to the FDA and to The Ohio State University Institutional Review Board (IRB) during the annual reporting period.

Relatedness will be determined for all events according to the following criteria:

- **Definitely related:** The event is resolved by discontinuing stimulation and another cause cannot be identified.
- **Probably related:** The event resolves upon discontinuing stimulation and cannot be reasonably explained by the subject's current clinical state or any other cause.

- **Possibly related:** The event was likely caused by the subject's current 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".

4.1.5 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;
- Included in the IRB Continuing Review; and
- Included in the FDA Annual Report.

4.2 Procedures for Minimizing Risks

Investigators involved with this study have a great deal of expertise with the management of tetraplegic patients and with craniotomies. The surgical team has over 16 years of experience with deep brain stimulation implants with over 1600 DBS implants for various indications. The study inclusion/exclusion criteria have been developed to select those who would most likely benefit from this study as well as excluding those with higher risks. Study participants will be monitored after surgical implantation in neurosurgical and physiological monitoring units with personnel experienced in the care of complex neurosurgical participants and monitoring neurological status. In the case of cerebrospinal (CSF) leakage or pain, patients will be managed per the standard clinical practice. In case of infection that is not responsive to antibiotic treatment or allergic reaction to the implanted device, the device will be explanted.

Upon completion of the study, participants will have the entire cortical implant system surgically removed. The procedure for removing the device is similar to those of the implant procedure.

Risks for removal are similar to insertion: infection, bleeding, need for further surgery, and seizures.

Post-surgical removal the participants will be asked to come for post-surgery follow up appointments to remove stitches/sutures and wound caring.

Risks are minimized in all of the non-surgical procedures including blood drawing and the neuroimaging procedures by having trained and highly experienced personnel performing all those tasks.

Participants may also terminate from the study if they wish at any time. Study participants may also wish to discontinue participation for any reason. Cortical implant systems will also be removed if the participant/representative asks for removal. Participants 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. In addition, a designated investigator will have access to treatment status at all times and provide that information to appropriate medical personnel in the event of medical emergencies. 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 Wexner Medical Center firewall. Data and safety monitoring activities for this study will continue until all participants have completed their participation in the study.

4.3 Potential Benefits

The intended purpose of neuroprosthetics is to develop devices to replace or improve the function of an impaired nervous system. Thus far, BCI systems have been successful in controlling power chairs, robotic devices and more recently, upper limb movement in animals. Functional electrical stimulation (FES) systems have been created that stimulate muscles and restores functional movement in paralyzed limbs. This is the first study in humans to combine both systems, a BCI and functional electrical stimulation, to produce real-time control of a paralyzed limb.

4.4 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 has no potential for additional neurological recovery 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 resolution stimulation system to bypass the injured spinal cord and produce volitional movement in humans.

The sleeve configuration of the NMES represents an incremental step toward portability for the system. The sleeve provides a less operator-dependent, more convenient application and removal of the electrode cuff. The electrodes and circuitry are otherwise identical to the cuff.

This reanimation study offers a unique opportunity to study the neural mechanisms of motor awareness, such as sense of agency or movement intentions. Agency is the sense that we control the actions of our own body (Gallagher, 2000; Jeannerod, 2003) and is a fundamental aspect of the experience of self. In this study, normal efferent and afferent sensorimotor information is replaced by the reanimation system and visual feedback, respectively. Congruent and incongruent visual feedback presented via virtual reality may provide important information about the fundamental mechanisms of self-awareness. This is clinically relevant to developing neuroprosthetics that maximize user acceptance by enhancing integration with the users' body image. In addition, we will study whether using virtual reality (VR) can provide a more efficient way to train motor cortex neural decoders.

4.5 Device Description

The Neural Bridging System (as shown in Figure 2) is comprised of a Blackrock Microsystems Neuroport device, a personal computer (PC) which runs the re-coding algorithm, and a non-invasive Neuromuscular Stimulator. The Neuromuscular Stimulator has been reviewed and

approved by a registered IRB for use in a study with human participants. In this study both wrist and individual finger movements have been demonstrated (Bouton and Annetta 2012).

The Neuromuscular Stimulator, designed by Battelle Medical Products, is a non-significant risk investigational device; however it is included in this submission for completeness (since the two devices will be used together in the study). In addition, note the Neural Bridging System will be used in support of an IDE study to demonstrate proof-of-concept in a clinical environment. As such, the results from this IDE study will be used to determine feasibility of the product concept and will not be used to support a regulatory clearance or approval submission.

4.5.1 Clinical Safety

Safety risk management for the Battelle BCI-NMES (updated and inclusive of VR device) was performed in accordance with Battelle Process and Product Development SOP 65, Safety Risk Management Procedure, which complies with the requirements of ISO 14971:2007*, Medical devices – Application of risk management to medical devices.* A safety risk management plan was put in place, and potential hazards associated with the use of the device were identified. The risks of the identified hazards were evaluated against the risk acceptability criteria documented in the plan, and controls identified for risks that exceeded the acceptability thresholds. The identified risk controls were incorporated into the product design or clinical trial protocol, as appropriate. A summary of the analysis is included below.

Hazard Analysis Summary (Without VR Device)

A hazard analysis was conducted in accordance with D8208-020 (a document within Battelle Medical Devices Quality System), Neurobridge Clinical Trial Safety Risk Management Plan, and identified the following potential hazards associated with the use of the device:

- Electromagnetic energy
- Thermal energy
- Biological
- Chemical
- Biocompatibility
- Functional
- Use error

- Installation/Service/Calibration
- Warnings

Analysis of potential hazard causes and evaluation of the risk of potential harm was conducted in accordance with D8208-020. The potential hazards required risk controls and the implemented risk control measures are detailed in the following table.

Potential Hazard	Potential Harm	Risk Control Measures
Electromagnetic energy	Participant/Operator electrical shock; burns	1. Design in accordance with Clause 8.5.1 of IEC 60601-1:2005 2. Current limiting safety circuit (on every channel) 3. Fuse on high voltage power 4. Clinical trial protocol excludes participants requiring use of life supporting/sustaining equipment 5. Clinical trial protocol excludes participants requiring use of critical health monitoring equipment 6. Electrostatic discharge warning label applied to device in area of NSC connectors
	Participant injury or unnecessary medical intervention	1. Clinical trial protocol excludes participants requiring use of life supporting/sustaining equipment
Biological	Participant contact dermatitis or infection	1. NSC materials and conduction enhancer in contact with the Participant are compliant with ISO 10993-1 requirements for limited exposure skin contact. 2. Clinical procedure specifies to not reuse the conduction enhancer.
Chemical	Participant/operator allergic reaction or infection	1. The conduction enhancer in contact with the Participant are compliant with ISO 10993-1 requirements for limited exposure skin contact

		2. The NSC materials in contact with the Participant are compliant with ISO 10993-1 requirements for limited exposure skin contact 3. Participant monitored for allergic reaction to conduction enhancer that could result in classification as clinical adverse event
Biocompatibility	Participant/operator allergic reaction or infection	1. The conduction enhancer in contact with the Participant are compliant with ISO 10993-1 requirements for limited exposure skin contact 2. The NSC electrode material in contact with the Participant are compliant with ISO 10993-1 requirements for limited exposure skin contact 3. Conduction enhancer formulation stable when subjected to anticipated storage conditions 4. Conduction enhancer formulation stable when subjected to electrical current
Function (inappropriate output)	Participant electrical shock; burns	1. Current limiting safety circuit 2. Fuse on high voltage power supply 3. Incoming parts inspection to verify electrode size
User error (improper operation)	Participant electrical shock; burns	1. Current limiting safety circuit (on every channel) 2. Fuse on high voltage power supply
Installation, service or maintenance	Participant electrical shock or burns	1. Operator trained on clinical procedure to ensure application of conduction enhancer

The risks of harm for all other identified potential hazards were deemed broadly acceptable under the risk acceptability criteria established in D8208-020. Details of the potential hazards identified and evaluation of the risk of potential harm are provided in D8208-022, Neurobridge Clinical Trial Hazard Analysis.

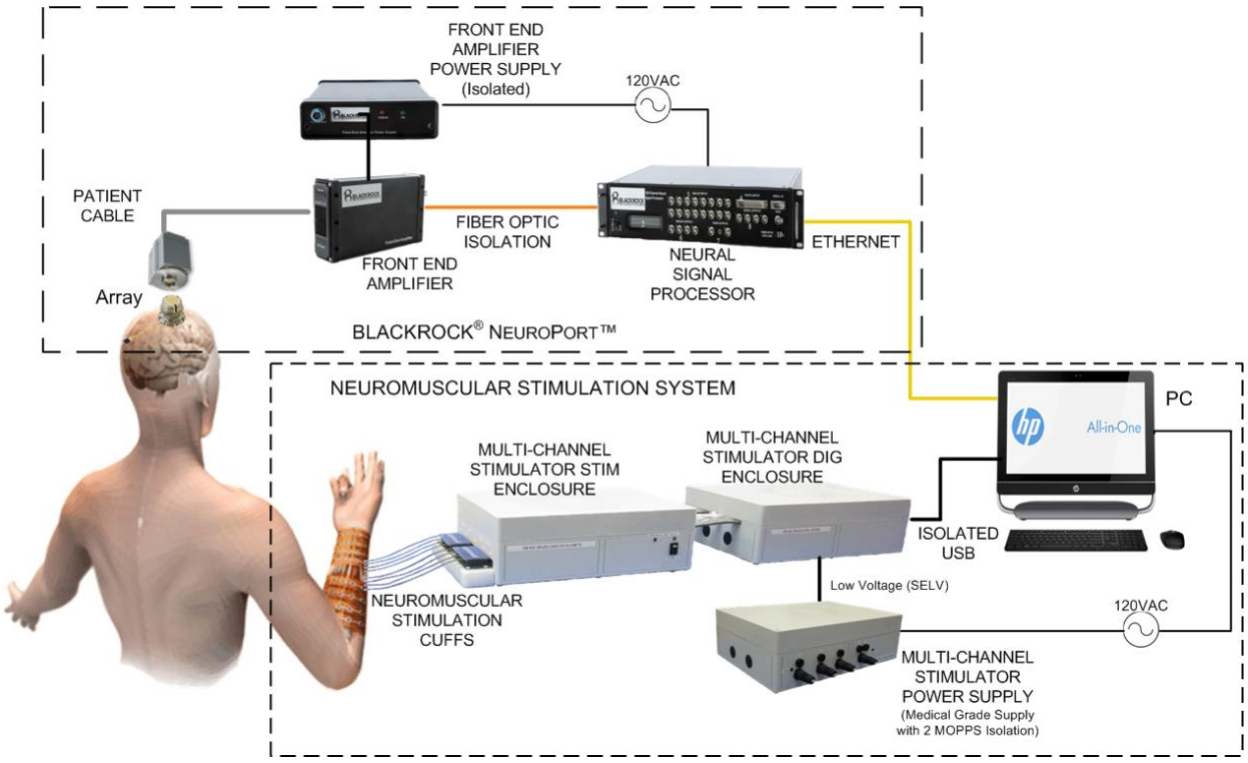

Figure 2. Overall System Diagram with Additional Details.

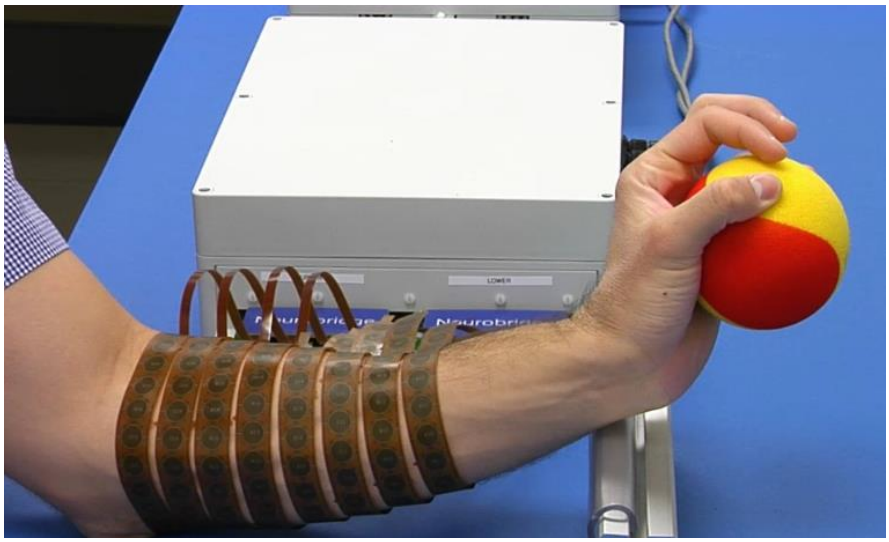

Figure 3. Neuromuscular Stimulator in Able-Bodied Study

Hazard Analysis Summary (With VR Device):

An analysis was conducted by Battelle concerning the use of the VR device with the Battelle BCI-NMES(D8208-051). The risks of adding the Oculus Rift virtual reality headset to the NBS may increase the risk of electrical shock, however, due to the design of the NBS, the risk is not perceived to be significantly increased over wearing the headset without the NBS.

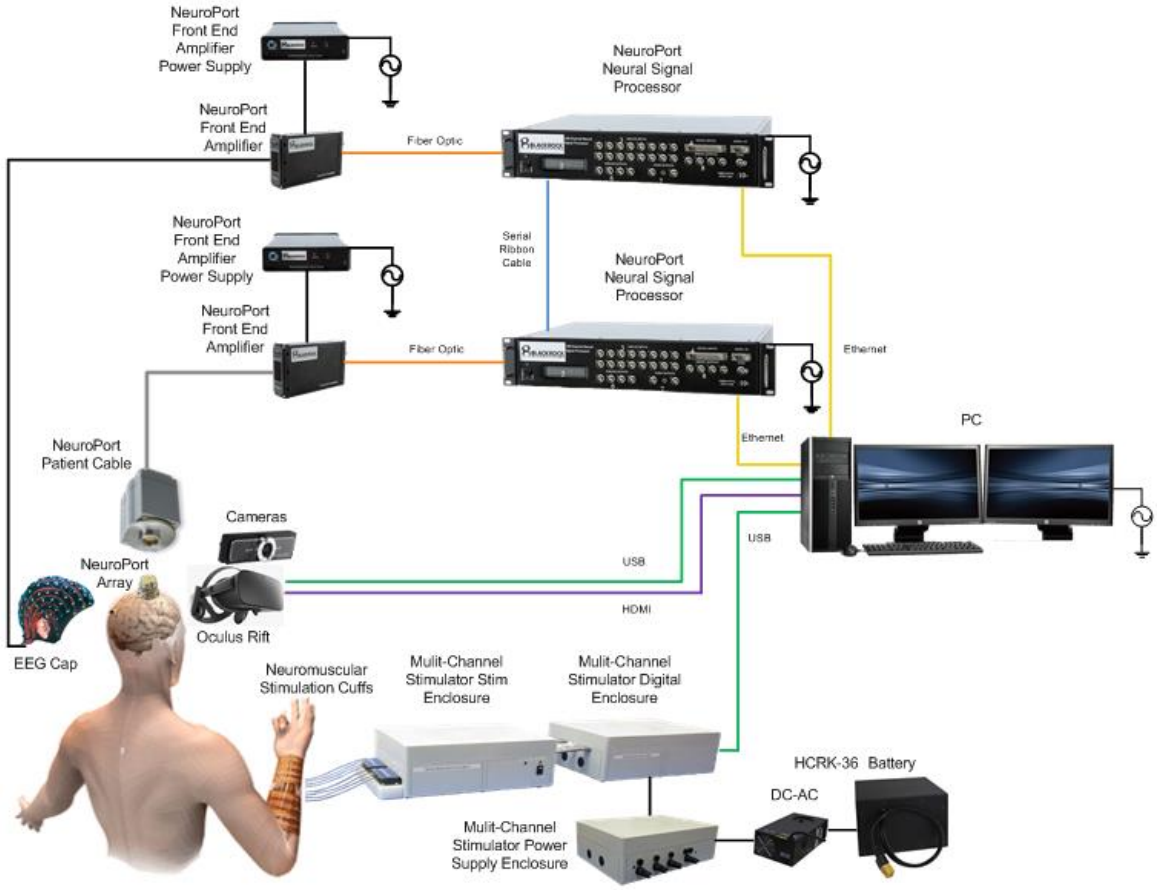

Figure 4. Block diagram of the virtual reality headset used with the Neural Briding System

Risks Associated with the Oculus Rift Virtual Reality Device Alone:

- Seizures (1 in 4000 people)
- Electrical shock
- Repetitive stress injury such as muscle, joint, or skin pain
- Eye discomfort, eye muscle twitching, visual problems
- Dizziness
- Skin irritation

Risks associated with VR use will be mitigated by close patient monitoring, exclusion of patients with history of seizure or pacemaker, electrical isolation from the Neural Bridging System, and periodic device monitoring by the OSU Clinical Engineering Department. The VR device has

passed Clinical Engineering inspection to verify that no significant current is leaking from the electrical components of the device.

4.5.2 Interaction between Devices

The Neuroport device will collect neural signals as a subject imagines various movements, the data will be processed in real-time, and corresponding stimulation patterns will be sent to the Neuromuscular Stimulator. For example, a subject will imagine the flexion of their wrist and the stimulation patterns required to cause wrist flexion will be provided (after a short delay).

The Neuroport device will continuously monitor neural activity, passing the data to the re-coding algorithms running in Matlab (Natick, MA) on the PC. These algorithms will first decode the neural data (as was done in the BrainGate study), and then will provide the spatial and temporal stimulation patterns required to the subject to achieve the imagined movement. The spatial and temporal stimulation patterns for each subject will be different due to differences in anatomy, but will be determined during a 'calibration' session to map the various electrodes to the desired movements.

Once the neural activity resulting from an imagined movement is recognized and re-coded to determine the appropriate stimulation patterns, the stimulation pattern commands are sent to the Neuromuscular Stimulator via a USB connection (that is electrically isolated). The Neuromuscular Stimulator will then activate the appropriate electrodes in the NMES to evoke the desired movement. Furthermore, the Blackrock Neuroport device is electrically isolated from mains power to the patient. In addition, 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 Neural Bridging subsystems that are in contact with the patient are electrically isolated and do not provide an unsafe current leakage path through the patient.

4.5.3 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.
- Nominal output voltage is 200V ± 10% with maximum output of 300V.
- Maximum average current density is 2 mA/cm^2 at the NMES
- electrode surface.
- Maximum average power density is 0.25 W/cm^2 at the NMES electrode surface.

4.5.4 Battelle Quality System

Battelle Medical Products is an operational entity within Battelle in Columbus, Ohio. Medical Products' operations are guided by a set of operating budgets and goals that are defined and updated on an annual basis. As such, Battelle Medical Products is operationally accountable for all projects assigned to the group, administratively accomplished under its organization code(s), which identify Medical Products as the controlling entity for the contractual obligation with our customers.

All projects conducted within Battelle Medical Products fall under the Quality System (QS). The Battelle Medical Products QS is certified to ISO 13485:2003 and ISO 9001:2008,in addition to being compliant with the FDA's Quality System Regulation (21CFR Part 820) and Electronic Records; Electronic Signatures Regulation (21CFR Part 11).

4.5.5 Battelle Software Development

The software used in this study in accordance with the Neural Bridge Software Development Plan (SDP), Document D8208-007 which is derived from the guidance provided by the ANSI/AAMI/IEC 62304:2006 *Medical device software – Software life cycle processes* standard. In addition, Battelle follows the FDA guidelines outlined in the *Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices* (issued on May 11, 2005).

5. Monitoring Plan

5.1 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, sponsors 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.

Study coordinators at the Ohio State University will perform primary data collection based on source documented hospital chart reviews. Paper case report forms (CRFs) will be used to collect study data. Study coordinators will complete all appropriate sections of the CRFs. The study sponsor/PI will review the information documented in the CRFs and verify the information recorded is consistent with medical records and other source documents. Study staff will rectify errors or incomplete entries. Final CRFs will be reviewed and signed by the principal investigator and/or trained study personnel.

A data and safety monitoring committee (DSMC) will be appointed by the principal investigator to evaluate the accumulating data in this trial (21 CFR 812.46). Members of the clinical trial DSMC, who will have pertinent expertise in their medical and/or scientific field, may be chosen from neurosurgery, neurology, physical medicine and rehabilitation, and neuropsychology. The DSMC can advise the principal investigator and make recommendations on the continuing safety of enrolled trial participants, as well as the continuing validity and scientific merit of the trial.

Regulations and Ethical Conduct of the Study

The study will be conducted according to the clinical investigational plan, and the laws and regulations of the United States, parts, 50, 54, 56 and 812 of the US FDA CFR.

PART III – Other Study Information

1. Manufacturing Information

Refer to documentation on file with FDA by Blackrock. For information on the specific devices to be used in this study, a right of reference letter written by Blackrock, granting permission for the FDA to access such documents will be provided.

2. Investigator Agreements

Sample Investigator Agreement Document (As provided for in 21 CFR 812.43)

I am a physician who is familiar with tetraplegic patients.

I have never been involved in an investigation that was terminated.

I am committed to conduct the investigation in accordance with the agreement, the investigational plan, the applicable FDA regulations and the conditions of the reviewing IRB and the FDA.

I will supervise all testing of the device involving human subjects.

I will ensure that the requirements for obtaining informed consent are met.

I am committed to providing sufficient and accurate financial disclosure information and update information if any relevant changes occur during the investigation and for one year following the completion of the study.

_____

Signature

_____

Name (print)

_____

Date

_____

Witness

3. List of Investigators:

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4. Certification of Investigator Agreement

I certify that all investigators have agreed to follow the applicable clinical investigator protocol in this application. I have submitted the written protocol to the Institutional Review Board. All participating investigators agree to conduct the investigation in accordance with the agreement, the investigational plan, the applicable FDA regulations, the conditions of the reviewing IRB and the FDA. I certify that the list of investigators in this application identifies all current investigators. Additional participating investigators will be added only when they have obtained IRB approval and have signed an investigator agreement.

_____

Signature

_____

Name (print)

_____

Date

5. IRB Information

IRB Chairperson:

Karla Zadnik, OD, PhD

IRB Locations:

Ohio State University

Office of Responsible Research Practices

300 Research Foundation Building

1960 Kenny Road

Columbus, OH 43210

6. Device Sales Information

This study is an investigator/sponsor initiated study utilizing commercially available devices for an unapproved indication. Study participants will not be charged for the device during the study,

and participants will not be paid to participate in the study. The conduct of this study does not involve the sale or commercialization of the therapeutic use of the devices.

7. Device Labeling

Caution: Investigational device. Limited by Federal law to investigational use only.
Blackrock Microsystems Neuroport device is a commercially available device being used outside its FDA-approved indications for use (it is being used greater than 30 days). The array used in the Neuroport system has been successfully used in study participants well beyond 30 days, as for example, 1000 days in the Braingate study (Simeral et al, 2011). This investigational system in conjunction with the Battelle Neuromuscular Stimulator or its package will be labeled with the following information: the name and place of business of the manufacturer, packer, or distributor (in accordance with 801.1), the quantity of contents, if appropriate, and the following statement: **"CAUTION--Investigational device. Limited by Federal (or United States) law to investigational use."** In addition, the label will describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions. The labeling of the device will not represent that the device is safe or effective for the purposes for which it is being investigated.

These devices will be treated as investigational-use devices since they are being used outside of approved indications and labeling. Information on each device used in the study will be documented, and device accountability for each device used will be maintained. Only approved investigators will implant devices in participants participating in this study.

8. Device Location

The study is based at Ohio State University Wexner Medical Center. The Neuromuscular Stimulation device is external and will be taken off study participants after each session.

9. Informed Consent Materials

A sample of the revised participant informed consent document is provided. Once this revised IDE is approved by FDA, the protocol and associated informed consent will be submitted to the

OSU IRB. All participant /legal representatives will sign an IRB approved informed consent for participation in research prior to enrollment in this study under this protocol.

10. Contact and Correspondence Address

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cc: Angela.Emerson@osumc.edu; Carson.Reider@osumc.edu

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