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CLOSED-LOOP AFFERENT NERVE ELECTRICAL STIMULATION FOR REHABILITATION OF HAND FUNCTION IN SUBJECTS WITH INCOMPLETE SPINAL CORD INJURY

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CLOSED-LOOP AFFERENT NERVE ELECTRICAL STIMULATION FOR REHABILITATION OF HAND FUNCTION IN SUBJECTS WITH INCOMPLETE SPINAL CORD INJURY

THESIS

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Biomedical Engineering in the College of Engineering at the University of Kentucky

By

Christopher John Schildt

Lexington, Kentucky

Director: Dr. Sridhar Sunderam, Associate Professor of Biomedical Engineering

Lexington, Kentucky

August 8, 2016

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ABSTRACT OF THESIS

CLOSED-LOOP AFFERENT NERVE ELECTRICAL STIMULATION FOR REHABILITATION OF HAND FUNCTION IN SUBJECTS WITH INCOMPLETE SPINAL CORD INJURY

Peripheral nerve stimulation (PNS) is commonly used to promote use-dependent cortical plasticity for rehabilitation of motor function in spinal cord injury. Pairing transcranial magnetic stimulation (TMS) with PNS has been shown to increase motor evoked potentials most when the two stimuli are timed to arrive in the cortex simultaneously. This suggests that a mechanism of timing-dependent plasticity (TDP) may be a more effective method of promoting motor rehabilitation. The following thesis is the result of applying a brain-computer interface to apply PNS in closed-loop simultaneously to movement intention onset as measured by EEG of the sensorimotor cortex to test whether TDP can be induced in incomplete spinal cord injured individuals with upper limb motor impairment. 4 motor incomplete SCI subjects have completed 12 sessions of closed-loop PNS delivered over 4-6 weeks. Benefit was observed for every subject although not consistently across metrics. 3 out of 4 subjects exhibited increased maximum voluntary contraction force (MVCF) between first and last interventions for one or both hands. TMS-measured motor map volume increased for both hemispheres in one subject, and TMS center of gravity shifted in 3 subjects consistent with studies in which motor function improved or was restored. These observations suggest that rehabilitation using similar designs for responsive stimulation could improve motor impairment in SCI.

KEYWORDS: EEG, PNS, nerve stimulation, TMS, spinal cord injury

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August 8, 2016

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Chapter 1: Introduction

1.1 Motivation

The brain and spinal cord are responsible for transmitting electrical signals to directly or indirectly control many complex functions of the body including movement, feeling, breathing, and hormone balance. When the electrical signal or nerve responsible for transmitting the signal is disrupted from reaching its target, impairment of any of these functions can result. SCI is a traumatic event that prevents signal transmission due to damage in the spinal cord and the resulting impairments can impact a person's physical, psychological, and social well-being (Singh 2014). The severity of impairment depends on both the spinal cord level and completeness of injury. Complete SCI is the total loss of function in parts of the body innervated by spinal segments at and below the level of injury. To date there are no practically effective means for regenerating tissue in the brain or spinal cord and therefore loss of function resulting from complete SCI is permanent. However, in incomplete SCI undamaged pathways preserve some sensory, motor, or autonomic function, and also provide potential for relearning lost motor function.

Motor therapy can sometimes help improve residual motor function in incomplete SCI. Plasticity is the property of nervous tissue to change the strength and number of synapsis over time, and use-dependent plasticity (UDP) is plastic change only in response to exercise and is thought to be crucial in motor recovery (Nudo 1996). Thus, motor rehabilitation is possible because synapses can be trained to enhance signal strength. Electrical stimulation can further augment UDP during motor therapy. Peripheral nerve stimulation (PNS) is commonly used for protocols in which electrical stimulation "strength" is dialed down to a level at which only afferent nerve fibers which transmit sensory information are targeted and avoids inducing muscle contractions. PNS can increase cortical excitability—an indicator of UDP—and increase the effectiveness of subsequent motor training if applied in tandem. Typical PNS protocols involve a couple of hours of regularly pulsed electrical stimulation of afferent nerves in the impaired limb prior to motor exercise. PNS delivered in this manner is 'open-loop' since delivery is preprogrammed for a fixed duration regardless of the patient's state of activity. These therapies attempt to "prime" the brain so that it responds better to subsequent motor

training. Since afferent feedback is essential for normal movement and the development of motor skills, it seems likely that PNS may be still more effective if applied in 'closed-loop': i.e., only in response to subject's volition or intent to move (IM). If delivered in a closely correlated manner with IM in a motor task, closed-loop PNS protocols may further increase cortical excitability via the mechanism of timing-dependent plasticity.

1.2 Spinal Cord Injury Prevalence

The National Spinal Cord Injury Statistics Center 2016 Data Sheet reports the number of people in the United States living with spinal cord injury (SCI) is approximately 282,000, and since 2010 45% of new SCIs result in incomplete tetraplegia. The National Institute of Neurological Disorders and Stroke states that the annual cost of managing spinal cord injuries in the United States is $3 billion each year (Updated April 5, 2016). The World Health Organization (2013) predicts the global incidence of SCI to be between 40 and 80 cases per million population and that SCI survivors tend to die 2 to 5 times earlier than those without SCI, and in both high and low-income countries there is increased rates of depression in SCI subjects. The World Health Organization also notes that caregivers typically experience isolation suggesting that more are individuals are affected than SCI patients alone. A better understanding of SCI and improved therapies to increase independence are needed to leverage the psychological and economic burden experienced by SCI subjects and caregivers alike.

1.3 Research Questions

This thesis describes a study in which we attempt to improve upon the effectiveness of current motor therapies for incomplete SCI through closed-loop application of PNS based on IM detected from the brain using an electroencephalogram (EEG). We hope to address the following primary research questions:

1) Do subjects with incomplete SCI benefit functionally from repeated sessions of closed-loop PNS therapy?

2) Does the correlation between PNS delivery and actual movement or IM explain functional changes observed over the course of intervention?

1.4 Thesis Outline

Chapter 2 (Background) introduces SCI, reviews research literature pertinent to the primary research questions, and covers methods to be employed in the analysis of outcomes. Chapter 3 (Methods) provides an overview of the study protocol and describes procedures and rationale for data collection and analysis. Chapter 4 (Results) presents the results of analysis using methods described in Chapter 3. The results are reviewed in Chapter 5 (Discussion) with reference to the aims of the study and placed in the broader context of the field. Since this thesis presents data from an ongoing study, it concludes in Chapter 6 with summary remarks directed toward the primary research questions and an outlook for future research directions. Each section is prefaced with an overview to motivate the organization of the sub-sections and simplify navigation.

Chapter 2: Background

2.0 Overview

Section 2.1 Spinal Cord Injury introduces SCI and presents the problem of motor impairment in incomplete SCI. Section 2.2 Motor Therapy covers clinical motor therapies: massed practice exercise, functional electrical stimulation, and peripheral nerve stimulation. The mechanisms of action of successful motor therapy outcomes are described: use-dependent plasticity and increased cortical excitability. Timing-dependent plasticity is introduced as a proposed mechanism not explicitly addressed in the design of current therapies, but which may further improve motor rehabilitation if it were. Open-loop therapies do not explicitly attempt to induce timing-dependent plasticity since they do not rely on the subject's intent to move (IM) for benefit. Transcranial Magnetic Stimulation (2.3) is both an important diagnostic and therapeutic device in clinical applications and the current study. A description of TMS function and utility is provided. In 2.4 Brain-Computer Interfaces in Movement Rehabilitation, examples of closed-loop protocols which have been employed for the delivery of stimulation from the detection of real, imagined, or intended movement are presented. Each example relates how corticospinal excitability or motor function is changed. 2.4 Machine Learning Methods briefly describes classifiers used in this study and commonly used in literature. We conclude the chapter with a restatement of the current study in section 2.5.

2.1 Spinal Cord Injury

The spinal cord is composed of many individual nerve cell projections called axons which transmit information between the body and brain, and run down the length of the spine through bones called vertebrae. Traumatic impact to the spine causes vertebrae to fracture or dislocate. Displaced vertebrae can bruise or tear the spinal cord destroying axons. When all the axons are destroyed in a cross-sectional area complete SCI results and function is lost below the level of injury. However, injury doesn't always destroy all the axons and otherwise results in incomplete SCI. Incomplete SCI is variable depending on which specific signaling pathways are preserved/damaged although the possible extent of impairment is still dependent on the highest spinal segment to be damaged.

Classifying SCI level requires a clear distinction between the spine, composed of vertebrae, and the spinal cord, which is enclosed by the vertebrae. The spinal cord is divided into neurological segments corresponding to a pair of spinal nerves and the area of the body each innervates. The spinal cord ends at the second lumbar vertebra (L2) in most adults, however spinal segments continue down to sacral levels below the lumbar vertebrae—the bottom of the spine. The arm and hands are innervated by segmental levels C5, C6, C7, C8, and T1. Thus, upper motor incomplete SCI can result when the spinal cord at the level of any of these segments are damaged.

2.2 Motor Therapies

In incomplete SCI some central nervous system pathways are preserved and permit some limited functioning of their innervated targets. Motor rehabilitation may increase residual function. Restoring the ability to perform activities of daily living—eating, bathing, dressing, continence, toileting, and walking or transferring—generally take priority in the design of motor therapy since they are most essential to increase quality of life (Collinger 2015). Motor rehabilitation is possible due to neuroplasticity in the nervous system—the ability of neural circuits to reorganize in response to experience, training, or learning. Rehabilitation is complicated by changes that occur automatically following SCI at multiple levels of the nervous system, which can be adaptive or maladaptive (Dobkin 2009). Thus, motor therapies are designed to promote adaptive changes.

Use-dependent plasticity (UDP), or neuroplastic change only in response to attempted or assisted movement underlies the primary mechanism of efficacy for motor therapies, and is heavily dependent on the frequency and intensity of practice (Dromerick 2013). The most basic approach for upper motor therapies often entails many repetitions of generalized whole limb movements to fine single finger manipulations and is referred to as massed practice.

Electrical stimulation offers a means of artificially inducing or boosting either afferent or efferent neural signals to aid motor therapy. In peripheral nerve stimulation (PNS), afferent nerve potentials are electrically induced to increase corticospinal tract excitability related to the targeted limb. Typical PNS protocols (Sawaki 2006, Ridding 2001) deliver pulsed electrical stimulation to the afferent nerves of the forearm for 2 hours

prior to upper motor exercise, leading to increased motor-evoked potential (MEP) amplitude and motor cortex area devoted to the innervated limb, as measured by transcranial magnetic stimulation (TMS) (Ridding 2001). This 'open-loop' PNS protocol can be coupled with subsequent motor training to augment UDP. In contrast with PNS, which activates afferent fibers to increase somatosensory cortical excitability, functional electrical stimulation (FES) is applied to induce muscle contractions required in the impaired limb to successfully execute a given motor task.

Somatosensory and motor cortices—the area of the brain most closely associated with touch and volitional movement execution, respectively—are strongly interconnected in humans (Kaas 1993 and 2004). Learning and properly executing directed motor movements is believed to be critically dependent on these interconnections (Asanuma 1981, Caria 1997). This underlies the critical role afferent sensory information has in motor rehabilitation. Increased excitability in these cortical areas is indicative of plastic change. Increased cortical excitability results in increased corticospinal excitability when motor commands of the same magnitude result in stronger excitation of target muscles (see 2.3).

PNS (when combined with motor therapy) and FES both increase corticospinal excitability through UDP (Andrews 2013, Popovic 2006, and Quandt 2014). However, PNS does not require volitional control of movement, and FES may be the sole cause of successful movement execution. FES provides the benefit of allowing a subject to receive visual confirmation of movement when afferent sensory pathways are severely impaired, but subject volition is not guaranteed for successful movement execution or stimulation.

Generally, PNS and FES protocols are administered regardless of subject volition or awareness. This could result in reduced effectiveness of motor therapy. Sustained, increased cortical excitability can be induced via timing-dependent plasticity. This has been demonstrated by synchronizing PNS to arrive at the sensorimotor cortex within 100ms of a transcranial magnetic stimulation (TMS) induced motor-evoked potential (MEP) (Wolters 2003, Stefan 2000). If pulsed TMS produces the same executive command signal that movement intent does in the primary motor cortex, perhaps motor therapies designed to induce timing-dependent plasticity via PNS applied only in response to

movement intent will better facilitate adaptive cortical change and therefore motor outcomes.

2.3 Transcranial Magnetic Stimulation

TMS is frequently employed to assess how easily the motor cortex can produce movement in a target limb or muscle, and can be used as a gauge of corticospinal excitability. In TMS a current is pulsed through a coil placed close to the scalp to produce a magnetic field which in turn induces an electric field in the cortex of the brain. The motor cortex is somatotopically arranged, meaning that each area of the body corresponds to an area of the cortex. When TMS is applied to a specific point in the motor cortex it may produce a corresponding muscle contraction referred to as a motor evoked potential (MEP) mediated by corticospinal tracts. The relative arrangement and representation of the body in the human cortex is commonly referred to as the homunculus because certain areas of the body such as the hands are over represented and the relative proportions to other body parts are grossly exaggerated compared to observed corporeal proportions. There is a separate homunculus for both the somatosensory and motor cortices although they are very similar in their relative arrangement. This is not surprising given that the two areas are adjacent and contain many interconnections. TMS can be used to derive a subject-specific 'motor map' by probing the motor cortex for every location which elicits an MEP in a specific muscle, for example the abductor pollicis brevis (APB) of the thumb.

2.4 Brain-Computer Interfaces in Movement Rehabilitation

The notion that closed-loop application of PNS can induce beneficial TDP requires the subject to deliberately produce executive motor commands which must be detectable using one or more physiological measurements (e.g., EEG, EMG, and force) so that PNS can be applied synchronously. In subjects with severe impairment, muscle activity associated with volitional effort may be hard to distinguish from the resting state. In such cases, a brain-computer interface (BCI) that detects volition using EEG signals may be helpful. A BCI uses neural signals to drive an external device and can be employed to determine the subject's intent to move to trigger afferent feedback in the form of PNS, effectively closing the control loop between volition and somatosensation. Detecting movement directly from the brain is useful because movement may not be observable or

easily derived from force measurement devices, but the attempt can be detected directly from electrical activity produced in the brain. BCIs have been implemented to move cursors on a computer screen, drive exoskeleton suits, and even transmit messages brain-to-brain using only thought (Wolpaw 1991, Elnady 2015, Grau 2014). BCIs have been explored as a means for restoring or replacing motor function in pathological conditions where normal use of the musculo-skeletal system have been compromised, i.e. amyotrophic lateral sclerosis, stroke, and SCI. Recording and processing brain activity in real time is possible with fMRI, MEG, ECoG, single neuron recordings, and surface EEG. Perhaps the most attractive of these is EEG since it is non-invasive, relatively inexpensive, easy to implement, and provides reasonably good temporal resolution of underlying neural processes in real-time.

Detecting movement from the EEG generally entails tracking changes in either slow motor related cortical potentials (MRCP) or sensorimotor rhythms (SMR). MRCPs are slow (typically 0.1 – 1Hz) cortical oscillations first documented by Kornhuber and Deecke in 1965. The MRCP is a slow transient change in EEG potential that precedes motor execution and is most frequently observed as an increasing negativity with peak negativity occurring at movement onset (Deecke 1969, Deecke 1976, Green 2003). In practice MRCPs are most closely associated with motor planning and generally occur about 2 seconds before motor execution and can be detected up to 1.5 seconds before execution (Shakeel 2015). MRCPs can be qualitatively divided into bereitschafts potential which occur during asynchronous, self-paced, un-cued movement and contingent negative variation, generated in synchronized, cued movement (Ren Xiu 2014). This distinction is important since it has been shown that bereitschafts potentials and contingent negative variations reflect different neural generators (Mads Jochumsen 2015). The SMR is an idling rhythm seen at rest that is modulated by imagined or real motor execution and occurs primarily over sensorimotor cortical areas. Generally the SMR has components in the 8 – 30Hz frequency range and in practice is separated into mu and beta bands (i.e., 8 – 13Hz and 16 – 30Hz, respectively). The BCI employed in this study uses the mu rhythm (8 – 13Hz) characterized by relatively increased amplitude during idle states and decreased amplitude during attempted movement. The mu rhythm amplitude is associated with increased cortical excitability as neuron ensembles generate action potentials out of phase

during movement. In practice, SMR desynchronization can be associated with a specific real or imagined movement task and is commonly referred to as event related desynchronization (ERD). After movement execution or once IM ceases sensorimotor neurons revert back to a less excited synchronized state referred to as event-related synchronization (ERS) which is detectable from EEG as a relatively higher SMR magnitude compared to ERD.

BCIs that attempt to increase the quality of movement-related afferent sensory feedback to improve task performance have been proposed and implemented in a number of studies, and a few are summarized in the following paragraphs. Soekadar et al., 2011 implemented a magnetoencephalographic BCI to detect ERD of the mu rhythm, which occurs during imagined hand opening movement to deliver proprioceptive feedback through an orthotic device that extended the fingers of the hand. ERD was computed as a percent of band power during imagined movement relative to a reference value during non-movement imagination. Increased BCI performance was observed in both healthy and stroke subjects when proprioceptive feedback was graded based on the magnitude of ERD and resulted in an increased ability to modulate SMR.

Niazi et al., 2012 used an EEG BCI trained on actual ankle dorsiflexion to predict self-paced imagination of the same movement from MRCPs and trigger closed-loop PNS. Stimulation was applied to the common peroneal nerve which innervates the tibialis anterior muscle—essential to dorsiflexion—and the intensity set so that it could be perceived, but not strong enough to induce muscle contraction. TMS-induced maximum MEP magnitude increased by 53 ±43% between pre and post intervention for eight healthy subjects indicating increased corticospinal excitability.

In order to correlate changes in cortical excitability with the phase or extent of ERD, Mitsuaki et al., 2013 used a BCI to deliver single and paired pulsed TMS to the right hand motor cortex during imagined right wrist movement. Subjects watched a bar on screen which appeared every seven seconds for five seconds to cue wrist movement. The bar grew to the right or left side of the screen representing magnitude of ERD with respect to EEG power during a reference period preceding the cue, which corresponded to SMR power decrease relative to ERS. When ERD magnitude crossed a predetermined threshold TMS

was applied and the resulting MEP, short-interval intracortical inhibition (SICI), and intracortical facilitation (ICF) responses were recorded in the agonist muscles. MEP magnitudes were measured at rest, 5% ERD, and 15% ERD where ERD was subject-specific and reflected SMR band frequency power contribution loss to total power in the EEG signal. MEP was found to be significantly larger for larger ERD, while SICI decreased and ICF showed no change confirming that increased ERD, corresponds to increased corticospinal excitability.

If TDP is critical to development of MEP then timing of stimulation must be closely tied to activation of the neural generators of movement. In the Niazi study above movement detection occurred on average 125±309 ms before MI onset, which overlaps a broader range than the optimal 100ms window suggested by Stefan et al., 2000. However, pre and post-intervention MEP recruitment curves revealed significant increases in cortical excitability of the tibialis anterior averaged over eight subjects. Two control groups one performing only movement imagination at their own pace without stimulation and the other receiving stimulation randomly without any movement imagination showed increased MEP amplitude, but changes were not significant.

Reynolds et al., 2015 conducted an FES study to compare the effect movement imagination (MI) of hand waving has on ERD from three bipolar EEG locations (C3, Cz, and C4, corresponding to sensorimotor cortical areas) in three protocols: MI before FES, MI before and during FES, and FES applied without any MI. Subjects performed 20 MI of left hand waving and 20 MI of right hand waving prompted by a cue for 3 seconds. FES was set between 10 mA and 17mA so that visible wrist extension occurred. The 3 second MI states and a non-MI state extending from 1.5 seconds to 0.5 seconds before MI were used offline to train a linear discriminant analysis (LDA) classifier. Closed-loop FES stimulation revealed strongest ERDs observed for MI before and during FES, and weakest for MI before FES. This suggests that timing while important may not be specifically critical to onset of timing specifically. In other words, while TDP may be experimentally induced by synchronizing pulsed MEP and PNS to produce increased cortical excitability compared to UDP, a positive reinforcement mechanism of sensory feedback in the form of PNS applied during sustained movement intent may be just a beneficial.

2.5 Classification Methods

To distinguish movement and non-movement states from mu rhythm modulation, machine learning methods are employed both in real-time and in post-hoc analysis. Linear discriminant analysis (LDA) and support vector machines (SVM) are frequently cited as the most successful classification methods for labeling EEG data (Yvonne Holler 2013, Bhagat 2014). LDA and SVM are used to separate data into groups or classes based on a boundary in the EEG feature space that is optimal by some criterion of classification accuracy. Classification usually involves training a discriminative model on data or features known to belong to one or more classes.

LDA reduces the dimensionality of data while preserving class discrimination by mapping features belonging to two or more classes along a hyperplane extending through the feature space such that their projection onto the hyperplane presents greatest separation of samples belonging to each class. SVM considers points from each class which are closest to points of the other class. Parallel support vectors represent the lines marking the boundary of each class and the decision boundary is the parallel line splitting the support vectors. LDA is intuitive, but SVM is more robust to non-normally distributed features since it focuses on the outliers belonging to each class to establish a decision boundary and tends to outperform LDA in EEG feature classification (Ahmad 2015, Garrett 2003). For a more exhaustive description of SVM, see Bennett and Bredensteiner. These classifiers can be utilized to label new data in real-time with limited training, but are used here for post-hoc analysis of EEG to determine movement intent and non-movement intent class discrimination.

2.6 Novel Closed-Loop Peripheral Nerve Stimulation.

There is increasing interest in the development of BCIs for closed-loop sensory feedback and their utility for motor therapy. What follows is the description of a novel closed-loop BCI for detecting and applying PNS in response to cued intent-to-move. Results from a sequence of 12 closed-loop PNS sessions in incomplete SCI subjects are presented through an analysis of functional outcomes, namely grip strength as measured by a hand dynamometer, cortical excitability as measured by TMS-induced MEP

amplitude, and ERD measured in terms of EEG feature contrast between intent to move and resting states.

Chapter 3: Methods

3.1 Study Overview

Subject recruitment and informed consent >> closed-loop PNS screening (>sub flow diagram for session protocol>) >> initial TMS mapping and MEP recruitment curves >> 4 weeks of interventional closed-loop PNS >> post TMS mapping and MEP recruitment curves (See Appendix for flow diagram)

Important terms used: Run (one continuous recording with one acting hand and either 15 or 20 cues), Session (the set of all right and left hand runs acquired in one sitting), Intervention (a collection of 12 sessions between pre TMS and post TMS mappings)

3.2 Subject Inclusion Criteria and Screening

All procedures were performed with the prior approval of the Human Subjects Committee of the University of Kentucky Institutional Review Board (IRB). After giving informed consent, subjects attended an initial screening session with closed-loop PNS, and were invited to participate in three (equally spaced) interventional sessions per week for four weeks. Subjects had been diagnosed with incomplete SCI sustained at least one year prior to their participation at vertebral level C4-C7 and satisfied criteria for a minimum score of D on the American Spinal Injury Association Impairment Scale (AIS), in which limited motor ability and sensation are retained.

3.3 TMS Evaluation

Within three days before the first session of intervention and three days after the last, a TMS map and recruitment curve were determined for the abductor pollicis brevis (APB) of each hand using a Magstim 200 stimulator connected to a figure-8 coil. The APB is critical to hand gripping and is innervated by the median nerve. EMG electrodes were placed over the contralateral APB and initial MEP hotspots determined by manually searching for the point over the ipsilateral sensorimotor cortex which most consistently produced a peak-to-peak response of at least 50μV for a given TMS intensity. The minimum TMS intensity which elicited a 50μVpp MEP response was recorded as the threshold intensity. The stimulation intensity was then set at 1.05 times threshold. The hotspot and surrounding area was then systematically probed at the stimulation intensity with 1 cm^2 resolution. Each location eliciting at least five MEPs > 50μVpp out of ten

stimulations were included in the TMS map. The number of MEP responses above threshold were used to derive a volumetric map of cortical excitability. This process was repeated once for each cortical hemisphere with corresponding contralateral APB muscle.

After TMS mapping recruitment curves were derived for both hands. Ten incremental stimulation intensities were derived at 90%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, and 180% of the threshold intensity. The average MEP peak-to-peak response at the hotspot was recorded out of ten stimulations of the 90% threshold intensity, then 100%, continuing through 180% and the resulting values plotted to derive the recruitment curve.

3.4 Task

Subjects remained seated in their personal wheelchair facing a computer monitor positioned at a comfortable height and distance for viewing. In each run the monitor alternated between Cue On and Cue Off states represented by the appearance and disappearance of a visual cue lasting 4 seconds and a variable 3 to 8 seconds, respectively; the Cue Off duration was randomized to make the appearance of the cue unpredictable. During Cue Off, crosshairs were presented centered on the monitor; this was replaced by three concentric circles during Cue On. Subjects were instructed before the run to remain as physically relaxed as possible while attending to the state of Cue. Subjects were asked to respond to Cue On by squeezing a hand grip dynamometer with a target force determined as a percentage of their maximal voluntary contraction force (MVCF); this was usually set at 20% MVCF. Feedback on the applied force was provided in the form of a gray solid filled circle which grew and shrunk in proportion to instantaneous grip force. Subjects attempted to squeeze hard enough to match the circumference of the gray solid filled circle with the middle of the three concentric circles. After 4 seconds the circles were replaced by the cross hairs and the subject would return to the relaxed state while maintaining attention on the screen. This process would repeat 15 times (15 Cue On state transitions) per run. Before each run MVCF was measured for the active hand, which was switched between left and right for every run. Five runs were recorded for each in hand every session to give a total of 150 cued executions of the gripping task, 75 per hand.

The last three subjects to complete intervention were presented with a total of 200 cued gripping tasks, or 100 per hand each in session; five runs were recorded for each hand, each run alternating to Cue On after Cue Off 20 times for three seconds and a variable four to eight seconds, respectively.

3.5 Data Acquisition and Setup

3.5.1 EEG

A 16-channel biosignal amplifier (g.USBamp, g.tec, Austria) with active electrodes (g.ladybird) embedded in an electrode cap (g.gammacap) was used to record EEG signals at locations C3, C4, CP1, CP2, CP5, CP6, FC1, FC2, FC5, FC6, P3, P4, PO1, PO2, PO7, and PO8 according to the international 10-20 system of electrode placement with AFz as ground and the left ear lobe as reference. All signals were sampled at 512Hz, bandpass-filtered from 0.5-100Hz, and notch filtered at 60Hz to remove power line noise. Recordings in the last three subjects did not include EEG channels PO1, PO2, PO7, and PO8 to make room for EMG signals (see below).

3.5.2 EMG

EMG was recorded over the flexor carpi radialis and flexor digitorum superficialis muscles of both forearms for the last three subjects. The distance from the medial epicondyle of the elbow to the styloid process of the radius was measured. The first electrode was placed a third of this total distance extending distally from the medial epicondyle. The second electrode was placed two inches distally from the first electrode towards the styloid process. EMG was recorded with EEG in place of channels PO1, PO2, PO7, and PO8 and at the same sampling rate and filter coefficients.

3.5.3 Grip Force

A hand dynamometer (Vernier, Oregon) was used to record hand grip force and provide force feedback. The analog voltage output of the dynamometer was sampled using an NI-USB-6009 data acquisition board (National Instruments, Texas). Measurements were collected at 512Hz and converted from Volts to Newtons using the calibration:

$$Newtons = 175.416(Volts) - 19.295$$

Provided by the manufacturer and saved in a file along with Cue state and PNS data.

3.5.4 PNS

PNS electrodes were affixed to the hand to perform afferent stimulation of the distal median nerve in both hands. Optimal electrode position was manually determined by varying the placement of a surface bar electrode with distal cathode until the highest amplitude compound muscle action potentials were elicited in APB as measured by EMG. Ag/AgCl electrodes were placed over the optimal position marked with ink. The cathode was placed proximally to generate afferent potentials. A stimulus isolation unit (models) connected to a square pulse stimulator (Grass Technologies, West Warwick, RI) was used to a deliver pulse train upon detection of movement intent in response to each cue. The pulse train consisted of 5 pulses, 1 ms each, delivered at 10Hz. Stimulus intensity was set in each session to elicit small compound muscle action potentials of 100μV as recorded by EMG without visible muscle contraction.

3.5.5 TMS

Stimulus sites were located using a latitute/longitude-based coordinate system co-registered with a template MRI in the Brainsight^{TM} neuronavigation system (Rogue Research Inc., Montreal, Canada). The frontoparietal region contralateral to each hand was systematically probed with the TMS coil to produce MEPs in the APB. The hot-spot was determined as the location which elicited highest amplitude MEPs. The resting motor threshold (RMT), defined as the minimum TMS intensity required to elicit MEPs ≥50μVpp in 5 or more of 10 consecutive stimulations was determined for the hot-spot, and stimulation intensity set to 110% of RMT. 10 stimuli were delivered to each scalp site at a rate of 1 stimulus every 5 seconds. Each site of the grid was probed until a border location without a response ≥50μV peak-to-peak was encountered for at least 5 of 10 stimuli. The average response, i.e., the proportion of responses above threshold in every series of 10 stimuli, was calculated and saved off-line.

Recruitment curves to measure cortical excitability were determined from the hot-spot by applying 10 incrementally larger intensities from 90% to 180% of RMT. 10 stimulations were delivered at 1 stimulus intensity every 5 seconds and the average MEP at the first intensity then repeated for the next intensity. The entire process was conducted for each hemisphere before and after intervention.

3.6 Detection of Intent-to-Move and Closed-Loop Peripheral Nerve Stimulation

A custom algorithm implemented in LabVIEW computed the current root mean square (RMS) EEG mu band power in consecutive non-overlapping 125 ms windows for all 16 channels of EEG. The cumulative average was updated every 125 ms during Cue Off as a reference. At the start of Cue On, the instantaneous 125 ms RMS mu power was divided by the cumulative average during Cue Off and tracked over time. PNS was applied when this ratio dropped below 1 (unity) for all EEG channels. PNS was also triggered if the measured grip force exceeded a threshold before a detection occurred on the EEG. This ensured that PNS was delivered for as many cues as possible to minimize false negatives. When Cue On transitioned back to Cue Off the cumulative RMS mu power was updated until the next Cue On and the process repeated.

The last three subjects to complete intervention only had 12 channels of EEG most centrally located over sensorimotor areas recorded. The four excluded EEG channels were replaced with EMG signals.

3.7 Outcome Measures

3.7.1 TMS Maps and Recruitment Curves

The normalized TMS map volume is a simple way to measure motor representation across the cortex. Any MEP recorded with muscle activation before stimulation above a threshold, typically 20uVpp, is removed. The exclusion threshold may be set above 20uVpp if the subject has steady pre-activation or if non-biological noise is present. The acceptable MEP intensities are averaged and saved for each location. Each location and average MEP is normalized by the single maximum amplitude measured in each hemisphere across both pre and post TMS sessions. The resulting normalized map volumes are presented in 4.2.1 and the table summarizes normalized map volume magnitude and change.

The TMS map center of gravity (table 3) is found using the average MEP of each location. This provides a simple measure of focal activation and changes between first and last sessions are reported in centimeters with a positive y-coordinate change indicating anterior shift of TMS map, and positive x-coordinate change indicating lateral shift.

For subjects with measurable TMS maps recruitment curves are presented in 4.2.2. Wilcoxon signed rank–sum tests and rank-sum tests are applied to Session 1 and 2 to determine whether changes measured post-intervention are significant. Since recruitment curves are acquired in a specified order from low intensity incremented to high intensity the same way each time a curve is recorded the signed rank-sum test is used to see if there is an order-dependent difference between samples of the first and second sessions. The rank-sum test is an unpaired sample test used to determine if there is a difference between the distribution of the first session MEPs and second session MEPs.

It is more common (Kaelin-Lang 2002, Kukke 2014) to fit TMS recruitment curves to a sigmoid function where complete curves were obtained for both sessions, and MEPs appear to not increase with increasing stimulation intensity. MEP amplitudes are fitted to the Boltzmann function (Capaday 1999) defined by

$$\mathrm{MEP(s)} = \frac{\mathrm{MEP}_{max}}{1 + e^{m(\mathrm{s50}-\mathrm{s})}}$$

The parameter *m* is a slope parameter and is directly proportional to the maximum slope of the curve that occurs at s50 or the stimulation intensity required to produce half of the maximum MEP.

$$\mathrm{slope}_{max} = \frac{\mathrm{MEP}_{max} m}{4}$$

A higher *m* indicates faster recruitment of neuronal MEP response for increasing stimulation intensity while a lateral shift in s50 indicates changes in recruitment threshold. A left shift and steeper slope are favorable outcomes for incremental stimulation intensities since this would indicate lower threshold to produce a MEP for a given intensity between the first and second TMS session. Together with MEPmax these parameters benchmark the recruitment curve and provide a reference in recruitment curve changes. MEPmax was derived by inspection. Parameters *m* and s50 were estimated using the Levenberg-Marquardt method for determining least-mean-square fit of a non-linear function implemented following methods described in Capaday 1999, Devanne 1997, and Willer 1987.

3.7.2 Maximal Voluntary Contraction Force

Except for Subject 1 MVCFs were recorded through the course of every session. Two-sample t-tests are applied to first and last session measurements to determine if changes are significant.

3.7.3 Hand Grip Related Latencies Estimated from the Dynamometer

Each cued hand gripping execution as measured by the dynamometer is summarized via four time points relative to the start of Cue On: (1) When intentional grip execution begins (Force On); (2) When target force is reached (Force Target); (3) When the grip on the dynamometer is relaxed (Force Quit); (4) When grip force has reached pre-grip execution levels and the subject is relaxed (Force Stop) (see appendix figure). Additionally, the duration of grip execution is reported as (5) The total length of time from the beginning of force execution (Force On) to the time when the subject stops exerting force above baseline (Force Stop). The force data consists of cued deviations from a relatively low and stable baseline to a sustained target force during the Cue On states. For each deviation from baseline the amplitude change can be modeled according to changes in acceleration of grip force with local maximum and minimum accelerations occurring at each of the first four time points listed above. The process employed to algorithmically mark these times involves:

1. The force signal for a single run is normalized and smoothed over a 1/4 s moving window with output returned to the center of each window.

2. The discrete second order difference of the smoothed force signal produces a new signal the same length as force minus two sample points and represents instantaneous acceleration.

3. The second order difference signal is again smoothed over a 1/4-s window at every point and zero phase shifted.

4. The local minimum and maximum are marked to indicate times of maximum acceleration and deceleration of applied force. Only concavities whose values exceed 5% of the range (maximum acceleration minus minimum acceleration) are considered local minima or maxima.

5. A Z-test is used to determine if force magnitude in two second windows with 1/4 s overlap during Cue On is significantly different from the baseline force magnitude in the first 1/4 s after Cue On. If any distribution is significantly above (right tail) baseline at 0.001 alpha then step 6 below occurs. If not then gripping is marked as unexecuted for that cue state.

6. The force signal is scanned from one-fourth of a second after each Cue On time through two seconds after Cue Off. The first positive local maximum is marked Force On, the first local minimum after Force On is marked Force Target, the next local minimum is marked Force Quit, and the following local maximum is marked Force Off.

3.7.4 Cued Grip Onsets and Related Latencies from EMG

EMG analysis generally follows procedures outlined by William Rose (2014) for detecting grip onset and offset times during each Cue. Two EMG time values are reported: (7) EMG On and (8) EMG Off, indicating onset and offset of muscle contraction, respectively, and are reported for those subjects where EMG was recorded. These values are also reported relative to Cue On.

EMG detection generally entails deriving the envelope of the EMG signal and searching for times when EMG crosses a threshold defined by baseline mean and standard deviation:

1. Load the two forearm EMG channels of the active arm and take the difference to obtain a single bipolar EMG signal.

2. A 4^{th} order Butterworth filter applied to the differential EMG with 10 Hz cutoff removes movement artifacts and any other DC offset.

3. The full wave rectified signal is obtained by taking the absolute value and then lowpass filtering at 50 Hz in the forward and reverse direction using a Butterworth filter to return the zero phase shifted signal.

4. EMG On and EMG Off times are computed based on the average of the enveloped EMG moving window of size 25ms. The threshold is computed as

$$Threshold = \mu + J\sigma$$

For EMG On times, μ is the mean of EMG from the last two seconds of inactivity in the previous Cue Off period ending at Cue On and σ is the standard deviation. For EMG Off the threshold is computed from the opposite direction; The EMG envelope is reversed and the same process is applied to find μ and σ except that the inactive 2 second window is taken from the start of the now previous Cue Off state extending to two seconds after start of Cue Off. The number of standard deviations, *J*, above the mean is set to 3. For practical matters of analysis, if EMG On is not detected then no EMG Off is reported. The earliest that EMG On may be reported is after 1/8s of Cue On and the latest that EMG Off may be reported is one second after Cue Off.

3.7.5 Classification of EEG

LDA and SVM classification models were trained in Matlab™ (MathWorks, Natick, Massachussetts) on EEG mu band power for each session and hand to determine if increased ERD occurred over the course of intervention. K-fold cross-validation with k = 5 determined the accuracy of each model: i.e., the paired Cue On/Cue Off movement EEG data from each session was randomly divided into k equal groups. Then the classifier was trained on k-1 groups and tested on the remaining samples of the k-th group. This was repeated k times until every group had been used as the test sample. This k-fold cross-validation was repeated 10 times (10×5CV) to derive a stable estimate of accuracies in each session of the intervention.

Models were trained in Matlab using functions 'fitcdiscr.m' and 'fitcsvm.m' for LDA and SVM classifiers, respectively. Two classes were used as input: movement and non-movement. Each training point was computed as the mu-band RMS power in two-second windows starting two seconds before Cue On for the non-movement class and starting one second after Cue On for the movement class for every Cue recorded during intervention. This was repeated for training points of RMS power in one second windows and the movement class referenced to the EMG Onset time and dynamometer Force Onset times. This was to determine if the separability of ERD from resting states is influenced by observable movement execution.

3.7.6 PNS Latencies Relative to Movement Execution

To benchmark system performance and subject compliance in the task, five additional times are recorded: (9) The time after Cue On when PNS was applied (PNS On); (10) The time from PNS On to Force On – negative values indicate that Force On occurred before PNS On; (11) PNS On to Force Off; (12) PNS On to EMG On – negative values indicate PNS On occurred after EMG On; and (13) PNS On to EMG Off.

Performance measures of the BCI during intervention is summarized to characterize how PNS was applied over the course of the intervention. True positive rate (TPR):

$$\mathrm{TPR} = \frac{\mathrm{TP}}{(\mathrm{TP} + \mathrm{FN})}$$

positive predictive value (PPV):

$$\mathrm{PPV} = \frac{\mathrm{TP}}{(\mathrm{TP} + \mathrm{FP})}$$

and accuracy:

$$\mathrm{accuracy} = \frac{(\mathrm{TP} + \mathrm{TN})}{(\mathrm{TP} + \mathrm{FP} + \ \mathrm{TN} + \mathrm{FN})}$$

are each reported for the last week of intervention relative to the first week of intervention. True positive (TP) is any stimulation that occurred after a 100ms of cue onset and before the cue offset. False positive (FP) is any stimulation that occurred during the initial 100ms after cue since subjects are assumed not to be able to respond before then. True negatives (TN) are the absence of PNS when the cue is off and subjects are not intending to move. TNs are partially ensured because stimulation cannot be triggered during Cue Off. False negatives (FN) occur when no PNS occurs during Cue On. We assume that subjects always adhered to the task and attempted to squeeze the hand dynamometer after seeing the cue. This method of classifying performance is useful since it does not rely on the EEG correlates of movement and can be used to support SMR analysis described in 3.7.5.

Chapter 4: Results

4.0 Subject Data

Table 1. Subject Demographics

Seven subjects have completed a screening session with closed-loop PNS. Five continued with 12 intervention sessions and four completed the intervention. One subject (SID-004) dropped out of the study after seven sessions but underwent a post-study TMS motor mapping session within three days of the final session.

Subject ID (SID)	Age (y)	Sex	Time since SCI (months)	AIS Score	Level of SCI
1	30	M	159	C	C6
2	62	M	27	C	C5
3	37	F	70	B	C6
4	55	M	61	C	C4
5	35	F	62	C	C6
6	58	M	245	B	C6
7	48	M	30	A	C5

4.1 TMS

4.1.1 TMS map

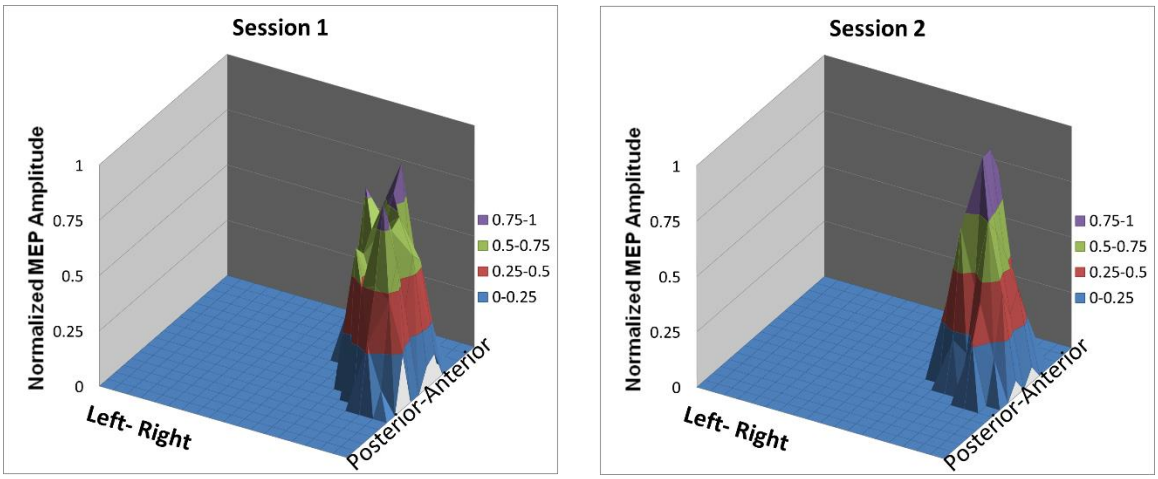


Figure 1. SID-001 TMS volume.

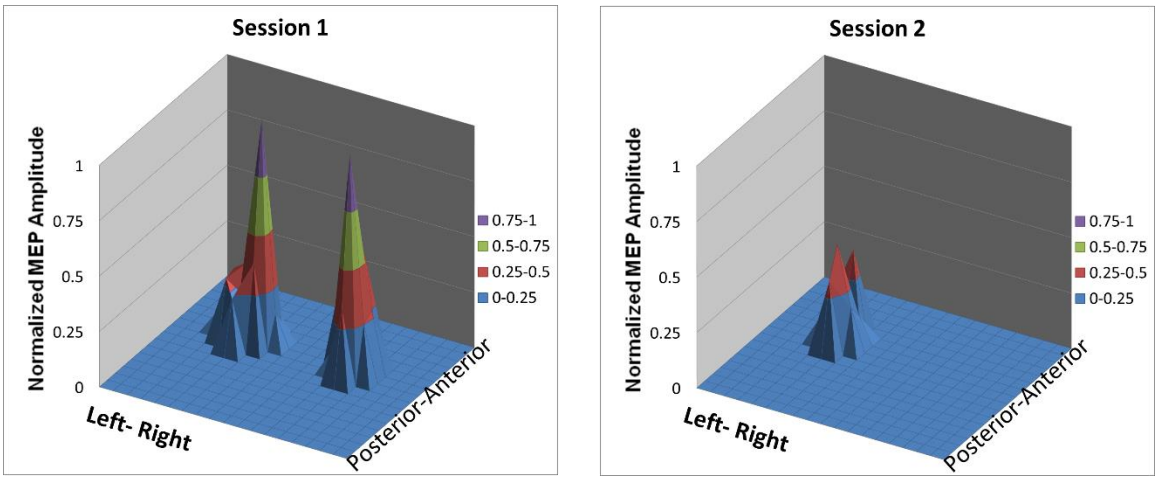


Figure 2. SID-003 TMS volume.

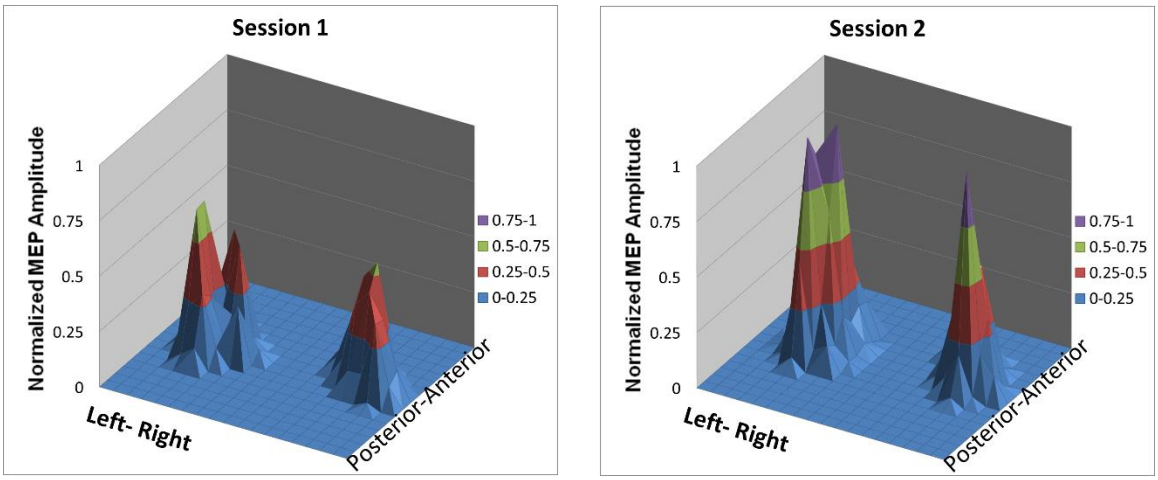


Figure 3. SID-007 TMS volume.

Table 2. TMS Session 1 and 2 Motor Volumes.

No pre or post-intervention TMS motor map could be detected in Subject 1's left hemisphere. There was decreased motor map volume following the intervention, however the cortical APB region seemed to more clearly defined. Subject 3 had both a left and right hemisphere TMS map during the pre-intervention session, but only a left hemisphere TMS map could be determined post-intervention. There was decreased TMS volume for the left hemisphere. Subject 7 had a map for both hemispheres pre and post-intervention, and had an increase volume in both hemispheres. It is possible that a motor map could have been determined for Subject 3 had a lower MEP threshold been used.

	Left APB TMS Volume			Right APB TMS Volume		
Subject	Session 1	Session 2	Change	Session 1	Session 2	Change
1	17.18	13.94	-3.241	NA	NA	NA
3	3.536	0.000	-3.536	3.505	1.884	-1.620
7	4.110	5.651	+1.541	4.622	7.045	+2.423

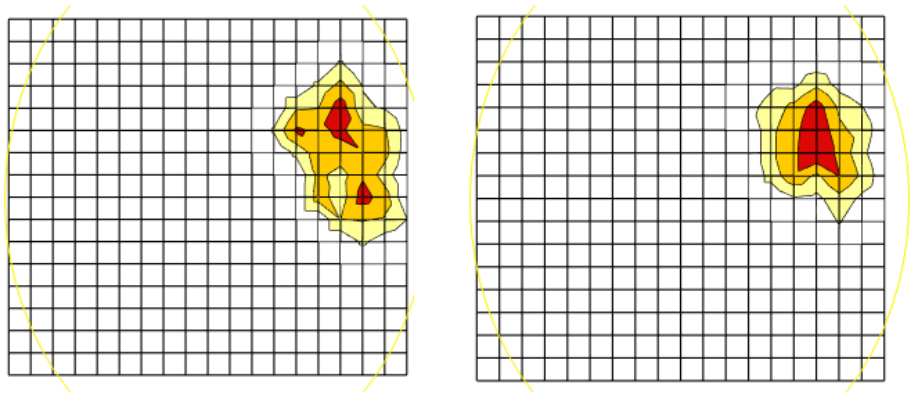


Figure 4. SID-001TMS volumetric heat map of APB motor area recruitment.

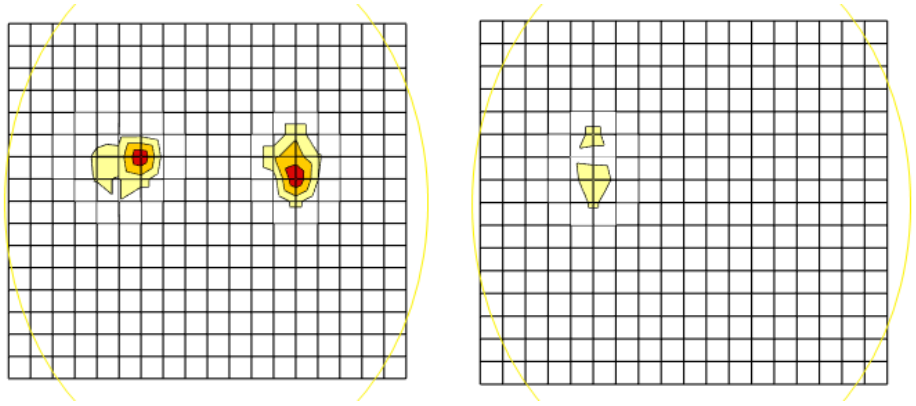


Figure 5. SID-003 TMS volumetric heat map of APB motor area recruitment.

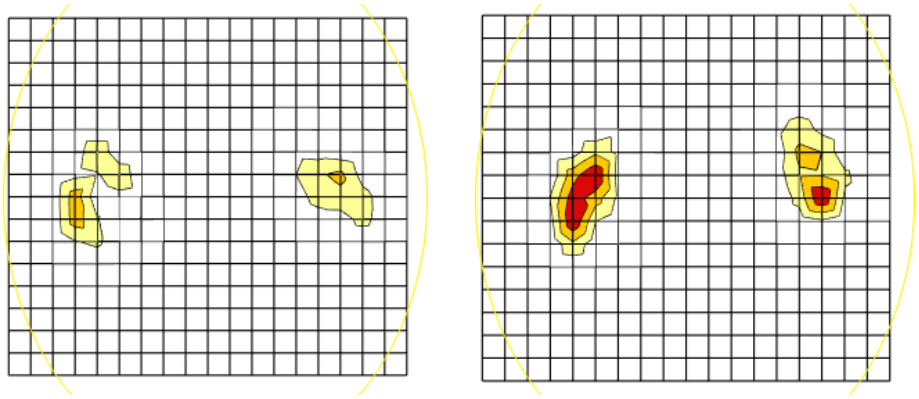


Figure 6. SID-007 TMS volumetric heat map of APB motor area recruitment.

2D TMS motor map volumes illustrate development of a well-defined map for Subjects 1 and 7, and dissipation of well-defined hot spots for Subject 3.

Table 3. Change in TMS Center of Gravity

Values listed by x-coordinate change then y-coordinate change of TMS map in centimeters (Δx, Δy). All subjects with pre and post-intervention TMS maps resulted in center of gravity shifting medially and anteriorly.

Subject	Left Hemisphere	Right Hemisphere
1	NA	-0.092, +0.475
3	-0.247, +0.301	NA
7	-0.009, +0.694	-0.604, +0.331

4.1.2 TMS Recruitment curves

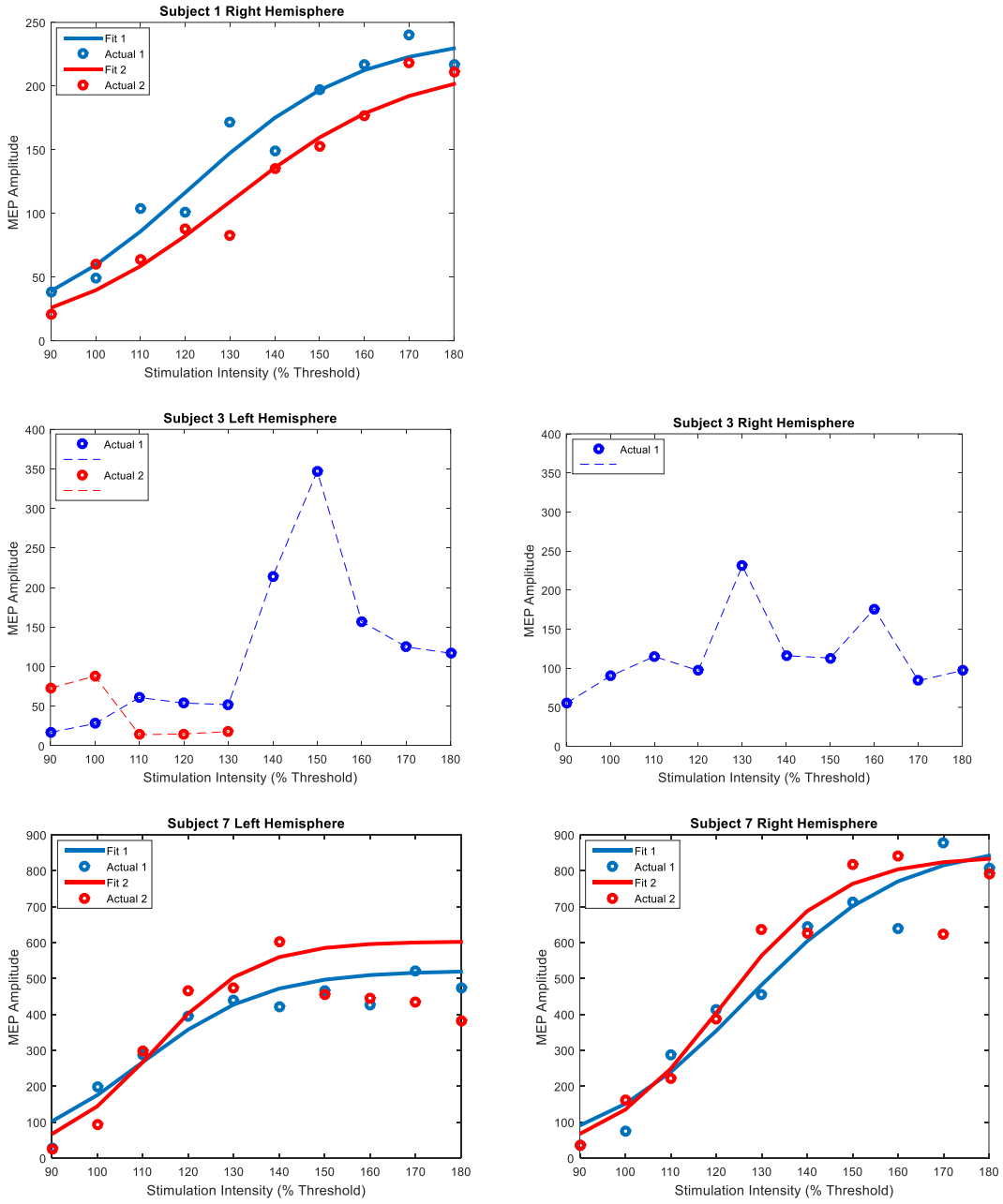


Figure 7, 8, 9. Subject 1, 3, 7 TMS Recruitment Curves With Boltzmann fit. First (blue) and second (red) session left and right brain hemisphere recruitment curves of average MEP (uVpp) over 10 stimulations of same intensity and 10 intensities starting from 90%, incrementing by 10% to 180% of RMT. Dots represent average recorded MEP amplitudes at each stimulation intensity and the curve is the result of fitting MEP amplitudes to the Boltzmann function (Eq. XX) by the Levenberg-Marquardt method.

Table 4. Two Sample Wilcoxon Tests of Significance of TMS Change.

Where a pre and post-intervention TMS map was obtained, Wilcoxon Rank Sum analysis indicated no significant changes between MEP recruitment curves.

Subject	Left Hemisphere Wilcoxon Test		Right Hemisphere Wilcoxon Test	
	rank sum	signed rank sum	rank sum	signed rank sum
1	NA	NA	0.427 decrease	0.005 decrease
3	0.099 decrease	0.812 decrease	NA	NA
7	0.820	1	0.909	0.845

Table 5. Changes (Δ) in Boltzmann function parameters of first and second TMS sessions.

Subject 3 did not produce a usable data set for comparing curves in the second TMS session and so a Boltzmann fit is not included.

Subject	Left Hemisphere			Right Hemisphere		
	Δ MEP max	Δ slope	Δ S_{50}	Δ MEP max	Δ slope	Δ S_{50}
1	NA	NA	NA	-22	-0.421	+8.816
7	+81	+1.877	0.000	-37	+3.632	-5.646

4.2 Dynamometer Measurements

Three MVCs were measured for SID-001 for each hand before the first and last sessions.

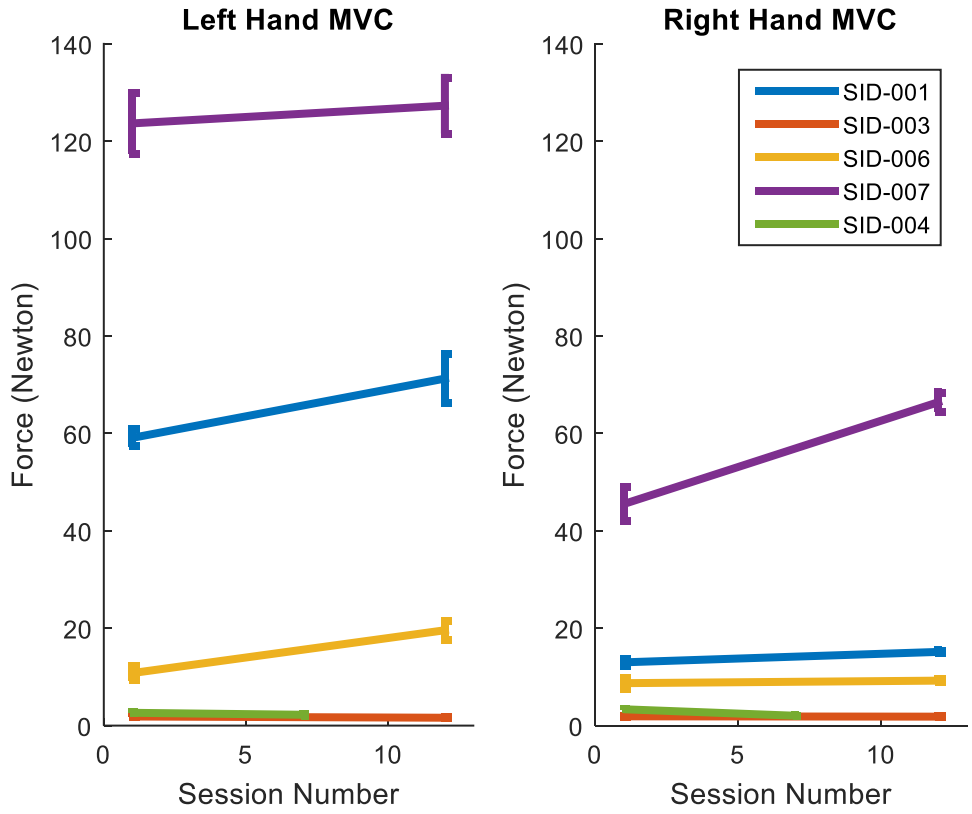


Figure 10. Mean and standard error of three MVCF measurements taken at the beginning of sessions 1 and 12 prior to the start of the first run.

Table 6. Two-sample t-test p-values.

Values in bold are below the chosen critical type I error probability alpha of 0.05. Significant changes ($p<0.05$) between MVCF measurements taken before the first and last sessions were observed for four subjects. Subjects 6 and 7 showed significant increases for the left hand and right hand, respectively. Subjects 3 and 4 showed a significant decrease in MVCF for the left and right hand, respectively. Even though significance was not met for the remaining samples mean MVC increased in both hands for subjects 1, 6, and 7.

SID	Left Hand p-value	Right Hand p-value
1	0.1333 (increase)	0.0725 (increase)
3	**0.0425** (decrease)	0.6654 (decrease)
6	**0.0420** (increase)	0.7318 (increase)
7	0.7435 (increase)	**0.0139** (increase)
4	0.1274 (decrease)	< **0.001** (decrease)

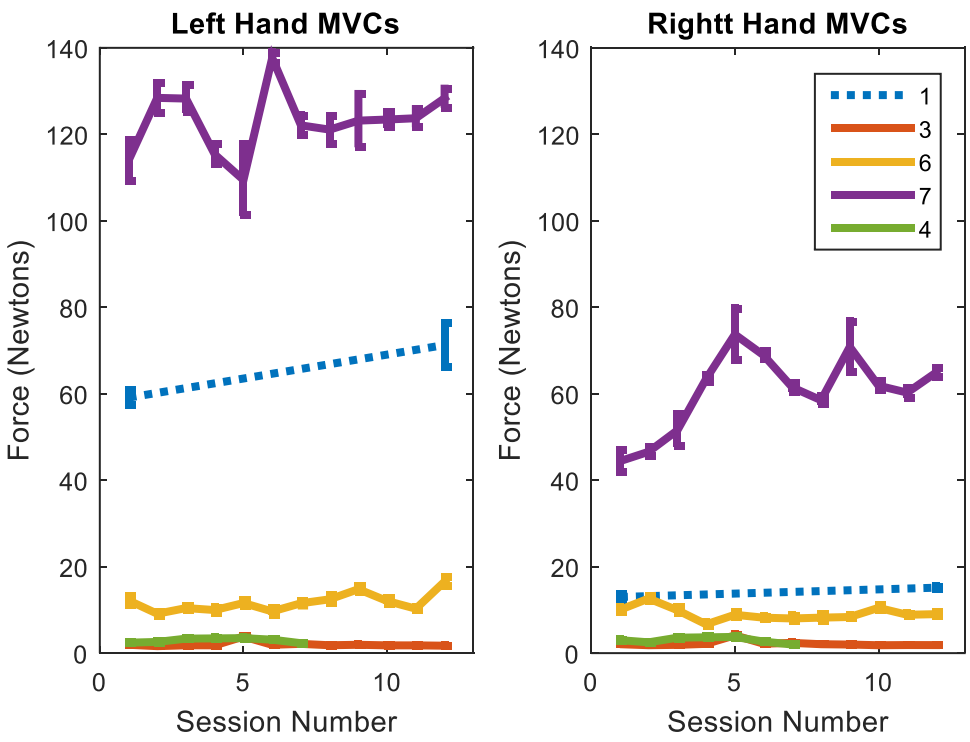


Figure 11. Mean and standard error of all MVC measurements (three repetitions before and after each session, and one measurement after each of the five runs; total 11) recorded over the course of each session. These values were not recorded for Subject 1 since the decision to make these measurements was taken later.

Table 7. Two-sample t-test p-values corresponding to figure 11.

Values in bold are below 0.05 alpha. Subject 1 did not have equivalent measurements. A similar trend as figure 10, but a significant decrease was determined in both hands of Subject 3 and significant increase in both hands for subject 7.

SID	Left Hand p-value	Right Hand p-value
1	NA	NA
3	< 0.001 decrease	0.050 decrease
6	0.008	0.169 decrease
7	0.013	< 0.001
4	0.376 decrease	< 0.001 decrease

4.3 EEG Feature Classification

The following attempts to summarize development of ERD in terms of task-related modulation of mu rhythm. LDA and SVM 10×5CV LDA and 10×5CV SVM are presented by week for all subjects including Subject 4 who dropped out of intervention after session 7.

4.3.1 10×5CV LDA Prediction Accuracy of 2 Second Sample Windows of Cue On and Cue Off

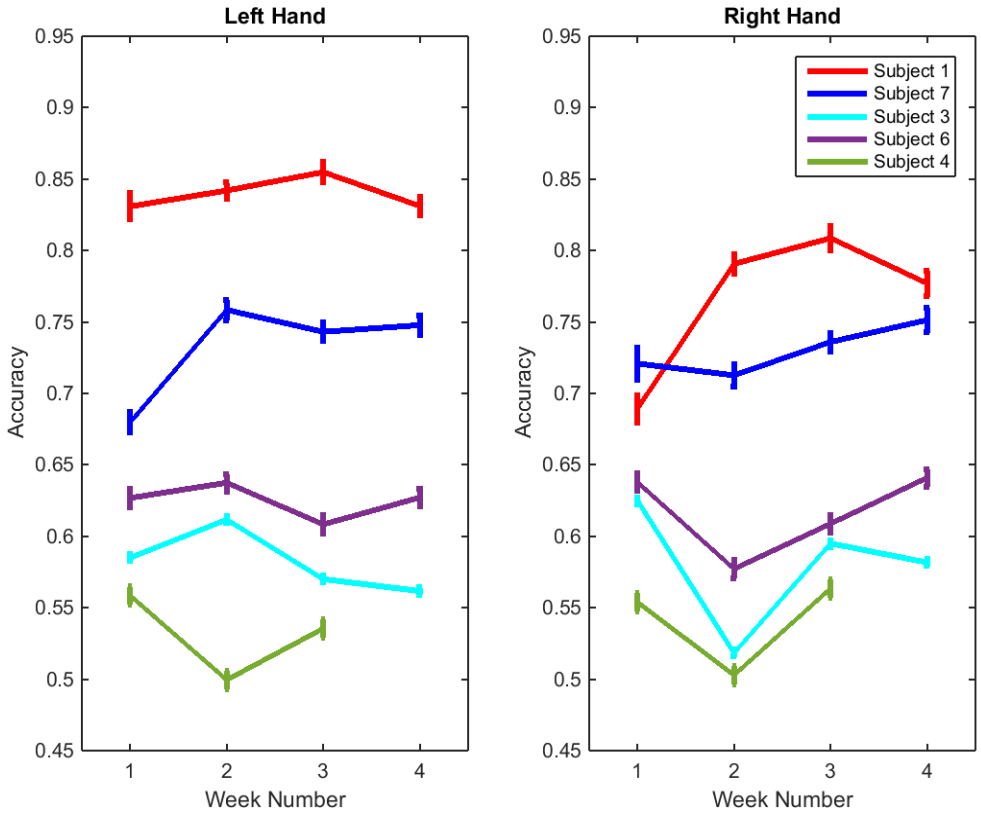


Figure 12. LDA classifier accuracies trained on 2-s windows 1-s after Cue On extending through 3-s after Cue On (intent-to-move state), and 2-s window starting 2-s before Cue On ending at Cue On (resting state). Cross-validation is performed on all cues from the five runs within each session individually and the prediction values grouped by week. Error bars represent standard error over total number of predictions averaged for each point.

Table 8. P-values (two-sample unpaired t-tests) for first versus last week LDA accuracies.

Subject	1		3		4		6		7	
Hand	L	R	L	R	L	R	L	R	L	R
p-value	0.59	0.02	0.414	0.126	NA	NA	0.969	0.716	0.019	0.002

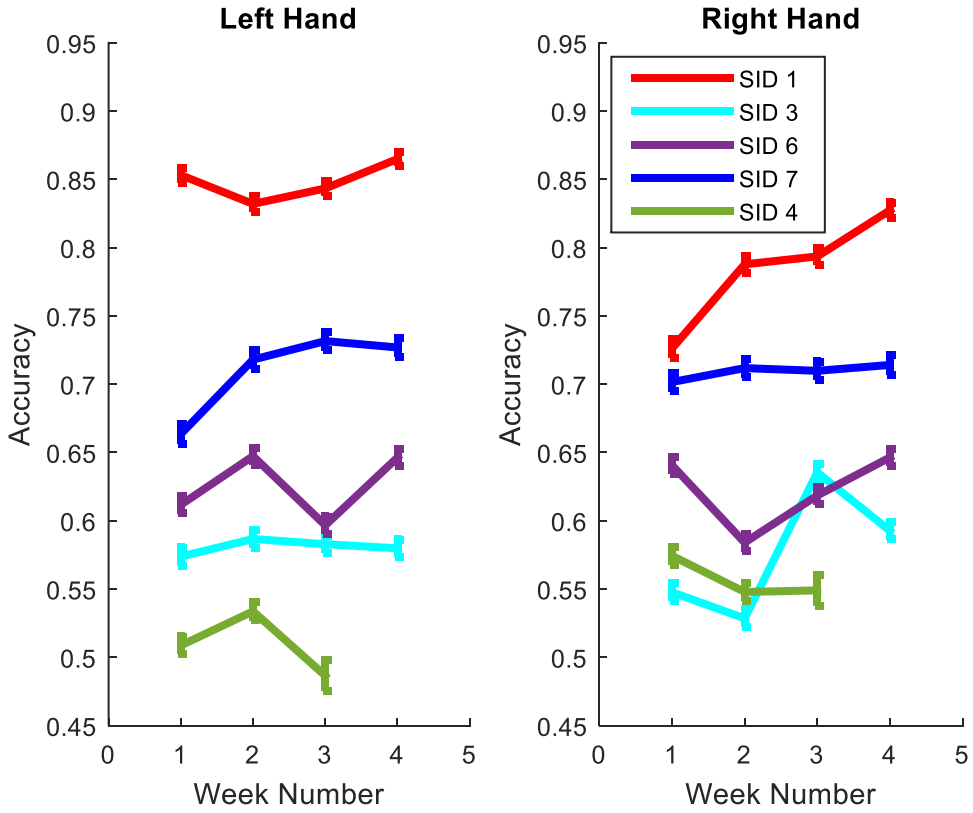


Figure 13. SVM classifier accuracies trained on 2-s windows 1-s after Cue On extending through 3-s after Cue On (intent-to-move state), and 2-s window starting 2-s before Cue On ending at Cue On (resting state). Cross-validation is performed on all cues from the five runs within each session individually and the prediction values grouped by week. Error bars represent standard error over total number of predictions averaged for each point.

Table 9. P-values (two-sample unpaired t-tests) for first versus last week SVM accuracies

Subject	1		3		4		6		7	
Hand	L	R	L	R	L	R	L	R	L	R
p-value	0.110	< 0.001	0.507	< 0.001	NA	NA	< 0.001	0.517	< 0.001	0.207

4.4 BCI Performance During Intervention

Table 10. Summary of motor intent detection measures and accuracy of PNS delivery.

#Cues is the number of cues presented per session; TPR is the sensitivity of task detection and PNS delivery; PPV is the precision of task detection and PNS delivery; PNS On is the average time after Cue On presentation that PNS was delivered for the entire intervention; PNS On to Force On is the time from PNS to Force detection (a negative value means PNS was delivered after Force On); PNS On to EMG On is the time from PNS to EMG detection (a negative value means PNS was delivered after EMG On). EMG was not recorded for subjects 1 and 7. Subject 6 had no FN because PNS was always delivered shortly after the Cue.

Subject	1		3		4		6		7	
Hand	L	R	L	R	L	R	L	R	L	R
#Cues	75	75	100	100	100	100	100	100	75	75
TPR	100	96	86	81	79	76	0	100	100	100
PPV	89	72	77	78	83	84	0	0.005	87	87
PNS On (s)	0.88 ±0.3	0.75 ±0.6	0.92 ±0.7	0.96 ±0.7	0.95 ±0.7	1.04 ±0.8	0.11 ±0.0	0.11 ±0.0	0.79 ±0.2	0.89 ±0.3
PNS On to Force On (s)	-0.35 ±0.3	-0.31 ±0.6	-0.18 ±0.8	-0.21 ±0.8	0.10 ±0.9	-0.26 ±0.9	0.48 ±0.2	0.46 ±0.2	-0.37 ±0.2	-0.48 ±0.3
PNS On to EMG On (s)	NA	NA	-0.52 ±0.8	-0.44 ±0.9	-0.48 ±0.8	-0.32 ±1	0.26 ±0.2	0.47 ±0.4	NA	NA

4.4.1 BCI Performance: First versus Last Week

Table 11. BCI performance reported as ratios of week 4 intervention performance over week 1 intervention performance.

Subject	1		3		4		6		7	
Hand	L	R	L	R	L	R	L	R	L	R
TPR	1.00	1.05	0.98	0.83	0.88	0.85	1.00	1.00	1.00	1.00
PPV	1.02	0.87	0.94	0.86	0.94	0.87	1.44	0.99	1.01	0.98
Accuracy	1.00	0.96	0.97	0.87	0.93	0.90	1.11	0.99	1.01	0.99

Chapter 5: Discussion

5.0 Overview

Closed-loop PNS has been implemented in this study as a novel means of providing sensory feedback and to augment therapy for recovery of upper motor function in incomplete SCI subjects. Results from this ongoing study, discussed in 5.1 below, revealed both functional changes in interventional outcome measures that could be seen as positive in some instances but negative or nonexistent in others. Given the considerable variability in the specifics of SCI between subjects and perhaps some variability in the implementation of closed-loop PNS for each individual the results should be viewed in the context of each subject's profile (5.2). There is no gold standard for BCI design; this study represents an attempt to tailor the design specifically to the task of closed-loop afferent electrical stimulation for recovery of hand function in incomplete SCI. Elements believed to have greatest impact on performance are addressed, and possible directions for future improvements in our BCI design are proposed.

5.1 Outcomes

5.1.1 TMS Maps

Only subjects 1, 3, and 7 had detectable RMTs and pre and post TMS maps. Subject 1 did not have a detectable RMT for the left hemisphere pre or post intervention so a TMS map was not obtained, but the map was clearly defined in both sessions for the right hemisphere (figure 1). A decrease in normalized MEP volume was observed following intervention in the right hemisphere (table 2), but the two-dimensional heat map (figure 4) suggests that cortical excitability was consolidated to a more clearly defined region with a broader upper quartile indicated by the central red area. Subject 3's pre-intervention map was small but clearly defined, but post-intervention there was a decrease in MEP volume for the left hemisphere and no detectable RMT in the right hemisphere (figures 2, 5, and table 2). The initial volume covered only four and two cortical TMS locations with MEPs above detection threshold, for left and right hemispheres respectively. MEP volume is normalized across only two sessions, and while a decrease in this metric may be viewed unfavorably, it should be noted that the initial RMT seemed absent until MEPs were suddenly detectable after readjusting the APB EMG electrodes slightly, and at a longer latency (~200ms). A similar complication could have resulted in RMT not being detected

in the right hemisphere following intervention, and could further be responsible for the missing RMT in Subjects 6 and 4. Subject 7 had the most notable increase in MEP volume for both hemispheres (figure 3 and table 2). The heat maps (figure 6) also indicate greater consolidation of the upper quartile of normalized MEP amplitude for the post-intervention map in both left and right hemispheres.

Subjects 4 and 6 did not have detectable RMTs to fix either a pre or post intervention TMS map. Subject 4 dropped out halfway into the intervention, but a post-study TMS mapping was still attempted to determine if any change could be observed. Subject 6 had persistent muscle tension and regular muscle spiking that peaked above the TMS threshold and prevented reliable detection of MEPs from the APB in pre and post interventional TMS sessions.

5.1.2 Recruitment Curves

Wilcoxon rank sum tests revealed no significant change in cortical excitability between pre and post TMS sessions as determined by progressively increasing the TMS intensity relative to RMT (figures 7, 8, and 9). A Wilcoxon signed rank sum test, which is a matched sample test, was also conducted since RC curves were determined from the same sequence of stimulation intensities relative to RMT in each session. There were still no significant changes except for Subject 1 who had a decreased MEP recruitment (p-value: 0.005) post-intervention in the right hemisphere (table 3).

A saturation of the MEP recruitment curve with detectable maximum was observed in session 1 and 2 (pre- and post-intervention, respectively) for Subjects 1 and 7, which allowed a comparison of Boltzmann parameters fitted to the data to be made. The Maximum MEP (MEPmax) increased in Subject 7's left hemisphere, while a decrease was observed for both Subject 1 and 7's right hemisphere. s50 shifted to the left suggesting an increase threshold sensitivity to TMS for Subject 7 right Hemisphere. S50 shifted to the right for Subject 7 left hemisphere and Subject 1 right hemisphere TMS recruitment curves indicating decreased threshold sensitivity relative to the resting motor threshold. The slope increased for Subject 7's left hemisphere indicating faster recruitment of corticospinal excitation for the same incremental stimulation relative to the first session. Subject 7 right hemisphere and Subject 1 right hemisphere had decreased slope parameters.

5.1.3 MVC Force Measurements

Subject 1 only had MVC measurements recorded for the first and final session of intervention and the corresponding measurements from all interventional subjects were therefore compared (figure 10). MVCs increased in both hands for subjects 1, 6, and 7, but decreased for subjects 3 and 4. Two-sample (unpaired) t-tests revealed significant MVC improvement for Subject 6's left hand and Subject 7's right hand (p-value: 0.0420 and 0.0139, respectively; table 4).

Subjects 3, 6, 7, and 4 had MVCs recorded 11 times for each hand over the course of each session (figure 11). Two-sample t-tests comparing the mean MVCFs from the 11 pre and 11 post TMS measurements for each hand confirmed the results above with stronger significance, except that subject 1 could not be included in the test and subject 6 showed no significant change (table 5).

5.1.4 Intervention-Related Changes in the EEG Sensorimotor Rhythm

Trends in the LDA classifier accuracy revealed significantly increased contrast from Week 1 to Week 4 for Subject 1's right hand task and for Subject 7's left and right hand tasks (figure 12 and table 6). Likewise, SVM classifier accuracy increased for one hand in every subject who completed the intervention (Subjects 1, 3, 6, and 7), and increased but not significantly for the contralateral hands (figure 13 and table 7). The LDA accuracies were marginally higher than those of the SVM, suggesting a clearer separation of ERD and ERS sample means used to train the classifier. The increase in SVM accuracy over time (in one hand) suggests there is less overlap of ERD and baseline training samples—or less ambiguity in the overlapping data points—as the intervention progresses.

5.2 Hurdles

Possibly the most difficult challenge faced in this study was subject recruitment and retention. Including the initial closed-loop PNS screening and two TMS mapping sessions, completion of intervention requires a time commitment of 15 days over an approximately five-week period, and keeping appointments at every other day on weekdays can be difficult as many subjects who satisfy the inclusion criteria cannot drive themselves, often have to commute a significant distance, and have a higher risk of health-related complications. Subject 1 took over 7 weeks to complete the intervention having

missed 10 days in between due to extreme weather and illness. Every subject who participated missed a session due to weather or illness, or experienced unrelated health issues during the course of intervention.

Subject 7 missed one visit, and had a urinary tract infection during the middle two weeks of the intervention. Subject 6 did not miss any sessions, but regularly expressed discomfort due to neuropathic pain that had worsened in the month preceding intervention. The presence of central neuropathic pain can influence BCI performance (Vuckovic 2015), and could be just as disruptive as missing consecutive sessions. Subject 4 was admitted to the ER before the third session for reasons unrelated to the study, missed a week of intervention, and eventually dropped out in week 3 after the seventh session. Subject 3 missed a session in the second and the third week. Such disruptions in the intervention schedule could well be considered valid grounds for exclusion from the study. Conversely, the schedule maintained in this study represents a realistic therapeutic regimen and possible day-to-day benefits from intervention should not be ignored even in the face of interruptions or complications like those listed above.

Many therapies designed to take advantage of UDP are not well established. Results in animal models that support the use of motor exercises to take advantage of UDP do not translate automatically into human clinical applications (Jones 2008), and entail as much as 20 times as many motor repetitions (Dromerick 2013). Open-loop PNS protocols in humans (Sawaki 2006) can involve as much as 100 times the stimulation applied in this closed-loop protocol.

The exclusion of subjects less than one year post injury is necessary to avoid complications arising due to a non-stabilized injury which can potentially undergo dramatic changes that may confound study outcomes. Stroke therapies have the best outcomes when started as soon as possible. It has been shown that peripheral nerve and axonal function deteriorates following SCI (Boland RA 2011), but sustained open-loop PNS can reverse dysfunctional change and maintain axonal function at normative levels when applied within six months of SCI (Lee 2015). The current study does not address how treatment could optimize adaptive rearrangement during the earliest post traumatic period when synaptic rearrangement is most amenable to healing. Subject 7 had the most positive

developments with increased TMS volume, MVC, and LDA-gauged SMR contrast over the course of the intervention and was also admitted to the intervention closest to the time of injury. At the same time, Subject 1 had comparably favorable results, but was the longest since time of injury to be enrolled in intervention.

The nature of SCI is highly variable in terms of defining the extent of subject-specific tissue damage and corresponding function. The AIS is a clinical tool for diagnosing sensory and motor function at the most rostral levels of the spinal cord and doesn't necessarily detail the extent of upper extremity impairment. Subject 7 was diagnosed as AIS grade A at the time of study which denotes the most severe SCI-induced functional deficit, but displayed the strongest MVC in both hands of any subject across all sessions, and had arguably the best dexterity in either hand. The label of incomplete SCI does not characterize completeness of upper motor function. Additionally, all participants in this study had a documented SCI, but it is not clear whether impairment resulted from or was intensified by a poly trauma in which peripheral nerves or the brain is also affected.

Only three of five subjects participating in the intervention had MEPs strong enough to obtain TMS maps. 50μVpp was used as the RMT in every subject to determine the APB cortical excitability. In subjects where no map was determined, a lower RMT, 10μVpp for instance, could have been used to quantify any residual function. This may have revealed a map, however weak, for Subject 1 who had no MEPs above RMT in either TMS session. Subject 6 had a resting APB EMG spiking pattern that exceeded the 50μVpp threshold and could not be alleviated by filtering or after stretching and massaging the muscles in both hands in both sessions. The flexor carpi radialis (FCR) and flexor digitorum superficialis muscles (FDS) of the forearm could have been assessed as a surrogate to the APB. Either of these alternatives may have been utilized to derive a metric of grip-related cortical excitability in subjects 1, 3, or 6 without detectable MEPs at APB.

Subjects 3 and 4 had the lowest ability to perform volitional grip executions as shown in figures 10 and 11 over the course of the intervention. BCI performance generally increases with greater proprioceptive feedback so it is possible that residual motor function may be correlated with proprioception.

Subject 1 generally had the highest task-related SMR contrast as revealed by figures 12 and 13 for either hand, although no detectable left hemisphere TMS map could be found before or after intervention. This is interesting since greater movement-related SMR modulation might imply increase cortical excitability (Mitsuaki 2013). The TMS volume for the right hemisphere resulted in a net decrease, however the 2-D heat map (figure 4) indicates consolidation of the map around a much stronger center of gravity. Subject 3 had small yet well-defined TMS maps for both hemispheres established during the first TMS session. TMS Session 2 motor maps (figures 2 and 5) revealed a decrease in the left hemisphere and no detectable map for the right hemisphere. Reducing the MEP threshold to 10 µVpp may have permitted successful mapping; however a fair comparison between pre and post-intervention maps would not have been possible.

The changes in center of gravity for every TMS map (Subject 1 right hemisphere, Subject 3 left, and Subject 7 left and right) resulted in a post-intervention shift in the anterior and medial directions. This is consistent with Green et al. (2003) who found MPs in SCI subjects were mapped to a more posterior location than in normal subjects and remapped more anteriorly in those who recovered function. The same overall trend in center of gravity shift for every subject with pre and post intervention TMS maps is the most consistent outcome measure from this study and suggests a positive benefit.

Does the correlation between PNS delivery and actual movement or IM explain functional changes observed over the course of intervention? This is a tricky question to address given the limited size of the cohort studied. Probing the results for consistencies between measures suggests that those with greater residual function of hand gripping (e.g. Subject 1 and 7) had best BCI performance and EEG sensorimotor rhythm development over the course of intervention (see tables 8, 9, and 11). Total number of PNS over the course of intervention seemed to be less important (table 10) than gripping ability measured by MVCF at the start of intervention (Figures 10 and 11).

5.3 BCI Future Directions

The SMR mu rhythm is not strictly 8-13Hz in all people (Vuckovic 2013, Neuper 2009), and some may not exhibit a detectable mu rhythm at all. Our current BCI system is being updated to optimize what bandwidth is observed in the EEG for intent-to-move

detection. Screening data is separated by EEG channel and the power spectral density generated with 1Hz resolution over the 2 second windows of Cue On and Cue Off. The sensorimotor bandwidth with greatest suppression during Cue On relative to Cue Off will be recorded for each channel and updated into the BCI for detection. Additionally, the sensorimotor rhythm can be observed to modulate over a broad region of the scalp, but subject-specific distribution and inconsistencies that occur during EEG preparation may not justify every channel be used for detection. When channels do not produce consistent modulation they will be excluded from influencing detection in the future.

TMS is a primary outcome measure of this study and was not always attainable during mapping sessions. We adhered strictly to using MEPs observed from the APB for all subjects and did not determine a central hotspot of cortical activation therein. A secondary TMS protocol has been proposed when no RMT can be determined at 50µVpp or in the APB to first try detecting MEPs at a lower activation threshold (e.g. 30µVpp) and recording from a secondary site such as the flexor muscles of the forearm (carpi radialis and flexor digitorum superficialis)

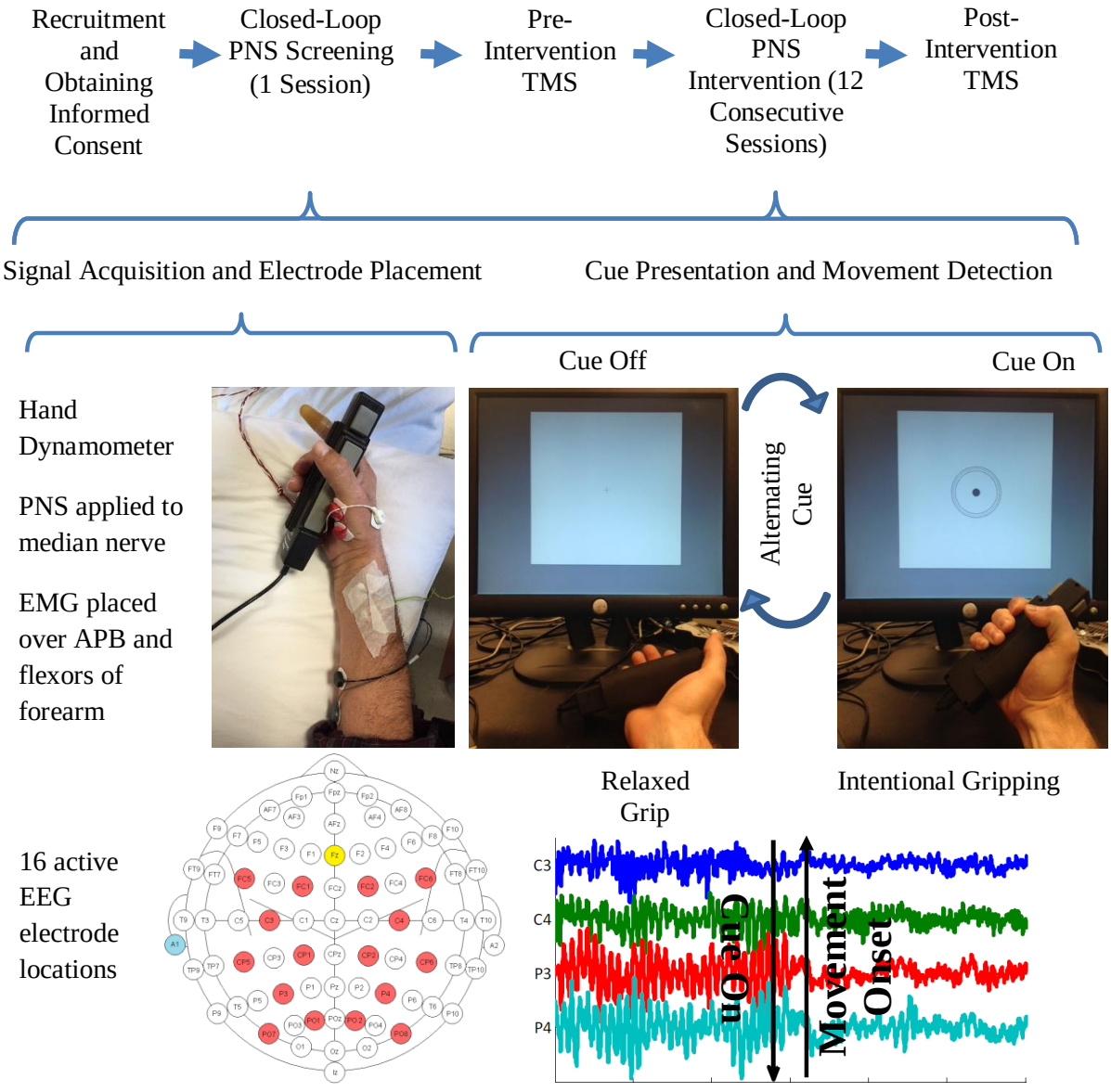
A common remark by participants in the study concerned how the visual feedback task was repetitive and mundane and often caused subjects to become tired shortly into a session. Subject engagement is assumed throughout every study and session coordinators ensure that subjects are awake throughout runs and attempting to respond to changing cue states. Intuitively, a subject's mental engagement will have an impact on performance and outcome measures, and can even influence a subject's willingness to complete the intervention. We are exploring methods for making the visual feedback more engaging to encourage subject willingness to participate in the tasks.

Chapter 6: Summary

The primary goal of this study is to determine whether PNS applied in closed-loop during attempted movement facilitates motor recovery. The variable nature of the effect SCI has on individual subject function and intact neural mechanisms make answering this question difficult especially given the small subject population. However, the results presented from the first five interventions suggest that positive reinforcement in the form of PNS applied during sustained movement intent may provide functional benefit.

Appendices

Appendix 1. Flow Diagram of Study



Appendix 2. Force Time Points

SID	1		3		4		6		7	
Hand	L	R	L	R	L	R	L	R	L	R
Force On	0.52 ±0.12	0.43 ±0.21	0.76 ±0.47	0.74 ±0.43	0.95 ±0.58	0.78 ±0.50	0.59 ±0.29	0.58 ±0.23	0.41 ±0.09	0.41 ±0.12
Force Target	0.97 ±0.18	0.81 ±0.25	1.14 ±0.59	1.16 ±0.59	1.52 ±0.73	1.30 ±0.64	1.16 ±0.46	1.04 ±0.32	0.80 ±0.11	0.80 ±0.19
Force Quit	2.62 ±1.51	3.69 ±1.07	2.47 ±1.21	2.53 ±1.13	2.49 ±1.05	2.53 ±0.98	3.07 ±0.65	3.13 ±0.59	4.25 ±0.19	4.22 ±0.35
Force Off	3.13 ±1.39	4.09 ±1.04	2.85 ±1.21	2.93 ±1.11	3.05 ±1.06	3.04 ±1.01	3.48 ±0.61	3.52 ±0.58	4.60 ±0.17	4.57 ±0.31
Force Length	2.60 ±1.37	3.65 ±1.05	2.12 ±1.21	2.19 ±1.10	2.15 ±1.04	2.28 ±1.02	2.88 ±0.65	2.93 ±0.60	4.18 ±0.20	4.16 ±0.34

Appendix 3. EMG Times Points

Subject	1		3		4		6		7	
Hand	L	R	L	R	L	R	L	R	L	R
EMG On	NA	NA	0.39 ±0.14	0.52 ±0.39	0.48 ±0.32	0.69 ±0.56	0.37 ±0.19	0.58 ±0.44	NA	NA
EMG Off	NA	NA	3.81 ±0.25	3.59 ±0.53	3.49 ±0.51	3.47 ±0.56	3.58 ±0.49	3.61 ±0.60	NA	NA
EMG Length	NA	NA	3.41 ±0.29	3.06 ±0.67	3.00 ±0.60	2.77 ±0.81	3.21 ±0.53	3.03 ±0.76	NA	NA

Appendix 4. Additional Latencies relating PNS On

SID	1		3		4		6		7	
Hand	L	R	L	R	L	R	L	R	L	R
PNS On to Force Off	1.73 ±1.52	2.94 ±1.27	1.55 ±1.39	1.60 ±1.39	1.61 ±1.31	1.48 ±1.29	2.96 ±0.65	3.01 ±0.59	3.46 ±0.32	3.32 ±0.51
PNS On to EMG Off	NA	NA	2.88 ±0.79	2.63 ±0.94	2.52 ±0.91	2.47 ±0.92	3.47 ±0.49	3.50 ±0.60	NA	NA

Appendix 5. List of Abbreviations

ADL: activities of daily living

APB: abductor pollicis brevis

ERD: event related desynchronization

ERS: event related synchronization

FES: functional electrical stimulation

LDA: (Fisher's) linear discriminant analysis

MEP: motor evoked potential

MRCP: motor related cortical potential

MVC: maximal voluntary contraction

IM: intent to move

PNS: peripheral nerve stimulation

SCI: spinal cord injury

SMR: sensorimotor rhythm

SVM: support vector machine

TMS: transcranial magnetic stimulation

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