2019

A BRAIN-COMPUTER INTERFACE FOR CLOSED-LOOP SENSORY STIMULATION DURING MOTOR TRAINING IN PATIENTS WITH TETRAPLEGIA

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Digital Object Identifier: https://doi.org/10.13023/etd.2019.001

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A BRAIN-COMPUTER INTERFACE FOR CLOSED-LOOP SENSORY STIMULATION DURING MOTOR TRAINING IN PATIENTS WITH TETRAPLEGIA

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

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2018

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ABSTRACT OF THESIS

A BRAIN-COMPUTER INTERFACE FOR CLOSED-LOOP SENSORY STIMULATION DURING MOTOR TRAINING IN PATIENTS WITH TETRAPLEGIA

Normal movement execution requires proper coupling of motor and sensory activation. An increasing body of literature supports the idea that incorporation of sensory stimulation into motor rehabilitation practices increases its effectiveness. Paired associative stimulation (PAS) studies, in which afferent and efferent pathways are activated in tandem, have brought attention to the importance of well-timed stimulation rather than non-associative (i.e., open-loop) activation. In patients with tetraplegia resulting from spinal cord injury (SCI), varying degrees of upper limb function may remain and could be harnessed for rehabilitation. Incorporating associative sensory stimulation coupled with self-paced motor training would be a means for supplementing sensory deficits and improving functional outcomes. In a motor rehabilitation setting, it seems plausible that sensory feedback stimulation in response to volitional movement execution (to the extent possible), which is not utilized in most PAS protocols, would produce greater benefits. This capability is developed and tested in the present study by implementing a brain-computer interface (BCI) to apply sensory stimulation synchronized with movement execution through the detection of movement intent in real time from electroencephalography (EEG). The results demonstrate that accurate sensory stimulation application in response to movement intent is feasible in SCI patients with chronic motor deficit and often precedes the onset of movement, which is deemed optimal by PAS investigations that do not involve a volitional movement task.

KEYWORDS: Brain-Computer Interface, Spinal Cord Injury, Sensory Stimulation, Mu rhythm, Neuromodulation

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12/07/2018

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DEDICATION

For Bub.

ACKNOWLEDGMENTS

The BCI system described and evaluated in this work was designed using previous versions as reference. These previous versions were developed by Elizabeth Powell, M.S., University of Kentucky, and Christopher Schildt, M.S., University of Kentucky.

A huge thank you is in store for all of the individuals that have helped in testing this system: Elizabeth Powell, Christopher Schildt, Matthew Ballard, and Dr. Yuvaraj Rajamanickam. Additionally, thank you to Dillon Huffman for all of your help with the system software and hardware over the years.

Special thanks to Matt Ballard for all of the help over the past year and a half. Your work has been instrumental in completing this project.

To my committee, thank you so much for your time and advisement.

Dr. Sunderam, thank you for your patience and guidance throughout my graduate career. I am so lucky to have had your mentorship. I can't begin to express how much I have learned from you. You go the extra mile to ensure your students' success and happiness.

Dr. Sawaki-Adams, thank you so much for your mentorship. You have always been there to listen and provide motivation. I have learned so much from you and feel blessed to know you.

Thank you to my Neural Systems lab group. It is so wonderful to work with individuals who are so helpful and kind. I feel so lucky to have gotten to know each and every one of you.

To my parents, thank you for all of your support and encouragement. I would not have been able to do this without you.

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CHAPTER 1. INTRODUCTION

1.1 Motivation

Spinal cord injury (SCI) is a debilitating condition that affects approximately 288,000 people in the U.S. alone (NSCISC 2018). In SCI, motor impairment is caused by the disruption of nerve pathways that conduct motor (efferent) and sensory (afferent) signals between the brain and the rest of the body. Motor impairment describes a variable loss in function (weakness, lack of control, or poor stamina) of a body part. Depending on the type and level of SCI injury, some muscles may have residual motor function with the possibility of rehabilitation (Raineteau et al 2001, Burns et al 2012). Tetraplegic patients, for whom upper extremity function may be impaired and not completely lost, prioritize hand function rehabilitation due to its importance in daily life activities (Anderson et al 2004, Snoek et al 2004, Collinger et al 2013). Research directed towards increasing the efficacy of motor rehabilitation techniques is crucial for helping SCI patients regain highly desired functions, and subsequent independence, sooner in life.

1.2 Sensory Feedback in Motor Training

Motor impairment in SCI is primarily caused by disruption of corticospinal tracts. In order for the nervous system to compensate for injury, the connections within the nervous system reorganize, a phenomenon known as neuroplasticity. This neuroplastic reorganization can occur passively through daily living or actively through therapeutic interventions. In some cases, reorganization can be detrimental and result in additional losses in motor function (Topka 1991, Green et al 1998, Curt, Alkadhi, et al 2002, Curt, Bruehlmeier, et al 2002). Interventions that harness use-dependent plasticity (UDP)

(Classen et al 1998) can strengthen spared pathways through repetitive exercise. However, while motor activation is required for functional recovery, sensory feedback has proven to be nearly as important. It is widely acknowledged that sensory feedback plays a vital role in normal motor learning and function (Rothwell et al 1982, Hamdy et al 1998, Rossi et al 1998). Previous work suggests that transcutaneous afferent peripheral nerve stimulation (commonly referred to as PNS) increases corticospinal excitability in healthy participants (Hamdy 1998 et al, Ridding 2001). In a motor-impaired cohort, PNS increased motor cortical excitability and muscle function when applied for a two-hour period prior to motor training (Conforto 2002, Sawaki 2006). Overall, these studies support the idea that sensory input can enhance the effects of motor training. However, these studies utilized repetitive sensory pathway activation not specifically and tightly coupled with motor execution.

It is now increasingly understood that the timing of sensory feedback is important in harnessing the full effects of motor training. Paired associative stimulation (PAS) studies have shown that PNS applied synchronously with transcranial magnetic stimulation (TMS) of the contralateral cortex creates increased, sustained cortical excitability (Stefan et al 2000). This emphasizes the role of timing-dependent plasticity (TDP) in determining synaptic strength: i.e., afferent PNS applied in synchrony with cortical stimulation enhances cortical excitability. While this concept has been demonstrated using TMS-evoked measurements, the rehabilitative potential of TDP induced by afferent PNS paired with motor volition have not been previously explored in patients with chronic, incomplete tetraplegia.

In PAS, motor pathways are activated using TMS, which does not require the subject's active participation. This does not accurately mirror what happens in motor

training, where the participant is consciously activating motor pathways. Therefore, it would be beneficial to explore the effects of TDP on motor rehabilitation when participants are actively performing motor tasks with or without assistance. Previous studies have shown that sensory stimulation applied in conjunction with motor training in patients with tetraplegia enhanced various aspects of motor training (Hoffman et al 2007, Beekhuizen et al 2008). However, the PNS timing was not tightly coupled with motor execution in these studies.

1.3 Overview of Approach

In order to time PNS in a way that would synchronize the activation of sensory and motor pathways, PNS application must occur prior to and closely correlated with movement execution, i.e., the activation of relevant skeletal muscle groups. Therefore, a brain-computer interface (BCI) was developed that utilizes EEG features to detect "movement intention", preceding the physical movement of the user in response to a visual cue, and subsequently trigger PNS. This work will describe the BCI system developed for PNS application during a hand grip task in patients with tetraplegia, and discuss its evaluation. The most updated version of the BCI developed for this study (BCI-PNS) will be described and compared to the old system (BCI*-PNS) as well as PNS not controlled by the BCI, applied at random, (Sham BCI-PNS). Participant specific functional outcomes will not be discussed in this work.

CHAPTER 2. BACKGROUND

2.1 Spinal Cord Injury

Spinal cord injury (SCI) is a debilitating condition that disrupts proper communication between the central nervous system (CNS) and peripheral nervous system (PNS). Spinal cord injuries are classified mainly by their neurologic level and the severity of subsequent motor and sensory impairment. The spinal cord exits the skull through the foramen magnum into the vertebral canal and extends to the lumbar vertebral level (L1/L2). Damage at any point along the spinal cord can result in a spinal cord injury. Injuries that affect the cervical segments of the spinal cord are known as cervical SCIs. Cervical SCI can result in functional impairment of all four limbs (tetraplegia).

Loss of motor and sensory function varies between injuries. Injury severity is clinically assessed using the American Spinal Injury Association Impairment Scale (AIS) which is the International Standard for Neurological Classification of SCI. An injury is classified as complete (AIS A) if there is complete loss of sensory and motor function in the patient's sacral segments (American Spinal Injury Association 2003). If an injury is not considered complete, it can be then classified as sensory incomplete or motor complete (B), motor incomplete (C), motor incomplete but with relatively low impairment (D), or normal (E) (American Spinal Injury Association 2003). With rehabilitation, patients with SCI have proven to be capable of substantial functional recovery following their injury (Raineteau et al 2001, Burns et al 2012)

2.2 Peripheral Nerve Stimulation & Timing-Dependent Plasticity

Stimulation of functionally associated cortical and peripheral neurons, first done by Mariorenzi et al in 1991, involves a peripheral or "conditioning" stimulation which precedes a cortical or "test" stimulation by a certain inter-stimulus interval (ISI). The effect of the associative stimulation is evaluated based on subsequent corticospinal output. Trans-cranial magnetic stimulation (TMS) is most commonly used to stimulate the motor cortex. Observing the amplitude of TMS induced motor evoked potentials (MEPs), recorded from electromyography (EMG), is a means of evaluating corticospinal excitability.

Different effects have been observed based on the ISI used during the associative stimulation. The paired associative stimulation technique (PAS), described by Stefan and colleagues in 2000, has become a widely used neuromodulation technique in the context of motor rehabilitation. During a PAS session, PNS of afferent nerve fibers associated with a target muscle group is repetitively paired with a single, non-invasive TMS pulse delivered to the contralateral motor cortex to activate that muscle group. The PNS precedes the TMS pulse at an ISI of 25 ms (Stefan et al 2002, Rossini et al 2015). In healthy subjects, increased topographically-specific cortical excitability is subsequently observed in the form of long lasting, increased amplitudes of TMS-induced MEPs. This paradigm was developed based on experiments in animal models of associative long-term potentiation (LTP), a mechanism which is widely thought to contribute to learning and memory (Stefan et al 2002; Wolters et al 2003). In other words, PAS is thought to take advantage of TDP at the cortical level (Stefan et al 2002), which would imply that the proper sequence of pathway activation is more advantageous to strengthening connections than the rate of

activation alone. Figure 2.1 demonstrates the differences between traditional PAS and BCI-PAS.

The dependence of connection strengthening on the stimulation timing of related pathways is further supported by the phenomena of short afferent inhibition (SAI) and long afferent inhibition (LAI) (Tokimura et al 2000; Chen et al 1999). In SAI and LAI, rather than increasing corticospinal excitability, the ISI used between the "conditioning" sensory stimulation and the "test" TMS stimulation inhibits corticospinal output. In healthy participants, these ISI values are ~20-25ms (SAI) and ~200ms (LAI) (Rossini et al 2015). However, this afferent inhibition is not always present in individuals with SCI (Bailey et al 2015).

2.3 Brain-Computer Interfaces

PNS coupling with movement execution was accomplished through a brain-computer interface (BCI). A BCI, also known as a brain-machine interface (BMI), is a system that utilizes the brain's electrical signals as controls for a desired output (Wolpaw 2012). This technology is most often used as a way to control an assistive technology by bypassing the peripheral nervous system. BCIs can be invasive or non-invasive; however, non-invasive brain signal monitoring, known as scalp electroencephalography (EEG), is most commonly used in BCI research due to its low cost and clinical practicality. Non-invasive EEG-based BCIs utilize electrodes affixed to the scalp and a biosignal amplifier to record electrical activity associated with field post-synaptic potential changes in the cortex.

Certain EEG rhythms observed over the sensorimotor cortex, collectively known as the sensorimotor rhythms (SMRs), undergo characteristic changes during motor intention, motor execution, or motor imagery tasks. These changes are characterized by signal attenuation, or event-related de-synchronization (ERD), of the ongoing rhythm in the 8-13 Hz (mu) and 14-26 Hz (beta) bands, with an increase in power, or event-related synchronization (ERS), in frequencies above 30 Hz (gamma) (Pfurtscheller et al 1999, Pfurtscheller et al 2012). BCIs that utilize SMR features have been considered extensively as means of communication and control for motor-impaired individuals, but only more recently as a valuable adjunct to motor rehabilitation therapy (Pfurtscheller et al 2012, Yuan et al 2014). The mu rhythm (8-13 Hz) was the EEG feature used in the BCI system described in this work. The goal in developing the described BCI system is to provide PNS, to patients with tetraplegia, with EEG-determined motor intent and assess its effect on hand grip rehabilitation in patients with chronic cervical spinal cord injury.

2.3.1 BCI-Driven Paired Associative Stimulation

Similar BCI-PAS paradigms to the one in the present study, have been utilized in healthy controls (Niazi et al 2012) and stroke patients (Mrachacz-Kersting et al 2016). However, these BCI systems utilize an EEG feature different from the mu rhythm, a feature known as the movement-related cortical potential (MRCP). Additionally, these systems utilize offline EEG analysis of the MRCPs to predetermine PNS timing (Niazi et al 2012, Mrachacz-Kersting et al 2016). BCI-PAS applied in this manner has been shown to elicit positive changes in cortical excitability for the tibialis anterior muscle of the leg. However, these studies did not involve real-time detection of the MRCP, only an estimate of its average timing relative to a cue in a training session to drive open-loop PNS feedback in

treatment sessions. To our knowledge, the BCI system described in this work is the first to use a BCI for real-time sensory feedback in tetraplegic patients with hand impairment.

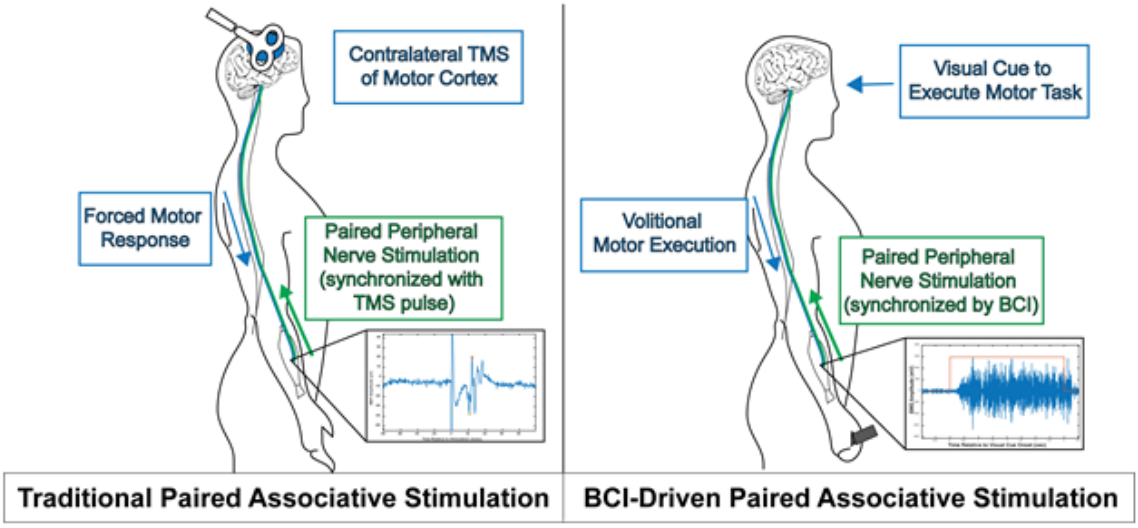

Figure 2.1 Traditional PAS vs. BCI-PAS. This figure compares the traditional PAS technique with the described BCI. Both utilize synchronicity of efferent and afferent activation. However, in the BCI system, motor activation is controlled by the participant (volitional movement) which is in contrast to the TMS-induced motor activation, which is unnatural and does not require participant volition or attention.

CHAPTER 3. METHODS

3.1 Participant Inclusion Criteria

With IRB approval at the University of Kentucky, thirteen (12 male, 1 female, mean age 45±12y, mean time since injury 115±131mo) of sixteen screened patients took part in a four-week visual cue-driven motor intervention with one participant dropping out after completing seven of the twelve planned sessions. Subjects took part in interventions that either applied BCI-driven PNS (closed-loop) or interventions in which PNS was applied at random relative to the motor task (Sham BCI or open-loop). The results presented in this thesis focus on the accuracy of detection of movement intent from the EEG and not on the outcomes of the intervention, which will be reported separately. Nine of twelve patients returned to take part in a second course of open-loop (or closed-loop) intervention that was at least 8 weeks removed from the first closed-loop (or open-loop) one. All patients gave informed consent and underwent a clinical screening session prior to enrollment. Inclusion criteria were: injury level from C4-C7, over six months post injury, presence of detectable hand grip force or muscle activation, no neurological disorders, and distinguishable EEG signals. Participant and intervention information are displayed in Table 3.1.

3.2 The Motor Task

Participants completed approximately 60 runs (1200 cues) per hand over eight (Tuesday/Thursday) or twelve (Monday/Wednesday/Friday) sessions over a 4-6 week intervention period based on participant availability. Each run consisted of 23 visual cues that prompted motor execution, with no PNS applied for the first three cues. Prior to the

start of the first cue, a baseline recording was collected in order to establish average EEG mu band power values at rest. Participants were instructed to execute a self-paced, unrestricted isometric power grip force on a hand-held dynamometer (HD-BTA, Vernier Software & Technology) in response to the cue, during which PNS was applied.

3.3 BCI System

3.3.1 Overview & Data Acquisition

Custom BCI software was developed using the LabVIEW platform (National Instruments). EEG and electromyogram (EMG) signals were collected using g.ladybird active electrodes (Guger Technologies). A g.USBamp biosignal amplifier (Guger Technologies) was used for all biosignal amplification, acquisition (512 Hz sampling frequency), notch filtering (60 Hz) and anti-aliasing (pass band 0.1-100 Hz). It was necessary to update the BCI system (previously described by Schildt, 2015) after the first five (including drop-out participant) interventions in order to improve PNS correlation with movement execution. In the update, the visual cue for motor execution was changed (from concentric circles to a hand animation), and the cue length was increased from 3 seconds to 4 seconds. The criteria for detection of motor intent from the EEG was also modified. The updated BCI system is the focus of this work.

3.3.2 Visual Cue

A screen positioned approximately two feet away from the participant displayed the visual cue. During the “cue off” state, the screen displayed a crosshair at the middle of the screen. During the “cue on” state, an open hand was displayed. Changes in force cause

the hand to close in order to give the participant visual confirmation of movement execution. The cue was randomly displayed at 3±2 second intervals in order to prevent participants from predicting the cue. The cue was displayed for 4 seconds (3 seconds before system update). The length of the cue was increased in order to allow time for deliberate, self-paced movements.

3.3.3 Movement Intent Detection

The BCI system utilized non-invasive surface EEG. Active electrodes were placed in a medium-sized standardized cap that allowed for 10/10 electrode system positioning (Guger Technologies). The EEG electrodes used were CP1, CP2, CP5, CP6, Cz, C3, C4, P3, and P4. The electrooculogram (EOG) was recorded by placing an active electrode over the left eye on the forehead (for SID-008 and SID-009, FC5 & FC6 were used instead of CZ and EOG). At the beginning of each intervention, for both BCI and Sham BCI interventions, the EEG cap containing the active electrodes was placed snugly on the participant's head and conductive gel was injected into each electrode cavity. The EEG signal-to-noise ratio was observed during setup and electrodes were adjusted until impedance was low and noise levels were acceptable.

The BCI software used an EEG feature commonly utilized in movement-related BCIs, the mu rhythm, to detect movement intent. The mu rhythm is an 8-13 Hz frequency band known to attenuate during movement execution and imagination. Changes in mu band power were tracked in real time. As the data was acquired (sampling rate of 512 Hz; analysis frame length = 64 samples), EEG data was filtered using a 4^{th} order Butterworth bandpass filter (8-13 Hz) and the mean mu power was calculated. If collected during the "cue off" state, the mean was incorporated into a running average of baseline mu power. If

collected during the "cue on" state, the mean is compared to the baseline mu power average via the mu power ratio (MPR):

$$MPR = \frac{Mu^2_{frame}}{Mu^2_{baseline}}$$

An MPR value under 1 was considered as mu rhythm suppression (i.e., ERD). This calculation was performed separately for each EEG channel. If over 50% of the EEG channels demonstrated suppression, PNS was triggered. This 50% threshold was adjusted slightly as needed based on the observed accuracy during sessions.

3.3.4 Afferent Peripheral Nerve Stimulation

Afferent Peripheral Nerve Stimulation (PNS) refers to electrical stimulation of the median nerve below the motor threshold (i.e., the intensity above which a motor response is induced). This was accomplished by delivering square, monophasic pulse trains (10 Hz, 500ms duration, 1 ms pulse width) (Ridding et al 2000, Kaelin-Lang et al 2002, Sawaki 2006) using an external electrical stimulator (Grass S8800; Astro-Med, Inc.), 6 mm gold cup electrodes (Grass; Astro-Med Inc.), and conductive paste (Ten20, Weaver and Co.). The stimulation parameters used are designed to preferentially activate primary afferent nerve fibers (Panizza et al 1992, Maugniére et al 1999). Electrodes were placed over the median nerve at the wrist location with the cathode 3cm proximal to the anode (Figure 3.1). Prior to the start of each session, stimulation intensity was adjusted so that observable compound muscle action potentials (CMAPs) were between 50-100uV (Kaelin-Lang et al 2002, Sawaki 2006). The PNS perceptual threshold was determined as the lowest

stimulation setting perceived by the participant. A computer containing the BCI software was connected to the stimulator in order to trigger stimulation.

3.4 BCI Evaluation

The goal of the described BCI system was to detect movement intent in order to trigger PNS. Therefore, the BCI's output, PNS, was used to evaluate the system's ability to detect movement intention. PNS timing was characterized in relation to participant movement execution. The timing of movement onset was determined manually from force and EMG signals and was compared to the timing of PNS onset. PNS timing was characterized for each type of intervention (BCI, BCI*, Sham BCI) and compared. Additionally, PNS and movement onsets were correlated to further test whether or not the BCI was detecting movement intent.

3.4.1 Determination of Movement Onset

Movement onset was determined using the force and EMG traces (except for SID-001 & SID-007). Onset was manually determined for each cue as the time point at which the force signal or EMG power deviated in the positive direction from its baseline. The EMG signal was bandpass filtered (50-100 Hz, 4^{th} order Butterworth zero-phase filter) and rectified prior to movement onset scoring.

The EMG signals were collected from either the abductor pollicis brevis (APB) muscle or flexor carpi radialis (FCR) muscle, depending on the EMG signal quality in each participant. Both the APB and FCR are innervated by the median nerve which has contributions from most nerve roots in the brachial plexus (C6-T1). The FCR muscle is an extrinsic muscle of the hand that contributes majorly to the force produced during a power

grip. The APB muscle is an intrinsic muscle of the hand that is utilized in all grip types (Dutton 2004, Magee 2014). The reliability of the force signal in determining movement onset depended on the participant's ability to produce force with their hand grip. The reliability of the EMG signal in determining movement onset depended on numerous factors including muscle weakness, atrophy, rigidity, and/or spasticity. PNS timing metrics were produced using the most reliable signal type. The force signal was more reliable than EMG in determining movement onset in all participants except for SID3. All offline analysis was completed in MATLAB (MathWorks, Inc.).

3.4.2 Movement-PNS Latency

A PNS latency relative to movement onset was calculated by subtracting the time of PNS onset from movement onset. Movement-PNS latency distributions were summarized for each intervention by calculating the minimum latency value, 10th, 25th, 50th, 75th, 90th percentiles, and the maximum latency value. These metrics were compared between intervention types.

3.4.3 Positive Predictive Value

The presence and timing of PNS application were used to characterize each stimulation opportunity as a true positive (TP), false positive (FP), true negative (TN), or false negative (FN). A TP was defined as a PNS that was triggered at least 31.25ms (16 samples) after cue start and before movement onset. In general, an FP was defined as a PNS triggered without movement execution (FP1) or a PNS trigger that was evoked by anything other than movement intention (FP2 & FP3). Detection frames – i.e., sequential chunks of EEG at the end of which a prediction of the subject's movement intent were

made in real time – were 125ms (64 samples) in size. A detection frame that could trigger PNS prior to 31.25ms after cue start would only be overlapping with the cue by less than 16 samples (25% of frame). Therefore, a PNS trigger occurring less than 31.25ms after cue start is most likely evoked by the cue state change and not movement intent (FP2). A PNS trigger occurring after movement onset is not evoked by movement intent because movement intention precedes movement execution (FP3). A TN was defined as a cue in which no movement execution occurred and no PNS was triggered (e.g., a lapse in concentration). A FN was defined as a cue in response to which movement execution occurred, but no PNS was triggered. Figure 3.2 demonstrates the classification of stimulations and cue without stimulations.

After all stimulations applied over an intervention were categorized, the total number of TP, FP, and FN stimulations across an intervention were used to calculate the positive predictive value (PPV) and sensitivity of each intervention; these are sometimes referred to as precision and recall respectively. A one-way ANOVA was performed to test for statistically significant differences in PPV and sensitivity values between intervention groups Post-hoc, one-tailed, two-sample t-tests were performed to test whether PPV and sensitivity values were greater for interventions in which the described BCI system was used to trigger PNS compared to the old system and PNS applied at random.

$$PPV = \frac{TP}{TP + FP}$$

$$FP = FP1 + FP2 + FP3$$

$$Sensitivity = \frac{TP}{TP + FN}$$

3.4.4 Movement Onset & PNS Correlation

Although the timing of PNS application prior to movement onset is important, the PNS timing requirements discussed could be satisfied by timing PNS delivery to occur a preset time after the cue state. Therefore, it must be determined whether BCI-driven PNS is actually correlated with movement rather than the cue state. This was accomplished by conducting both a Pearson's correlation and Spearman's rank correlation of PNS-Cue latencies and Movement-Cue latencies. The PNS-Cue latency (Δt_{PNS}) was calculated by subtracting the time of PNS onset from the time of cue onset. The Movement-Cue latency ($\Delta t_{Movement}$) was calculated by subtracting the time of cue onset from movement onset. Only stimulations characterized as TPs were included in this analysis. Latency variables were expressed in milliseconds and then log transformed to reduce skewness prior to correlation.

Table 3.1 Participant Demographics. This table displays the subject ID (SID), gender, ASIA grade, neurologic level of injury, age, time since injury, and intervention type completed. Age and time from injury were given based on their value at intervention start.

SID	Gender	ASIA Grade	Neurologic Level	Age (y)	Time from Injury (mo)	Intervention Type
1^{+}	M	C	C6	30	159	BCI*
				34	204	BCI
3^{+}	F	B	C6	37	70	BCI*
				38	83	BCI
4^{-}	M	C	C4	55	61	BCI*
6^{+}	M	B	C6	58	245	BCI*
				60	263	Sham BCI
7^{+}	M	A	C5	48	30	BCI*
				49	42	BCI
8^{+}	M	C	C5	50	10	BCI
				51	24	Sham BCI
10	M	C	C5	54	468	BCI
12^{+}	M	A	C7	40	96	BCI
				41	104	Sham BCI
14^{+}	M	C	C6	46	14	BCI
				47	24	Sham BCI
15^{+}	M	B	C6	45	224	BCI
				46	230	Sham BCI
16	M	C	C4	35	59	BCI
17^{+}	M	D	C6	68	16	BCI
				69	33	Sham BCI
18	M	A	C4	25	46	Sham BCI

* Intervention performed before BCI system update
- Dropped out after 7 sessions
+ Repeat Participant
ASIA: American Spinal Injury Association (A: Complete, B: Sensory Incomplete, C: Motor Incomplete, D: Motor Incomplete, E: Normal)
BCI: PNS controlled by brain-computer interface
BCI*: PNS controlled by brain-computer interface (old system)
Sham BCI: PNS delivered at random during motor task

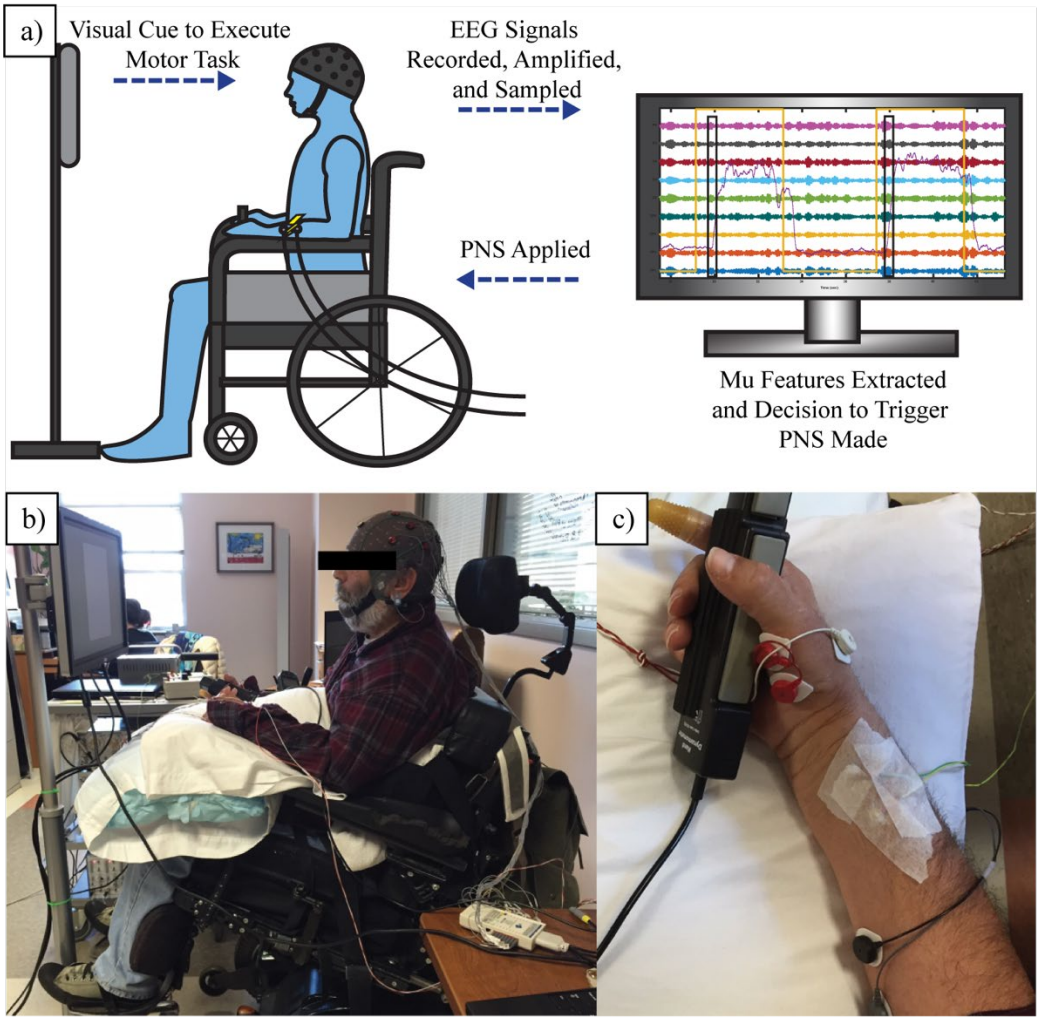

Figure 3.1 Experimental set-up. A schematic that highlights the main components of the BCI system. (b) A photograph of a participant with the BCI set-up. The participant is wearing an EEG cap containing active electrodes that are gelled prior to the start of each session. (c) A photograph of the participant's forearm with FCR/APB EMG electrodes, and PNS electrodes in place. The participant is also holding the dynamometer used during interventions.

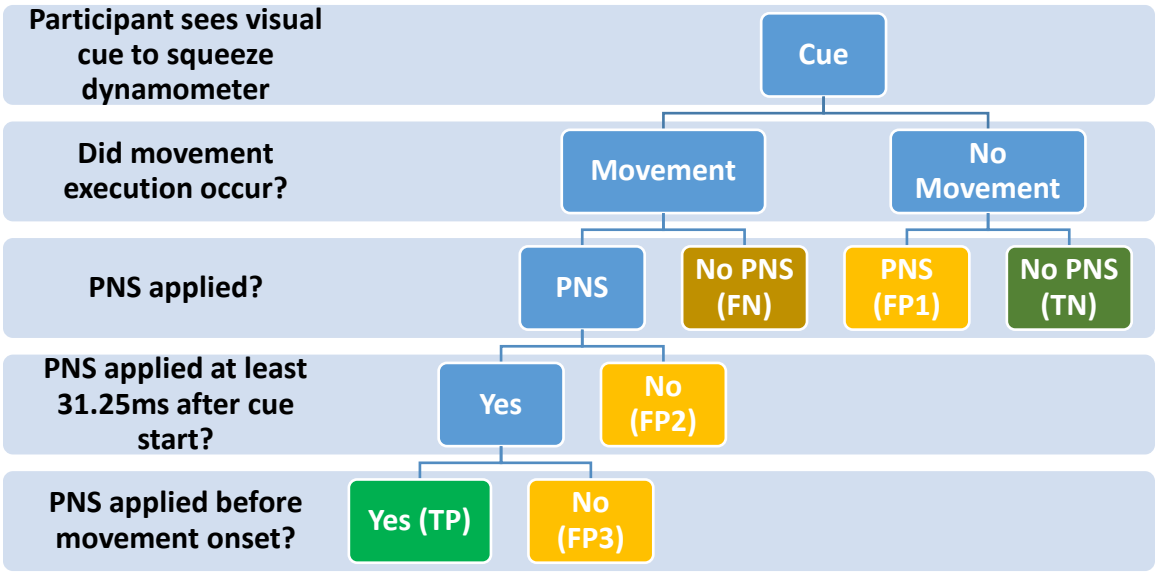

Figure 3.2 Classification diagram of movement intent detection. A decision to apply PNS was made by the BCI for every cue. That decision can be classified as a true positive (TP), true negative (TN), false positive (FP), or false negative (FN) based on whether there was (1) motor execution present during the cue and (2) the decision was made at the appropriate time. Since motor intention necessarily precedes movement onset, the appropriate time for PNS to be applied is before movement onset.

CHAPTER 4. RESULTS

4.1 Movement-PNS Latency Distributions

Bowley's seven-figure summary was used to describe the distribution of stimulations for each intervention. The minimum value, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th} percentiles, and maximum value of the Movement-PNS latencies for each intervention type are displayed in Table 4.1, Table 4.2, and Table 4.3 and displayed in Figures 4.1 and 4.2. For the described BCI system, the average quartile values across left hand interventions are: 133±90ms (Q1), 275±91ms (Q2), and 396±137ms (Q3). Average quartile values across right hand interventions are: 108±84ms (Q1), 253±76ms (Q2), and 364±111ms (Q3). For the old BCI system, the average quartile values across left hand interventions are: -426±408ms (Q1), -116±355ms (Q2), and 102±391ms (Q3). Average quartile values across right hand interventions are: -516±448ms (Q1), -98±334ms (Q2), and 182±347ms (Q3). For the Sham BCI PNS, the average quartile values across left hand interventions are: -1211±185ms (Q1), 515±188ms (Q2), and 2445±64ms (Q3). Average quartile values across right hand interventions are: -1239±186ms (Q1), 497±159ms (Q2), and 2445±95ms (Q3).

4.2 Positive Prediction Value & Sensitivity Metrics

The mean PPV of interventions with BCI--PNS (n=10) were 69±8% for both left hand and right hand runs. The mean PPVs of interventions with BCI*-PNS (n = 5) were 41±30 % (left hand runs) and 44±28 % (right hand runs). The mean PPVs of interventions Sham BCI-PNS (n=7) were 8±3% (left hand runs) and 7±3 % (right hand runs). The mean sensitivity values of interventions with BCI-PNS (n=10) were 100±1% for both left hand

and right hand runs. The mean PPV of interventions with BCI*-PNS (n = 5) were 88±17% (left hand runs) and 83±21% (right hand runs). The mean PPVs of interventions with Sham BCI-PNS (n=7) were 75±10% (left hand runs) and 73±13 % (right hand runs). Average PPV and sensitivity values are displayed by intervention type in Figure 4.3. The stimulation classifications used to calculate the PPV and sensitivity values are displayed in Tables 4.4, 4.5, and 4.6.

There was a statistically significant difference between group PPV means, ANOVA ($F(2,19) = 34.52$, $p < 0.001$), and group sensitivity means, ANOVA ($F(2,19) = 10.69$, $p < 0.001$. Post-hoc analysis showed that interventions in which PNS was driven by the described BCI system, had significantly higher PPV values compared to interventions with PNS driven by the old BCI system ($p = 0.010$ (LH), $p = 0.014$ (RH)), and PNS applied at random ($p<0.001$ (LH & RH)). Post-hoc analysis showed that interventions in which PNS was driven by the described BCI system, had significantly higher sensitivity values compared to interventions with PNS driven by the old BCI system ($p = 0.021$ (LH), $p = 0.010$ (RH)), and PNS applied at random ($p<0.001$ (LH & RH)).

4.3 Time Correlation between PNS & Movement

One-tailed Pearson's and Spearman's rank correlations were performed on movement and PNS onset times relative to the cue to test for the presence of a significant positive relationship. The correlation values and corresponding p-values are displayed in Table 4.7. All BCI-driven PNS and Movement onset correlations, except SID 14 (LH), SID 8 (RH), and SID 16 (RH), demonstrated significant monotonic relationships between the two variables.

Table 4.1 Movement Onset-PNS latency distributions of BCI-PNS. In the first three columns, this table displays the subject ID (SID), intervention type, and the total number of stimulations that occurred with movement during the intervention (n). The remaining columns display the minimum latency value, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th} percentiles, and maximum latency value of each latency distribution. All latency values are given in milliseconds.

Left Hand									
SID	Intervention Type	n	Min	10^{th}	25^{th}	50^{th}	75^{th}	90^{th}	Max
1^{+}	BCI	1198	-1299	-228	119	248	377	525	2129
3^{+}	BCI	1178	-1605	-421	76	277	406	574	1764
7^{+}	BCI	1200	-2604	-467	-86	135	217	326	727
8^{+}	BCI	1072	-2926	-119	252	463	648	887	3482
10	BCI	1180	-1621	3	180	244	309	388	732
12^{+}	BCI	1179	-947	-86	109	146	181	229	797
14^{+}	BCI	1144	-1650	19	176	271	396	579	3217
15^{+}	BCI	1185	-1834	-139	119	342	585	892	2848
16	BCI	1198	-1816	64	230	342	451	600	2111
17^{+}	BCI	1200	-1188	-94	156	285	385	488	1668
Right Hand									
SID	Intervention Type	n	Min	10^{th}	25^{th}	50^{th}	75^{th}	90^{th}	Max
1^{+}	BCI	1196	-1061	-295	64	193	285	377	2377
3^{+}	BCI	1199	-1453	-462	37	260	391	547	1459
7^{+}	BCI	1198	-2533	-428	-70	139	213	314	2451
8^{+}	BCI	1127	-1854	-266	119	330	490	755	3285
10	BCI	1180	-1328	37	162	207	260	314	668
12^{+}	BCI	1180	-1209	-104	98	146	211	287	727
14^{+}	BCI	1147	-986	27	182	305	414	580	2953
15^{+}	BCI	1190	-1189	-248	82	305	508	748	3145
16	BCI	1200	-838	94	250	377	508	647	1484
17^{+}	BCI	1199	-1281	-82	156	271	359	462	1133

- Dropped out after 7 sessions

$^{+}$ Repeat Participant

BCI: PNS controlled by brain-computer interface

Table 4.2 Movement Onset-PNS latency distributions of BCI*-PNS. In the first three columns, this table displays the subject ID (SID), intervention type, and the total number of stimulations that occurred with movement during the intervention (n). The remaining columns display the minimum latency value, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th} percentiles, and maximum latency value of each latency distribution. All latency values are given in milliseconds.

Left Hand									
SID	Intervention Type	n	Min	10^{th}	25^{th}	50^{th}	75^{th}	90^{th}	Max
1^{+}	BCI*	883	-1617	-663	-586	-494	-314	168	635
3^{+}	BCI*	1074	-5584	-1551	-846	-55	293	400	4740
4^{-}	BCI*	500	-2662	-1271	-500	-2	380	731	2365
6^{+}	BCI*	1187	-693	277	354	461	564	688	2619
7^{+}	BCI*	870	-818	-604	-553	-488	-412	125	717
Right Hand									
SID	Intervention Type	n	Min	10^{th}	25^{th}	50^{th}	75^{th}	90^{th}	Max
1^{+}	BCI*	858	-3195	-1047	-570	-277	189	412	1963
3^{+}	BCI*	992	-3223	-1563	-946	16	314	439	2881
4^{-}	BCI*	488	-2707	-1687	-781	-112	317	626	2012
6^{+}	BCI*	1185	-928	256	342	445	559	689	2588
7^{+}	BCI*	839	-3248	-699	-623	-564	-469	60	482

- Dropped out after 7 sessions

$^{+}$ Repeat Participant

BCI*: PNS controlled by brain-computer interface (old system)

Table 4.3 Movement Onset-PNS latency distributions of Sham-BCI PNS. In the first three columns, this table displays the subject ID (SID), intervention type, and the total number of stimulations that occurred with movement during the intervention (n). The remaining columns display the minimum latency value, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th} percentiles, and maximum latency value of each latency distribution. All latency values are given in milliseconds.

Left Hand									
SID	Intervention Type	n	Min	10^{th}	25^{th}	50^{th}	75^{th}	90^{th}	Max
6^{+}	Sham BCI	1217	-4236	-2376	-1183	557	2452	3722	5771
8^{+}	Sham BCI	1074	-4342	-2176	-1072	779	2533	3927	5783
12^{+}	Sham BCI	1186	-4482	-2430	-1271	444	2441	3527	5111
14^{+}	Sham BCI	1163	-4963	-2475	-1218	580	2478	3741	7430
15^{+}	Sham BCI	1180	-4434	-2148	-950	530	2378	3874	6938
17^{+}	Sham BCI	1187	-4604	-2466	-1186	600	2500	3691	5055
18	Sham BCI	1268	-6119	-2943	-1594	116	2333	3543	5650
Right Hand									
SID	Intervention Type	n	Min	10^{th}	25^{th}	50^{th}	75^{th}	90^{th}	Max
6^{+}	Sham BCI	1208	-4453	-2371	-1217	638	2537	3692	5412
8^{+}	Sham BCI	1103	-4682	-2204	-1116	393	2513	3835	6912
12^{+}	Sham BCI	1181	-4508	-2500	-1286	689	2458	3589	5148
14^{+}	Sham BCI	1172	-5377	-2336	-1150	626	2556	3779	6594
15^{+}	Sham BCI	1170	-4365	-2311	-1023	452	2375	3766	6049
17^{+}	Sham BCI	1185	-4615	-2447	-1231	486	2411	3549	5350
18	Sham BCI	1279	-5215	-2920	-1651	195	2268	3575	5449

$^{+}$ Repeat Participant

Sham BCI: PNS delivered at random

Table 4.4 Stimulation classifications of BCI-PNS. This table displays the subject ID (SID), intervention type, total number of stimulations delivered over the intervention, and the number of stimulations characterized as true positives (TP), false positives (FP), true negatives (TN), and false negatives (FN), respectively.

Left Hand

SID	Intervention Type	Total	TN	FN	FP1	FP2	FP3	TP
1+	BCI	1200	0	0	2	177	217	804
3+	BCI	1179	0	1	1	148	261	769
7+	BCI	1200	0	0	0	196	387	617
8+	BCI	1147	0	20	75	228	145	699
10	BCI	1180	0	0	0	141	118	921
12+	BCI	1179	0	1	0	151	180	848
14+	BCI	1159	0	1	15	141	122	881
15+	BCI	1198	0	2	13	140	238	807
16	BCI	1199	0	1	1	154	79	965
17+	BCI	1200	0	0	0	154	157	889

Right Hand

SID	Intervention Type	Total	TN	FN	FP1	FP2	FP3	TP
1+	BCI	1197	0	3	1	175	256	765
3+	BCI	1199	0	1	0	134	282	783
7+	BCI	1198	0	2	0	177	362	659
8+	BCI	1149	1	19	22	174	227	726
10	BCI	1180	0	0	0	147	98	935
12+	BCI	1180	0	0	0	151	237	792
14+	BCI	1160	0	0	13	169	103	875
15+	BCI	1200	0	0	10	138	206	846
16	BCI	1200	0	0	0	167	74	959
17+	BCI	1199	0	1	0	159	162	878

+ Repeat Participant

BCI: PNS controlled by brain-computer interface

TP: # of stimulations applied at least 31.25ms after cue start and prior to movement onset

FP1: # of stimulations applied during cues in which there was no movement

FP2: # of stimulations applied within 31.25ms of cue start

FP3: # of stimulations applied after movement onset

TN: # cues in which there was no movement and no stimulation

FN: # of cues in which there was a movement attempt and no stimulation

Table 4.5 Stimulation classifications of BCI*- PNS. This table displays the subject ID (SID), intervention type, total number of stimulations delivered over the intervention, and the number of stimulations characterized as true positives (TP), false positives (FP), true negatives (TN), and false negatives (FN), respectively.

Left Hand								
SID	Type	Total	TN	FN	FP1	FP2	FP3	TP
1^{+}	BCI*	885	0	0	2	10	777	96
3^{+}	BCI*	1086	0	150	12	25	587	462
4^{-}	BCI*	531	3	148	31	2	249	249
6^{+}	BCI*	1200	0	0	13	78	7	1102
7^{+}	BCI*	870	0	0	0	0	759	111
Right Hand								
SID	Type	Total	TN	FN	FP1	FP2	FP3	TP
1^{+}	BCI*	858	0	25	0	46	554	258
3^{+}	BCI*	992	1	208	0	6	511	475
4^{-}	BCI*	515	1	185	27	1	279	208
6^{+}	BCI*	1200	0	0	15	46	18	1121
7^{+}	BCI*	840	0	0	1	1	754	84

- Dropped out after 7 sessions

$^{+}$ Repeat Participant

BCI*: PNS controlled by brain-computer interface (old system)

TP: # of stimulations applied at least 31.25ms after cue start and prior to movement onset

FP1: # of stimulations applied during cues in which there was no movement

FP2: # of stimulations applied within 31.25ms of cue start

FP3: # of stimulations applied after movement onset

TN: # cues in which there was no movement and no stimulation

FN: # of cues in which there was a movement attempt and no stimulation

Table 4.6 Stimulation classifications of Sham BCI-PNS. This table displays the subject ID (SID), intervention type, total number of stimulations delivered over the intervention, and the number of stimulations characterized as true positives (TP), false positives (FP), true negatives (TN), and false negatives (FN), respectively.

Left Hand								
SID	Type	Total	TN	FN	FP1	FP2	FP3	TP
6+	Sham BCI	1225	1	17	8	634	487	96
8+	Sham BCI	1186	2	27	112	565	403	106
12+	Sham BCI	1186	0	20	0	618	519	49
14+	Sham BCI	1182	0	24	19	603	484	76
15+	Sham BCI	1184	0	28	4	571	444	165
17+	Sham BCI	1188	0	25	1	637	478	72
18	Sham BCI	1268	0	58	0	608	584	76
Right Hand								
SID	Type	Total	TN	FN	FP1	FP2	FP3	TP
6+	Sham BCI	1226	0	21	18	634	501	73
8+	Sham BCI	1178	3	25	75	568	459	76
12+	Sham BCI	1181	0	27	0	655	486	40
14+	Sham BCI	1188	0	16	16	600	482	90
15+	Sham BCI	1184	0	25	14	549	458	163
17+	Sham BCI	1186	0	20	1	614	513	58
18	Sham BCI	1282	0	51	3	637	585	57

+ Repeat Participant

Sham BCI: PNS delivered at random

TP: # of stimulations applied at least 31.25ms after cue start and prior to movement onset

FP1: # of stimulations applied during cues in which there was no movement

FP2: # of stimulations applied within 31.25ms of cue start

FP3: # of stimulations applied after movement onset

TN: # cues in which there was no movement and no stimulation

FN: # of cues in which there was a movement attempt and no stimulation

Table 4.7 PNS-Cue latency and Movement Onset-Cue latency correlation values. This table displays the values from one-tailed Pearson's (ρ) and Spearman's rank (ρ_s) correlations and their corresponding p-values.

Left Hand				
SID	Intervention Type	N	Pearson correlation ρ (p-value)	Spearman's correlation ρ_s (p-value)
1^+	BCI	804	0.19 (<0.001)	0.15 (<0.001)
3^+	BCI	769	0.13 (<0.001)	0.12 (<0.001)
7^+	BCI	617	0.43 (<0.001)	0.46 (<0.001)
8^+	BCI	699	0.17 (<0.001)	0.16 (<0.001)
10	BCI	921	0.52 (<0.001)	0.53 (<0.001)
12^+	BCI	848	0.74 (<0.001)	0.73 (<0.001)
14^+	BCI	881	0.06 (0.045)	0.05 (0.070)
15^+	BCI	807	0.26 (<0.001)	0.21 (<0.001)
16	BCI	965	0.15 (<0.001)	0.14 (<0.001)
17^+	BCI	889	0.25 (<0.001)	0.24 (<0.001)
Right Hand				
SID	Intervention Type	N	Pearson correlation ρ (p-value)	Spearman's correlation ρ_s (p-value)
1^+	BCI	765	0.13 (<0.001)	0.12 (<0.001)
3^+	BCI	783	0.23 (<0.001)	0.19 (<0.001)
7^+	BCI	659	0.27 (<0.001)	0.26 (<0.001)
8^+	BCI	726	0.09 (0.006)	0.06 (0.052)
10	BCI	935	0.65 (<0.001)	0.64 (<0.001)
12^+	BCI	792	0.15 (<0.001)	0.14 (<0.001)
14^+	BCI	875	0.14 (<0.001)	0.1 (0.001)
15^+	BCI	846	0.29 (<0.001)	0.25 (<0.001)
16	BCI	959	0.09 (0.003)	0.05 (0.060)
17^+	BCI	878	0.19 (<0.001)	0.16 (<0.001)

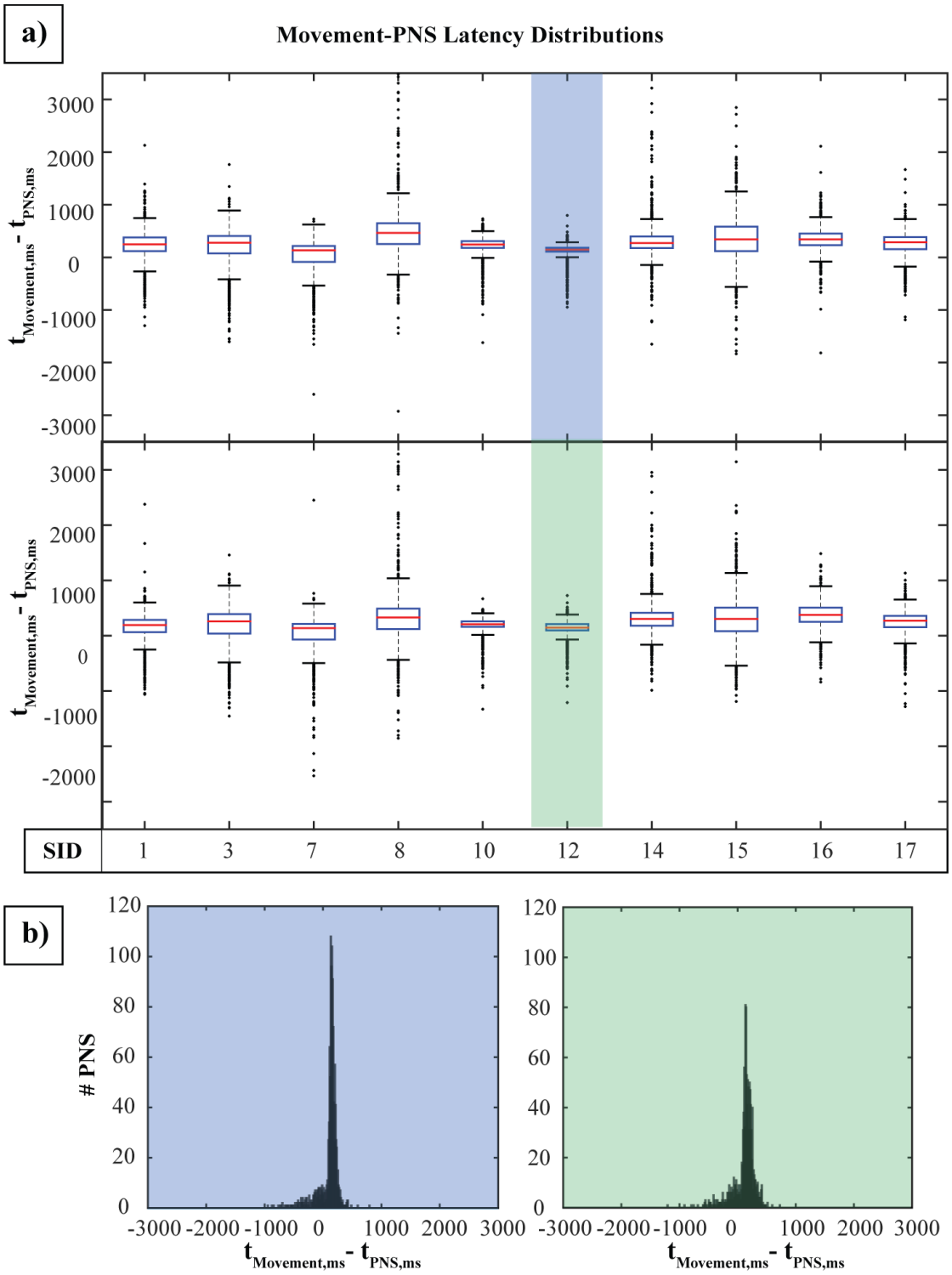

Figure 4.1 Movement-PNS Latency Distributions of Interventions with BCI-PNS. Positive latencies correspond with PNS that occurred prior to movement onset. (a) The distributions of the Movement-PNS latencies for each intervention are plotted using traditional boxplots (top: left hand). (b) Histograms of the latencies from SID12's BCI-driven intervention. For the left hand (blue), n = 1179, Q1= 109ms, Q2 = 181ms, Q3 = 229ms. For the right hand (green), n = 1180, Q1 = 98ms, Q2 = 146ms, Q3 = 211ms.

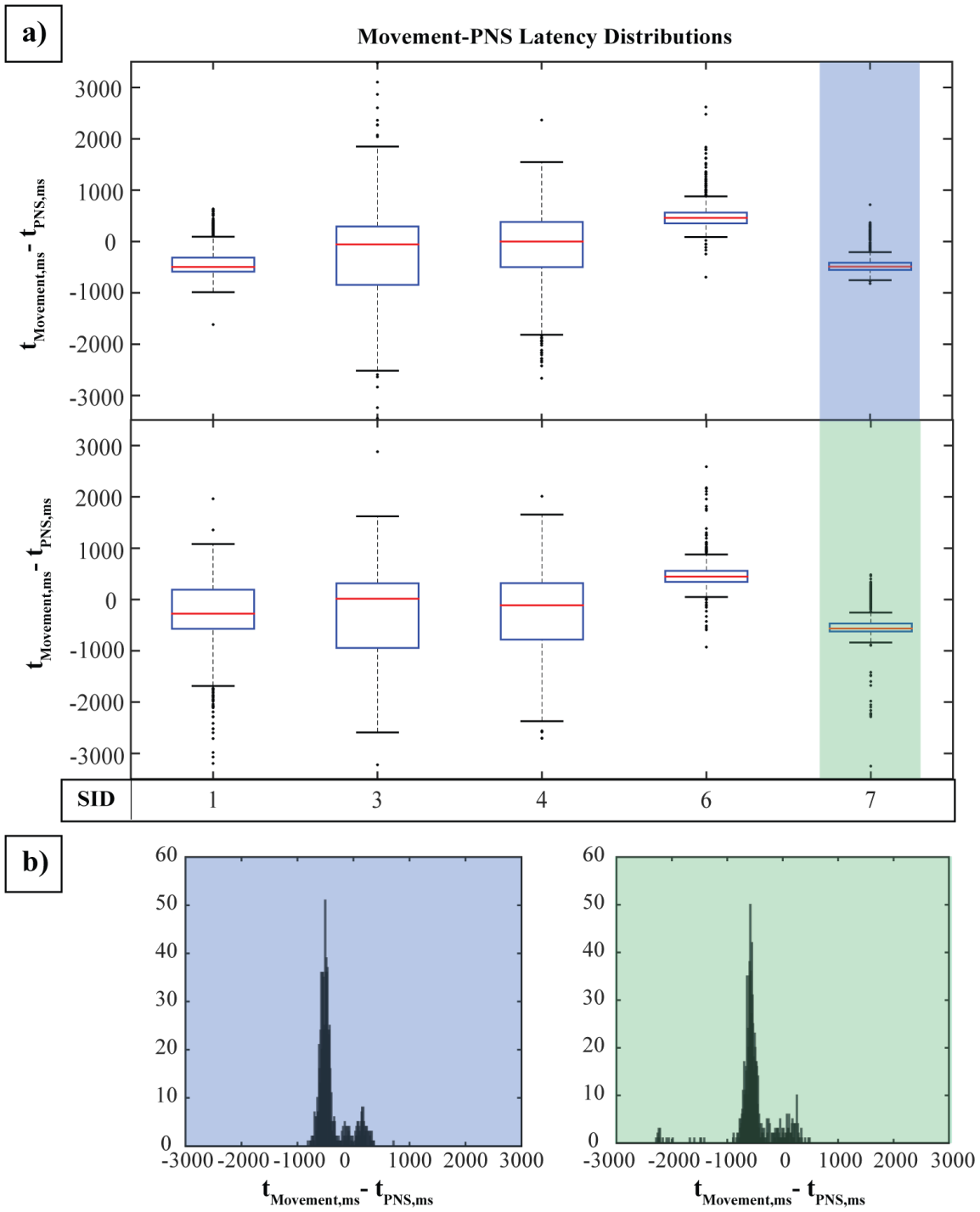

Figure 4.2 Movement-PNS Latency Distributions of Interventions with BCI*-PNS. Positive latencies correspond with PNS that occurred prior to movement onset. (a) The distributions of the Movement-PNS latencies for each intervention are plotted using traditional boxplots (top: left hand). (b) Histograms of the latencies from SID7's BCI-driven intervention prior to the update. For the left hand (blue), n = 870, Q1= -553ms, Q2 = -488ms, Q3 = -412ms. For the right hand (green), n = 839, Q1 = -623ms, Q2 = -564ms, Q3 = -469ms.

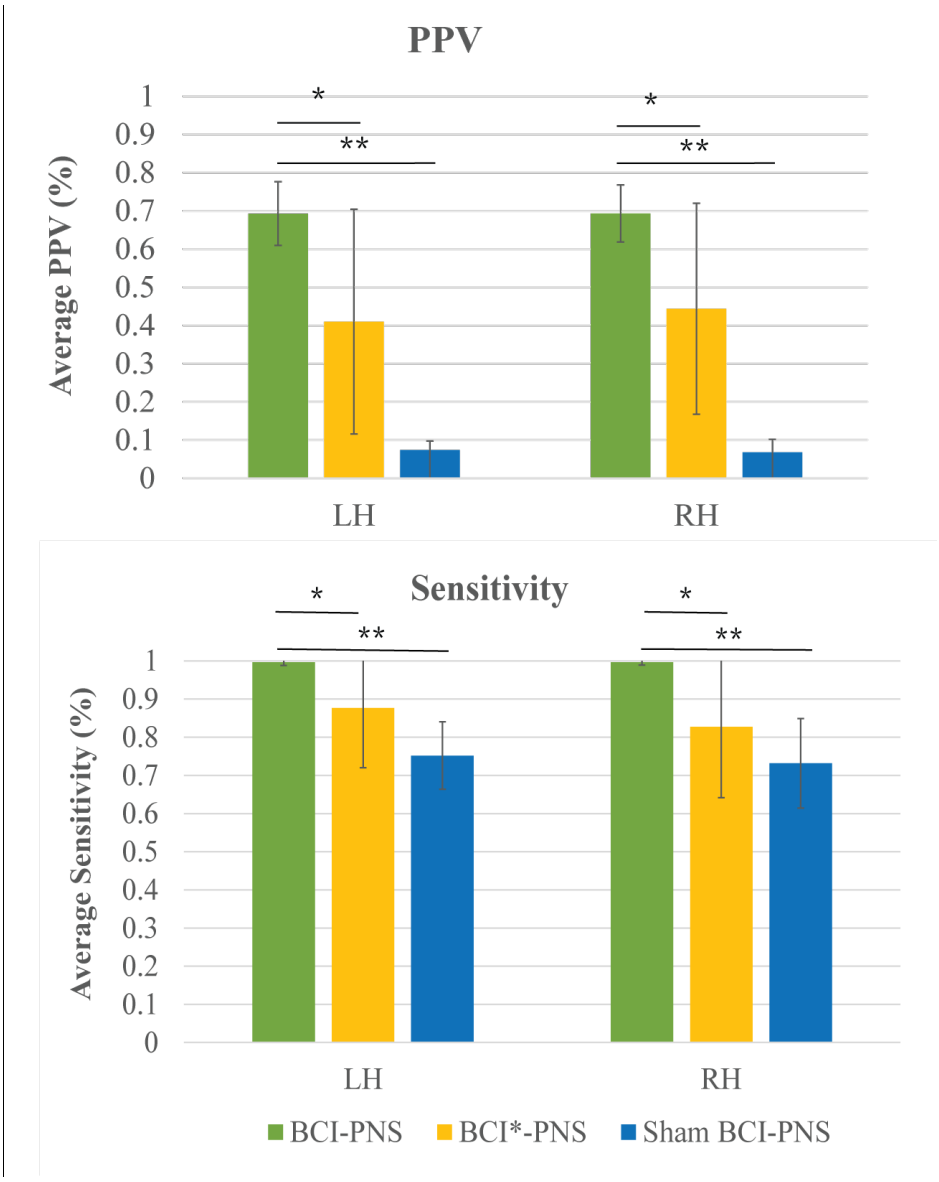

Figure 4.3 Average PPV & Sensitivity Values by Intervention Type. This figure shows the average PPV (top) and sensitivity values (bottom) for interventions with PNS applied using the described system (BCI-PNS), the old system (BCI*-PNS), and at random (Sham BCI-PNS). These values were calculated by classifying stimulations as either TP or FP based on their timing relative to movement onset and by classifying cues where movement executions occurred and PNS did not as FNs.

*$p = 0.01$

**$p < 0.001$

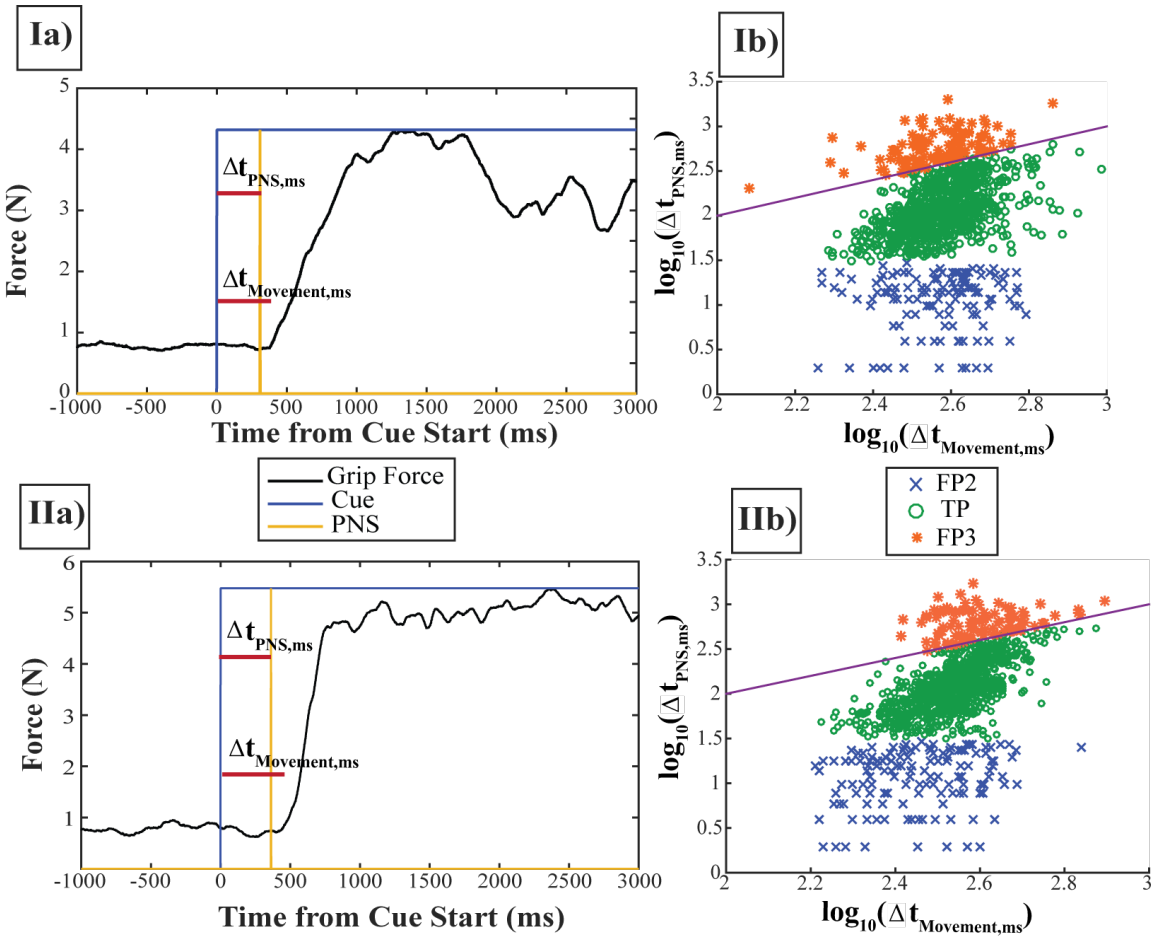

Figure 4.4 Example of movement responses (Ia) a left hand movement (hand grip) response to a cue and (IIa) a right hand movement response to a cue. This data is from SID-010's intervention in which PNS was applied using the BCI described in this work. These examples help to demonstrate the PNS-Cue latency ($\Delta t_{PNS,ms}$) and Movement-Cue latency ($\Delta t_{Movement,ms}$). The log transformed PNS-Cue latencies and Movement-Cue latencies from SID-010's entire intervention have been plotted for the (Ib) left and (IIb) right hand.

CHAPTER 5. DISCUSSION

5.1 Overview

This work has demonstrated the feasibility of online movement intention detection in a motor-impaired cohort. The described BCI system had significantly better performance than both the old BCI system (BCI*-PNS) and the Sham BCI-PNS. Additionally, BCI-PNS showed significant correlation with movement onset in the majority of interventions. This suggests that the system was triggering PNS based on task-related dynamical changes in brain activity and not at random.

5.2 BCI System Evaluation

In this setting, the PPV indicates the likelihood that PNS was triggered by the detection of movement intent. The sensitivity metric indicates the likelihood that PNS was applied when movement execution occurred. The interventions in which PNS was controlled by the described BCI system had significantly higher PPV and sensitivity values compared to interventions with BCI*-PNS and Sham BCI-PNS. This supports the idea that BCI-PNS was more likely to be applied based on movement intent than the other PNS types.

Since BCI-driven PNS could only be applied during the cue, the correlation of PNS onset with movement onset times was important in showing that PNS was not being triggered simply by the change in cue state. All BCI-driven PNS and movement onset correlations, except SID14 (LH), SID 8 (RH), and SID16 (RH), demonstrated significant monotonic relationships between the two variables. This strongly suggests that the

described BCI system applied PNS prior to movement onset due to the detection of a movement intention.

5.3 Challenges

There were a number of challenges in developing a BCI system for motor rehabilitation of patients with incomplete tetraplegia. A major hurdle was recruitment, due to the time commitment required by the intervention sessions and the need for reliable transportation to the sessions. Another challenge was determining the time of movement onset in participants that had limited hand grip ability and little to no discernable EMG activation. For these participants, it's likely that movement onset determination was not as accurate as the other participants, which could affect BCI evaluation. For example, SID10 demonstrated relatively high correlation values between PNS-cue latencies and Movement-cue latencies for left (ρ_s=0.53, $p<0.001$) and right hand (ρ_s=0.64, $p<0.001$) intervention data. The contrast in SID10's force signal between rest and movement made determining movement onsets easy and, most likely, fairly accurate. In contrast, SID16 demonstrated low correlation values between PNS-cue latencies and Movement-cue latencies for left (ρ_s=0.14, $p<0.001$) and right hand (ρ_s=0.05, $p = 0.060$) intervention data. While the force signal was more reliable than EMG in determining movement onset, there was still very little contrast in SID16's force signal between movement states making movement onset determination difficult and most likely inaccurate. A way to address this in the future could be through the use of motor-related cortical potentials (MRCPs) in determining movement onset. MRCPs are slow, cortical EEG deflections associated with motor planning that reach peak negativity at the start of movement onset.

5.4 BCI-PNS Timing vs. Paired Associated Stimulation

The timing of PNS applied by the described BCI was variably related to movement onset. The quartile values of the Movement-PNS latency distributions for BCI-PNS demonstrated that most instances of BCI-PNS occurred prior to movement onset. If a stimulation window is created based on the ISI values used in PAS and LAI trials with healthy controls (25ms-200ms), this will give a window for comparison with the Movement-PNS latency distributions of BCI-PNS. In our case, PNS timing is being compared to movement onset rather than motor cortex stimulation. Therefore, 25ms (Devanne et al 1997) can be added to the comparison window to account for conduction time. Based on the first and third quartile values in Table 4.1, on average, there was a high likelihood of PNS occurring from 133±90ms to 396±137m (LH) and 108±84ms to 364±111ms (RH) during BCI-driven interventions. There is overlap between these average intervals and the 50ms-225ms window. This suggests that, on average, subjects that receive PNS controlled by the described BCI system would likely receive positively conditioning PNS prior to movement. The 50ms-225ms window was not used to determine BCI performance because of the potential variability of that window in the individual case.

5.5 Future Directions

This work was aimed at describing and evaluating the BCI system used to deliver synchronous sensory stimulation with movement execution. The next step is to summarize participant outcome data and correlate the outcomes with BCI accuracy in terms of PNS timing relative to attempted movement.

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