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Side Effect Mitigation Methods
for Closed-Loop Deep Brain Stimulation

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Abstract

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Advances in deep brain stimulation, such as the development of closed-loop algorithms that sense and respond to patient symptoms in real time, promise to deliver therapy that is increasingly tailored to individual patients and their day-to-day variations in symptoms. However, while the potential for better side-effect management through closed-loop deep brain stimulation (CLDBS) has been recognized, the majority of CLDBS research to date has focused only on tradeoffs between power savings and symptom reduction with little consideration for side-effects. Given that side-effects, when present, can be inconvenient for some patients and have a severe impact on well-being for others, developing a better understanding of side-effects and creating CLDBS algorithms for side-effect mitigation could greatly improve outcomes for recipients of DBS therapy. This dissertation describes research investigating two novel approaches to side effect mitigation for individuals with neurological movement disorders: first, the identification and use of involuntary neural biomarkers of side-effects as triggers for changes in stimulation; and second, the use of voluntarily-controlled, brain-computer interface (BCI) methods to give patients the ability to consciously adjust stimulation parameters to balance trade-offs (such as those between symptom reduction and side effect mitigation). These approaches were designed and tested with two groups of human subjects: Parkinsons disease patients at University of California, San Francisco and essential

tremor patients at University of Washington. In addition to piloting new approaches to CLDBS therapy, this research demonstrates the importance of such systems as investigative tools to better understand the underlying neuroscience of these disorders. In addition to presenting contributions to side-effect mitigation in CLDBS, this dissertation explores certain neuroethical challenges that arose within the aforementioned neural engineering research. The concept of BCI illiteracy is critiqued as a framework that is commonly used in BCI research that is intellectually and ethically problematic. Lastly, the structure and function of an ongoing ethics collaboration conducted during this research is described and recommendations are compiled for future neural engineering research teams who are considering ways to apply ethics considerations to their research projects. This research in neuroethics provides new insight into existing neural engineering topics such as BCI illiteracy; it also has potential to enable future science and engineering researchers to better approach neuroethics in their own areas of expertise.

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GLOSSARY

BCI: Brain-computer interface.

CLDBS: Closed-loop deep brain stimulation.

CSNE: Center for Sensorimotor Neural Engineering

DBS: Deep brain stimulation.

ECOG: Electrocorticography.

EEG: Electroencephalography.

ET: Essential tremor.

GPI: Globus pallidus internus.

IPG: Implanted pulse generator.

LFP: Local field potential.

PD: Parkinson's disease.

STN: Subthalamic nucleus.

UCD: User-centered design.

UCSF: University of California, San Francisco

UW: University of Washington

VIM: Ventral intermediate nucleus (of the thalamus).

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Chapter 1

INTRODUCTION

Advances in deep brain stimulation (DBS), such as the development of closed-loop (or adaptive) algorithms that sense and respond to patient symptoms in real time, promise to deliver therapy that is increasingly tailored to individual patients and their day-to-day variations in symptoms. Efforts in this domain have often acknowledged the potential for increased stimulator battery life as well as fewer side-effects for patients as a result of CLDBS technologies. However, while the opportunity for better side-effect management through closed-loop deep brain stimulation (CLDBS) has been recognized [77] [50], the majority of CLDBS research to date has focused only on trade-offs between power savings and symptom reduction with little consideration for side-effects. Given that side-effects, when present, can be inconvenient for some patients and have a severe impact on well-being for others [72] [8] [34], developing a better understanding of side-effects and creating CLDBS algorithms for side-effect mitigation could greatly improve outcomes for recipients of DBS therapy.

My dissertation research investigates two general approaches to side effect mitigation for individuals with neurological movement disorders: first, the identification and use of involuntary neural biomarkers of side-effects as triggers for changes in stimulation; and second, the use of voluntarily-controlled brain-computer interface (BCI) methods to give patients the ability to consciously adjust stimulation parameters to balance trade-offs (such as those between symptom reduction and side effect mitigation). I have designed and tested initial demonstrations of these approaches with two groups of human subjects: Parkinson's disease patients at University of California, San Francisco and essential tremor patients at University of Washington.

The two new methods for side-effect mitigation that I have piloted may be used in clin-

ically deployed systems in the future through the help of collaborators at Medtronic. Additionally, the CLDBS systems that I have engineered and tested have allowed us to learn more about the underlying neuroscience of PD and ET, which could have impact beyond the nominal goal of side-effect mitigation. Given that one of my side-effect mitigation schemes leverages a chronic fully-implanted BCI, my research may also provide insight into design of fully-implanted BCIs which have previously been confined to animal models.

Because my research is rich in neuroethical questions, I have also engaged in an embedded-ethics style collaboration with scholars from the neuroethics thrust of the Center for Sensorimotor Neural Engineering (CSNE) throughout the design, implementation, testing, and documentation of my side-effect mitigation approaches. As a result of this interdisciplinary collaboration, I have developed a critique of select engineering design decisions within my own research area, specifically surrounding how BCI designers characterize user performance for their systems. I have also worked with my neuroethics collaborators to generate an account of our team's experience to inform other engineering research teams on how to engage in effective ethics collaborations.

My research aims are enumerated at the end of this introduction. The remainder of my dissertation is divided into the following chapters: Chapter 2 summarizes general background material on DBS and CLDBS research; Chapter 3 describes the experimental platform used in my experiments and presents data validating its use as a stable, chronic platform for CLDBS and BCI over multiple years; Chapter 4 presents the design and pilot testing of a biomarker-based CLDBS algorithm for dyskinesia mitigation in Parkinsons disease; Chapter 5 presents the design and pilot testing of a BCI-based CLDBS algorithm for voluntary stimulation adjustment; Chapter 6 presents my critique of BCI illiteracy, a concept commonly used for characterizing user performance in BCI systems; and Chapter 7 describes my collaborative efforts with scholars from the neuroethics thrust at the Center for Sensorimotor Neural Engineering (CSNE), including a survey of the field of embedded ethics collaborations. Chapter 8 concludes my dissertation by summarizing my research contributions and indicating promising directions for future work.

1.1 Summary of Research Aims

1.1.1 Aim 1: CLDBS for dyskinesia mitigation in Parkinsons disease

My first research aim was to develop and demonstrate a biomarker-based CLDBS algorithm for mitigating dyskinesias for patients with Parkinsons Disease (PD). The novel algorithm utilized an involuntary cortical biomarker of dyskinesia to modulate stimulation levels depending on patient state. The system I developed is the first demonstrated use of cortical signals in a fully implanted CLDBS system for PD.

1.1.2 Aim 2: CLDBS for voluntary stimulation adjustment

My second research aim was to develop a BCI-based algorithm that provides patients with voluntary control of their stimulation levels. My work towards this aim assessed the feasibility of a number of necessary subsystems for a BCI-controlled CLDBS system, including: control strategies for executing stimulation adjustments; the types of feedback that patients are conscious of as a result of their stimulation parameters; and the types of BCI tasks that might be used for patient training and assessment. My work identifies key considerations and challenges towards future deployment of a BCI-controlled DBS system.

1.1.3 Aim 3: Frameworks for improving embedded ethics collaborations

My third research aim was to examine an ethical challenge in my own research areas of CLDBS and BCI in collaboration with neuroethics researchers at the CSNE. Specifically, I produced commentary and recommendations on the concept of BCI illiteracy and how we classify user performance in BCI systems, which is extremely relevant to subjects engaged in my own BCI experiments. Additionally, I reflected on our teams embedded ethics collaboration as it is situated in the broader field of applied ethics approaches, and considered key features of our approach that might inform future research teams interested in pursuing a similar collaboration.

Chapter 2

BACKGROUND

2.1 Deep Brain Stimulation for Neurological Movement Disorders

Deep brain stimulation is an FDA-approved treatment for neurological movement disorders (such as Parkinsons disease (PD), essential tremor (ET), and dystonia) where electrical stimulation is applied to deep brain structures to reduce symptoms such as tremor, bradykinesia, and more [99] [32] [64] [93]. Current DBS systems are fully implanted and consist of (1) an implanted pulse generator (IPG), which houses the battery, stimulation controller, and sensing module for the unit, and (2) the electrodes which are used for therapeutic stimulation and/or neural sensing.

Although DBS is an effective treatment for many patients, the mechanism by which DBS operates remains under debate; as summarized in a recent review of DBS for treatment of movement disorders,

DBS increases output from the stimulated nucleus and activates surrounding fiber pathways resulting in a complex pattern of excitatory and inhibitory effects that modulate the entire basal ganglia thalamocortical network. The stimulation-induced regularization of neuronal patterns prevents transmission of pathological bursting and oscillatory activity within the network, resulting in improved processing of sensorimotor information and reduction of disease symptoms. [110]

DBS mechanisms also depend on the deep brain structure into which therapy electrodes are implanted, which varies with the disease being treated. For PD, the most common electrode sites are the subthalamic nucleus (STN) of the thalamus or the globus pallidus internus (GPi). For ET, including our patients at UW, the most common electrode site is the ventral intermediate nucleus (VIM) of the thalamus [110].

Today, DBS research is focused on topics including identifying new target populations,

including psychiatric disorders such as depression, obsessive compulsive disorder, Tourette syndrome, Alzheimers disease, obesity/eating disorders, and addiction [66]; developing new electrodes configurations with current steering capabilities that allow for more unique charge distribution geometries [18]; and, as will be discussed in the next section, closed-loop algorithms that sense patient state in real time and modulate stimulation accordingly.

2.2 Closed-loop deep brain stimulation

Although DBS as prescribed today provides therapeutic benefit to many patients for whom pharmaceuticals were inadequate, it still has limitations as a treatment option. While symptoms of neurological movement disorders may be intermittent in nature as well as task-dependent [150], current DBS treatment does not consider underlying changes in patient state. Instead, a single stimulation setting is applied regardless of the presence or absence of symptoms at a given moment; this mode of operation has been termed “open-loop” stimulation. Open-loop stimulation may shorten battery life by applying stimulation when the patient does not need it, and similarly can expose the patient to unnecessary side effects. For these reasons, recent DBS research has focused on developing “closed-loop” DBS (CLDBS) algorithms that sense patient state and make corresponding stimulation updates in real time [150] [49].

CLDBS may rely on a variety of sensing modes to determine relevant information about patient state. Wearable sensors (such as inertial measurement units (IMUs) found in commercial smartwatches or electromyography (EMG) sensed through surface electrodes placed on arm muscles) can help identify periods of tremor during which stimulation should be applied [150] [12] [53]. More recently, CLDBS systems using neural signals (measured from either the therapy electrode or from cortical sites related to motor function) have been designed and tested. Initial neural-triggered CLDBS testing were performed using symptom-triggered static stimulation waveform [77] [150], and subsequent studies using adaptive algorithms with real-time parameter updates have demonstrated that CLDBS can provide similar therapeutic benefit to open-loop DBS while greatly reducing power use [51]. While studies of CLDBS

to date have been mainly proof-of-concept in highly structured tasks, these algorithms are currently being investigated for potential incorporation into future FDA-approved systems.

CLDBS studies to date have focused almost exclusively on matching open-loop algorithms in terms of symptom reduction and exceeding open-loop algorithms in terms of power savings. Beyond acknowledging that decreasing exposure to stimulation may decrease exposure to side effects [77] [50] [51], the possibility of side effect/symptom tradeoffs through a closed-loop algorithm has been minimally explored in prior work. A single study demonstrated that CLDBS for PD patients reduced reversible speech side effects while improving motor function as compared to open-loop DBS [78]. Since side effects of DBS or combined pharmaceutical/DBS treatment are sometimes severe, occasionally to the point of negating the benefits for which stimulation was originally prescribed [72] [8] [34], substantial research remains to be done on how CLDBS can be used mitigate the side effects experienced during traditional DBS.

There are at least two prospective approaches to side-effect mitigation that could prove viable. Just as biomarkers of patient symptoms such as tremor are used to modulate stimulation in a CLDBS system, biomarkers of patient side effects could be used to comodulate stimulation in balance with the need for effective therapy. Alternatively, it may be possible to give patients voluntary control over their stimulation through the use of a brain-computer interface (BCI), such that they could make their own decisions as to how to balance symptom control versus exposure to side effects. My research will constitute the first demonstrated use of neural biomarkers to mitigate side effects in CLDBS systems; I will also assess the feasibility of a voluntarily-controlled CLDBS system using a BCI.

2.3 Brain-computer interfaces with electrocorticography

A BCI is a promising way to allow a user to control a device using voluntarily modulated brain-signals. BCI research has been in part directed toward developing assistive technologies for patients with high-level spinal cord injury [123] [145], communication interfaces for individuals with locked-in syndrome [67], or for intuitive prosthetic control [47] [87]. In

my research, I assessed the feasibility of a BCI system that allows patients to control their stimulation levels voluntarily.

The control signal in my BCI system is sensed from a set of chronic fully-implanted electrocorticography (ECoG) electrodes that interface with the implanted DBS system. ECoG is a promising chronic signal source for fully-implanted BCIs due to the potential for stable long-term recordings [145] [74] [24] [9], and prior work with electrocorticography has shown that human subjects can control one dimensional BCIs [75] [36] [144] or higher [145] [113] with better-than-chance accuracy. Furthermore, ECoG can provide higher quality signals (in terms of spatial resolution, reliable frequency range, etc.) than BCIs using electroencephalography (EEG) [74]. It has the potential to be learned more quickly [149], and has fewer artifacts since ECoG electrodes are implanted rather than worn [130] [10].

Although prior ECoG BCI research has demonstrated that human subjects can obtain sufficient performance for simple cursor tasks, these studies have generally been very limited in duration [111]. In addition to demonstrating a novel CLDBS paradigm that may give patients better control over therapeutic tradeoffs, my research uses chronic ECoG, facilitates exploration of neuroplasticity and adaptation, and increases understanding of how end-users of assistive BCI technologies might control their devices over months or years.

My research also explores ethical considerations surrounding how user performance in BCI systems is characterized. Despite advances in many aspects of BCI performance, a subset of potential BCI users are unable to operate some or all types of BCI despite undergoing the same training proficient users do. This inability to reach proficiency in BCI performance has often been termed BCI illiteracy, and many researchers engaged in BCI research have applied the concept to unsuccessful users in their respective BCI studies [5] [71] [91] [101] [2] [61] [126]. The implications of categorizing users as BCI illiterate may not be initially apparent. However, in using BCI illiteracy as a concept, BCI researchers face a number of scientific and ethical challenges, the outcomes of which stand to directly impact BCI users. I critique current norms of classifying user performance, including BCI illiteracy, and suggest alternatives that may provide better outcomes for end-users

Chapter 3

EXPERIMENTAL PLATFORM & VALIDATION

This section describes the experimental platform that I used to develop and test my CLDBS side-effect mitigation schemes. First, I describe the implanted DBS hardware, communication channel, and software platform that was used in my experiments, including relevant system limitations. Second, I describe preliminary work I conducted to validate the system as a stable chronic recording platform.

3.1 Recording unit & communication channel

To record neural data from ambulatory human subjects, my experiments use an implanted Medtronic Activa PC+S DBS device as a signal recording platform. In addition to implanting a DBS system, a Resume II strip of 4 spinal-stimulation electrodes are implanted over the hand area of the motor (M1) and somatosensory (S1) cortices (2 electrodes are placed over each cortex respectively). A diagram of the implanted system is shown in Figure 3.1. This system is investigational and is used with approval through an FDA investigational device exemption (IDE) and UW and UCSF’s respective IRBs.

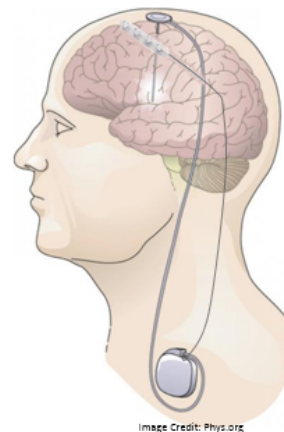


Figure 3.1: Diagram of implanted DBS and cortical sensing system.

Signal processing and control decisions for stimulation updates may be made onboard the IPG or on an external PC (the next section describes the differences between these configurations). A block diagram of the system, including communication between the PC and the Activa PC+S, is shown in Figure 3.2. Prior work in the lab

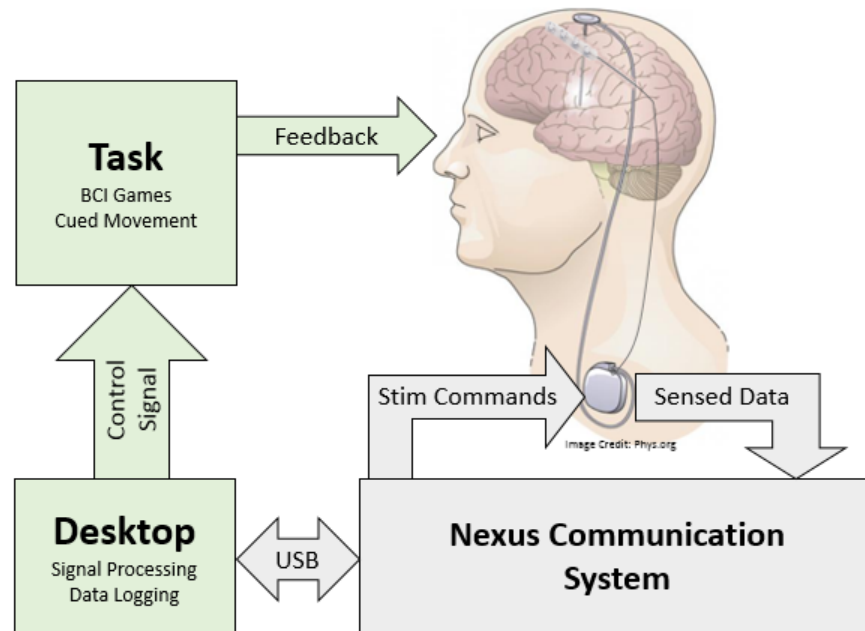


Figure 3.2: Block diagram of communication interface between external computer and implanted DBS stimulation and sensing system.

conducted by Dr. Jeffrey Herron included the development of a software library to more easily code closed-loop systems around the Activa PC+S’s communication protocol. I have since used this software library to develop my own CLDBS and BCI experiments for the purpose of my research aims.

3.2 Computation off- and on-board: Nexus D3 vs. Nexus E

My research uses two available modes for CLDBS operation: a streaming mode called “Nexus D3” which uses a modified patient programmer to send sensed neural data to an external computer and return stimulation commands to the IPG; and a fully embedded mode called “Nexus E” which performs all computations onboard the IPG [1] [22]. These modes have particular capabilities and limitations which influence when I have employed them for my research aims.

Nexus D3 allows streaming of sensed neural data through one of a single time-domain channel sampled at 422 Hz, two time-domain channels sampled at 200 Hz each, or multiple power-domain channels. Exchange of sensed data from the IPG to the external computer and of stimulation commands from the external computer to the IPG is performed every 400 ms. On the external computer, sensed data is processed and stimulation commands are calculated using a set of C# Windows Form applications that I and other team members have written for various experimental protocols described in subsequent chapters.

Nexus E eliminates substantial communication delays by performing required computation onboard the IPG. However, this limits available classification schemes to a linear discriminant type classification with up to four power channels of neural data as features. Power channels may be configured with a center frequency and a window width; for example, a power channel may be set with a center frequency of $20 \text{ Hz} \pm 8 \text{ Hz}$, giving a channel that sums the power from 12 Hz to 28 Hz. These features are then used to calculate

$$z = \begin{cases} 0, & c + \sum_{i=1}^4 w_i x_i \leq 0 \\ 1, & c + \sum_{i=1}^4 w_i x_i > 0 \end{cases}$$

where

$$x_i = \begin{cases} (\bar{p}_i - a_i)b_i, & \text{channel } i \text{ is a power channel} \\ 0, & \text{otherwise} \end{cases}$$

where z is the binary classifier output and x_i are the power channel outputs. The parameters w_i , a_i , b_i , and c in this equation must be trained offline, written to an XML file, and loaded onto the IPG before operation of Nexus E.

3.3 System limitations

The recording platform which I used in my experiments has some limitations given that neither the IPG nor the electrode strip were originally designed for BCI applications. First, my setup uses far fewer ECoG electrodes compared to typical clinical grids—only four as

compared to tens or hundreds of contacts respectively. While this reduces the capacity for multichannel processing or analysis of spatial relationships over large areas of the cortex, my results related to human learning during BCI tasks can be extrapolated to BCI systems with larger electrode grids.

Second, the system does not have a separate reference electrode, and referencing cannot be done compared to a surrounding set of electrodes due to the single-strip geometry. Instead, referencing for the recording electrode could only be performed differentially relative to another electrode on the strip. Again, this potentially limits performance given that it is an unconventional referencing scheme that may not isolate the signal at the control electrode from surrounding activity; however, preliminary results presented in the following sections demonstrate that significant information related to hand and arm motor function is still preserved with this referencing scheme.

The platform also has limitations in recorded frequency range. Initial analyses showed that there was limited reliability for recording higher-frequency features of motor function such as features in the gamma-band (35-45 Hz) or high gamma-band (70-200 Hz). These features have been effectively used for ECoG BCI control signals in both humans [144] [113] [119] and non-human primates [109] [148]. Although gamma-band features were noted for some patients (for example, work described in Chapter 4 relies on a gamma-band side-effect biomarker), broadband power increases typically noted in gamma band frequencies during movement [144] were not observed in all of our subjects. My studies were not always able to leverage the higher-frequency band (which typically has increased spatial specificity) which would likely improve performance in certain tasks since band power would be more differentiated between motor and rest states. This is an area for future investigation if higher-frequency features become available.

3.4 Validation of long-term recordings

To determine if neural recordings were stable and replicable across different experimental sessions, I recorded cortical signals during experimental sessions 1 week, 1 month, 3 months,

and 4 months after implantation while ET Patient 1 rested and performed overt movement with his right hand (details of ET Patient 1s treatment and preliminary CLDBS results are described in [53]). During experimental sessions 2 and 4, approximately 20 two-second periods were recorded during periods where the patient was explicitly prompted to (1) rest, (2) open and close his right hand, or (3) imagine opening and closing his right hand. During experimental sessions 1 and 3, although the same prompting task was not conducted, periods of rest and movement were identified using accelerometry data from a commercial smartwatch. Across all sessions, a time signal was collected from the cortical electrodes at a rate of 422 Hz and time-synchronized with the inertial recordings as described in [52]. As the Activa PC+S can only record signals referenced between cortical electrodes, the signal was referenced from the most anterior motor cortex electrode to the most anterior somatosensory cortex electrode. This reference pair was chosen because it exhibited the largest beta-band peak, recorded at rest, compared to all other reference pairs.

Frequency spectra during rest and movement were compared across multiple months to verify that recordings were stable and that cortical signals were not attenuated with increased time since electrode implantation. After each visit, periodograms were calculated of the recorded signal during periods of rest and overt movement. These periodograms are shown in Figure 3.3.

Across all four sessions (up to four months after implantation), the patient exhibited clear beta-band power desynchronization during overt hand movement as compared to rest periods within a single session. Furthermore, the level of desynchronization also remained stable across different sessions; for example, desynchronization due to overt hand movement in the 4th visit was distinguishable from synchronization due to rest at any other visit. These results demonstrate that ECoG recordings on my experimental platform are stable in the beta-band over months of recordings. These stable recordings are crucial in enabling the long-term ECoG studies which I performed.

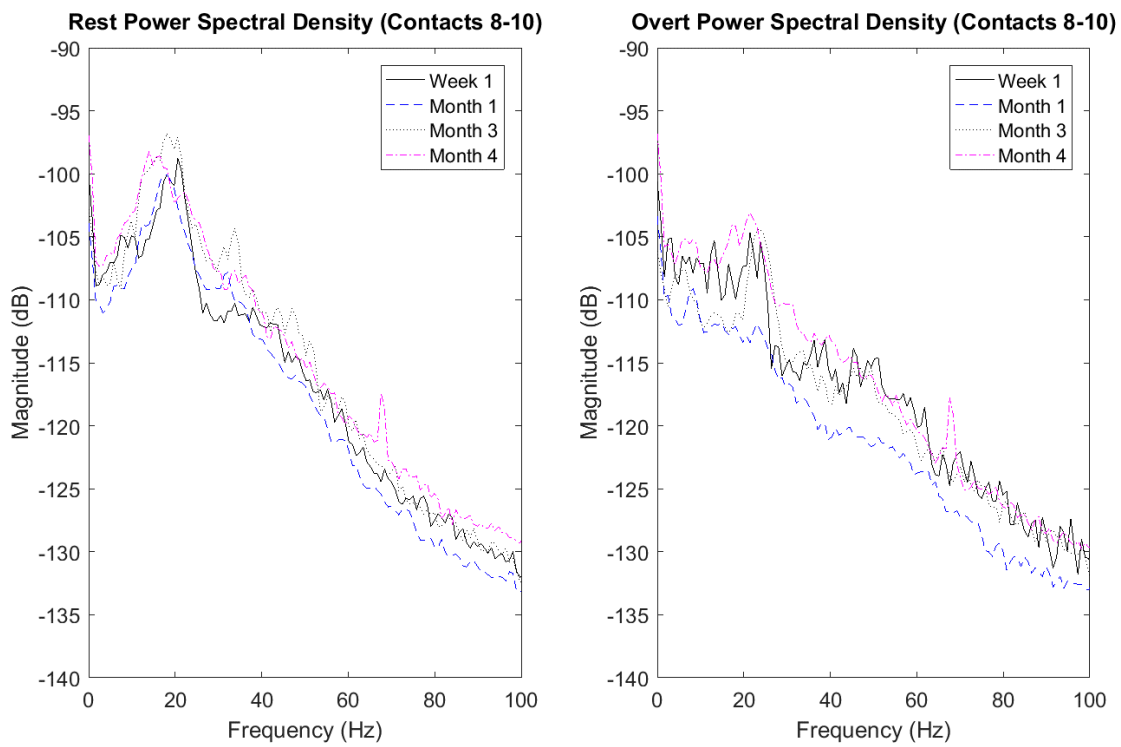


Figure 3.3: Periodograms over four months of recordings demonstrating relative stability of cortical power spectra.

Chapter 4

BIOMARKER-BASED CLDBS: DYSKINESIA MITIGATION IN PARKINSON'S DISEASE

Aim 1 of my thesis was to demonstrate a biomarker-based CLDBS system for side effect mitigation. Specifically, I aimed to design a system for mitigating dyskinesias in PD patients. This chapter describes the known physiology of dyskinesias, my CLDBS algorithm design for dyskinesia mitigation, and collaborative pilot testing with researchers at UCSF toward the validation of this algorithm. Lastly, I discuss the implications of my results for biomarker-based CLDBS approaches and describe future work that ought to be conducted to best expand on my contributions.

Dyskinesias are involuntary, erratic movements that may result as a side effect of either levadopa or DBS treatments for PD [11]. Prior work by Dr. Phil Starr and Dr. Nicole Swann at UCSF demonstrated that an increase in motor cortex band power in a narrow region of gamma-band frequencies (less than 5 Hz wide centered between 60-80 Hz) may be a biomarker for dyskinesia in patients with PD; furthermore, this dyskinesia peak becomes entrained to half of the stimulation frequency in patients with DBS [128]. This well-correlated and highly specific biomarker is a good candidate for triggering stimulation changes in a CLDBS system.

In collaboration with Dr. Starr and Dr. Swann, I designed, implemented, and piloted an initial CLDBS algorithm for biomarker-based dyskinesia mitigation for PD patients. Dr. Starr's group uses an identical experimental setup (described in Chapter 3) as our work at UW, allowing us to collaborate easily on CLDBS experiments under an institutional licensing agreement¹ despite working in different patient populations (ET at UW and PD at UCSF). We tested this algorithm using Nexus D3, where data is streamed from the IPG to the

¹UW licensed software and hardware related to the streaming interface and desktop Windows form applications to UCSF.

experimental laptop, in one dyskinetic PD patient, and the group at UCSF subsequently tested a closely related Nexus E fully embedded algorithm in two dyskinetic PD patients. I summarize results from both the streaming and onboard approaches in subsequent sections.

4.1 Dyskinesia: A possible side-effect of PD treatment

Dyskinesias, which are defined as erratic, involuntary movements distinct from rhythmic tremors, are a known side-effect of dopaminergic medication and DBS treatments for PD [11]. Before the advent of DBS therapy, dyskinesias were observed in response to dopaminergic medications such as levodopa. In contrast to PD symptoms, which in simple terms are linked to the death of dopamine producing cells in certain brain areas [92], dyskinesias may occur under an excess of dopamine resulting from administered dopaminergic medication. Although not all PD patients experience dyskinesias, they are a particularly debilitating side-effect that can be as severe as the original symptoms of PD.

DBS may be recommended for PD patients experiencing severe dopamine-induced dyskinesias since stimulation can allow for a reduction of levodopa dosage [11] [143]. However, while treatment with DBS may reduce dyskinesias for many PD patients, some do not experience this benefit. Particularly, patients undergoing STN stimulation are more likely to experience dyskinesias than patients undergoing GPi stimulation. Additionally, regardless of target, continuous DBS therapy does not account for temporal variations in underlying symptoms or side effects of PD resulting from patient responses to PD medications administered throughout the day. Due to fluctuating levels of dopaminergic medications such as levodopa, patients undergoing continuous DBS may be overstimulated at times, resulting in adverse effects including dyskinesias [152] [128].

Especially after extended treatment with levodopa, some patients may display dyskinesias whenever they are medicated—although additional pharmaceuticals and changes in dosing may reduce the appearance of dopamine-induced dyskinesias [73]. These subset of patients have been described as having a “brittle response” to PD therapy. Also termed “brittle Parkinsonism,” such patients fluctuate between bradykinetic and dyskinetic states

in response to dopaminergic medication or DBS therapy with little time in an optimally medicated state [81] [125]. This response is most commonly seen in younger female patients, and is also correlated with early disease onset and greater duration since diagnosis [146]. Although brittle response patients are rare—making up at most 5% of PD patients [81]—their options for improved treatment are limited. Corrective GPi stimulation may reduce dyskinesias in some cases, but is not effective for everyone and requires additional surgeries [125]. A responsive, real-time system such as CLDBS that could adjust STN stimulation parameters to the fluctuating symptoms and side-effects of brittle responders may provide better outcomes than current approaches.

4.2 Dyskinesia biomarkers in primary motor cortex

Prior work by Dr. Phil Starr and Dr. Nicole Swann at UCSF has demonstrated that a narrow-band increase in motor cortex band power in high-gamma-band frequencies is highly correlated with dyskinesia and robust to concurrent voluntary movements in patients with PD. During treatment with levodopa, dyskinetic patients experience this peak—hereafter referred to as the “dyskinesia peak”—which is less than 5Hz wide, at a range of natural frequencies between 60-90Hz in the motor cortex. An example periodogram calculated from cortical recordings from a single patient during dyskinetic versus nondyskinetic periods is shown in Figure 4.1. Similar oscillatory behavior also appears more weakly in amplitude in the STN,

Biomarker related to dyskinesia

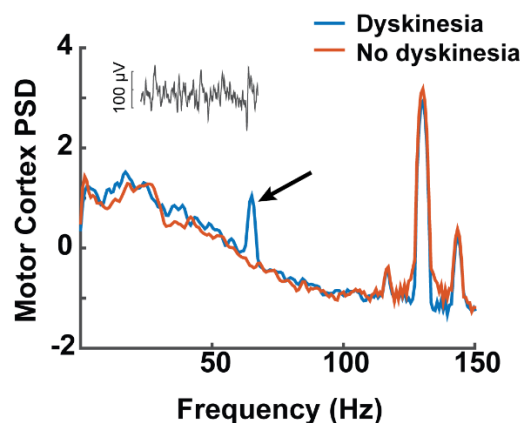


Figure 4.1: Examples of the dyskinesia peak recorded in PD patients at UCSF. Patients who are dyskinetic exhibit a distinct, narrow-band cortical biomarker centered between 60-90 Hz (blue) compared to their non-dyskinetic cortical spectra (red). When treated with DBS, the dyskinesia peak entrains to one half of the stimulation frequency. Figure credit: Dr. Nicole Swann [128].

and STN activity is highly phase-coherent with motor cortex activity [128].

The neural mechanisms for the dyskinesia peak are unclear; Starr and Swann speculate that

given the presence of gamma oscillations in the thalamus in several nondyskinetic conditions (Kempf et al., 2009), it is possible that dyskinesia arises when subcortical gamma rhythms are excessively propagated throughout the basal ganglia-thalamocortical loop, with a prominent representation in the motor cortex. In support of this view, motor cortex recordings in a rodent model of parkinsonism showed a gamma oscillation during dyskinesia remarkably similar to that reported here (Halje et al., 2012). [128]

Starr and Swann go on to suggest that the presence of exaggerated gamma oscillations in primary motor cortex could facilitate activation and allow small neuronal populations to release locally encoded “fragments of movement”, resulting in the observed choreiform activity at the behavioral level [128].

Regardless of neural mechanism, a cortical biomarker that is so highly correlated with a specific side-effect of PD treatment is already a promising candidate for use in a CLDBS algorithm on our experimental platform. Furthermore, Starr and Swann showed that the dyskinesia peak becomes entrained to half of the stimulation frequency in dyskinetic patients treated with DBS [128]. As with the neural mechanism that generates the original dyskinesia peak, the entrainment of the dyskinesia peak to one half of the stimulation frequency is not well understood. DBS is known to entrain axonal activity during stimulation, but it is possible that this entrainment does not happen after every pulse [76] [128]. Axonal entrainment that occurred following every other pulse at DBS frequencies would explain the observed result that the dyskinesia peak entrains to half of the stimulation frequency [128].

For a number of reasons, the dyskinesia peak is a good candidate for triggering stimulation changes in a CLDBS system. First, dyskinesias are a potentially severe side effect of DBS that we would like to mitigate. Second, the dyskinesia peak biomarker is highly correlated with observed dyskinesias; it is present during all observed dyskinesias and rarely present when dyskinesias are not observed². Third, the dyskinesia peak is very easily characterized

²It is possible that the dyskinesia peak presents even when dyskinesias are extremely mild, i.e. below the

because of entrainment. While DBS is being applied at therapeutic values, we can expect the dyskinesia peak to emerge at one half of the stimulation frequency within a very narrow (less than 5 Hz) bandwidth. This greatly simplifies the necessary algorithm design for a CLDBS system for detecting dyskinesias, which is discussed in the following section.

4.3 *CLDBS algorithm design*

This section describes the design of the CLDBS dyskinesia-mitigation algorithm. The algorithm relies on a number of known inputs related to the patients' open-loop clinical DBS settings, including the stimulation frequency. A diagram of the CLDBS dyskinesia-detection algorithm I have designed is shown in Figure 4.2. The algorithm functions by comparing the power level summed in a 5 Hz wide window around the dyskinesia peaks center frequency—known to be one half of the stimulation frequency—to a calibrated baseline. This 5 Hz region is referred to subsequently as the dyskinesia window and represented in blue on the Cortical Periodogram in Figure 4.2. An increase in power in the dyskinesia window indicates that dyskinesias are likely present, triggering a stimulation decrease; in contrast, decreases in dyskinesia window power trigger a stimulation increase.

4.3.1 *Calibration method*

The baseline power level for use in computing the update threshold is calibrated in one of two ways depending upon whether the patient is dyskinetic at the time of calibration. If the patient is not dyskinetic at calibration, the power in the dyskinesia window is averaged and the standard deviation is computed over a 10-30 second window (essentially until the average and standard deviation appear stable). If the patient is dyskinetic at the time of calibration, the power is averaged and the standard deviation is computed over a 10-30 second window with center frequency 10 Hz greater than the dyskinesia window. Calibrating in a higher window is expected to provide a fair comparison given that the baseline power level does not

threshold for observation by a clinician. For example, at times during our experiments we had to remove patients' shoes to observe that they were dyskinetic only in their toes.

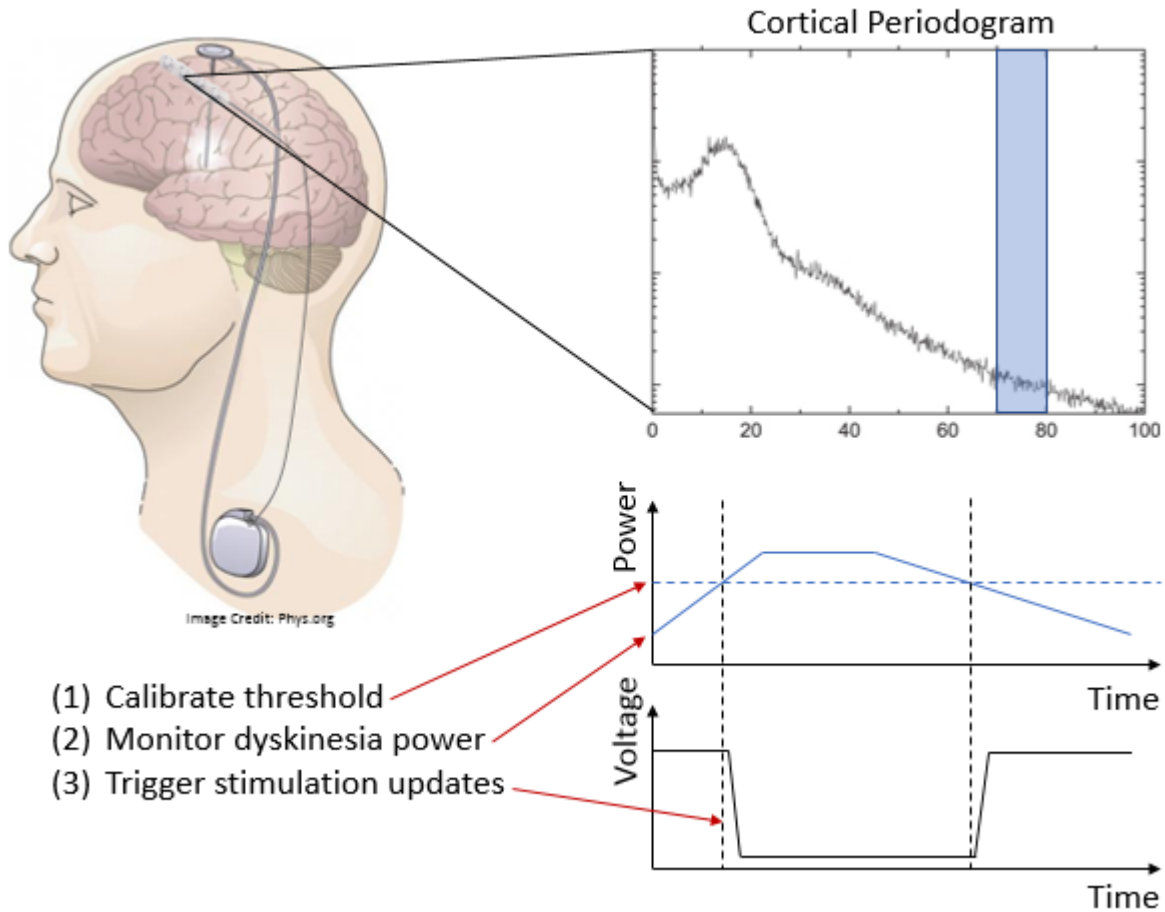


Figure 4.2: Diagram of dyskinesia mitigation algorithm. First, a threshold for stimulation updates is calibrated by determining (A) the average the power in the dyskinesia window (or in a window centered 10 Hz higher if the patient is already dyskinetic at the time of calibration) and (B) the standard deviation of the power in the dyskinesia window. The threshold is set at two standard deviations above the average power to minimize false-alarms. Second, the CLDBS algorithm calculates the power in the dyskinesia window in real-time and compares the power level to the calibrated threshold. If the dyskinesia window power exceeds the calibrated threshold, a stimulation update is triggered to decrease stimulation from the HIGH (clinical/therapeutic) amplitude value to the LOW (sub-therapeutic) amplitude. If the dyskinesia window power recedes below the calibrated threshold, stimulation is increased from the LOW voltage amplitude to the HIGH amplitude.

differ greatly, or have steep roll-off, for this region of the power spectrum.

Once the average and standard deviation are computed, the stimulation update threshold is set to two standard deviations above the computed average. This threshold setting was found through pilot testing to provide a good balance between minimizing false-alarms while still providing a rapid enough response to the emergence of dyskinesias.

4.3.2 Real-time detection of dyskinesias

Once calibration has been performed, as demonstrated in Step (2) in Figure 4, the algorithm compares the calibrated baseline power to the power calculated in the dyskinesia window every 400ms (the rate at which packets are streamed from the device to the experimental laptop). Voltage data is sensed differentially at 422Hz from a differential pair of cortical leads, one lead over primary motor cortex referenced to another lead over somatosensory cortex. At each time step, the power spectral density (PSD) is computed for the last 256 samples of the voltage data, providing resolution in the power spectral density of approximately 1.6Hz per bin. The algorithm functions by comparing the power level summed in the dyskinesia window (the PSD bins surrounding one half of the stimulation frequency) to the calibrated update threshold.

Stimulation defaults to the HIGH, clinically therapeutic amplitude. As demonstrated in Step (3) in Figure 4.2, if the power calculated in the dyskinesia window is determined to be greater than the calibrated update threshold, the algorithm identifies that the patient is likely experiencing dyskinesias and will decrease stimulation to a LOW amplitude. After the stimulation change has been made, the algorithm waits 10 seconds for the patients' response to stabilize before comparing the power to the update threshold again. If the power calculated in the dyskinesia window is later determined to be less than 2 standard deviations above the calibrated average, the algorithm identifies that the patient is likely no longer experiencing dyskinesias and will return the stimulation voltage to their HIGH amplitude.

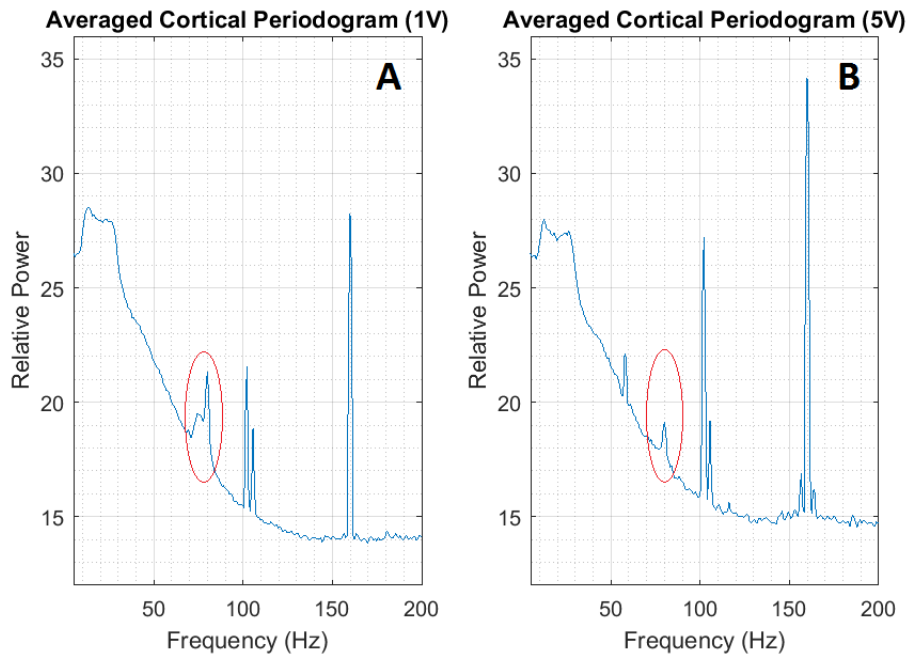


Figure 4.3: Example of poor entrainment at lower voltage (left) and full entrainment at a higher voltage (right). At high voltage values, the power in the dyskinesia peak is reliably in a narrow band at one-half the stimulation frequency. In contrast, for lower voltage values the power is mixed between a peak at one-half the stimulation frequency and the “natural” dyskinesia peak frequency.

4.3.3 Additional Considerations: Entrainment Voltage

The dyskinesia-mitigation algorithm determines whether stimulation should be in a HIGH or LOW voltage state. In initial testing of the CLDBS system, little attention was given to the precise voltages chosen for these states. The HIGH voltage state was chosen to be on the upper end of a typical voltage setting with the intention of evoking dyskinesias at this setting during the test. The LOW voltage state was simply chosen at 1V so that some stimulation was applied, but at a level intended to ease dyskinesias.

Initial tests with a single PD patient at UCSF revealed that certain LOW state voltages were not sufficient to ensure entrainment of the dyskinesia peak. Figure 4.3 shows summed periodograms during dyskinetic periods for a stimulation amplitude of 1V (left) and 5V (right). At the 5V setting, strong entrainment is observed with the dyskinesia peak power

confined to a narrow region at precisely 80Hz, or one half of the stimulation frequency. In contrast at the 1V setting the dyskinesia peak is only weakly entrained, with power mixed between a peak centered at 80Hz and the “natural” peak value of approximately 75Hz.

Recall that the algorithm as designed assumes that the peak will be present at one-half the stimulation frequency—no search is performed in the PSD to determine if the peak is at a different frequency. This is both a simplifying assumption and a reassurance that we are not triggering stimulation changes off of unrelated phenomena. However, due to this choice in algorithm design, when a dyskinesia is detected the algorithm will move stimulation to the LOW voltage state, at which point the dyskinesia peak may no longer remain entrained if the LOW voltage is too low. If the dyskinesia peak returns to its natural, unentrained frequency, it is likely to move outside of the dyskinesia window monitored by the algorithm. To the algorithm, this appears to mean that dyskinesias have subsided, at which point it will increase stimulation back to the HIGH voltage setting. Once stimulation is returned to the HIGH value, the voltage is sufficient to once again entrain the dyskinesia peak to the expected value. What may result are oscillations between the HIGH and LOW voltage states as the dyskinesia peak entrains and unentrains. Figure 4.4 shows an example of oscillatory stimulation updates resulting from a LOW voltage value that provided insufficient entrainment of the dyskinesia peak.

In summary, for the algorithm design as presented, it is necessary to ensure that the LOW voltage setting is high enough to entrain the dyskinesia peak. Our initial testing found that a value of 1.5V or greater typically provided sufficient entrainment. This finding may be of use in future efforts to understand the neural mechanisms of dyskinesias and their response to DBS therapy.

4.4 Experimental protocol

The CLDBS algorithm described in the previous section was tested with two male patients prescribed DBS for PD. Each patient experienced mild to moderate dyskinesias during everyday life even after receiving continuous DBS implanted in the STN. Clinical data, including

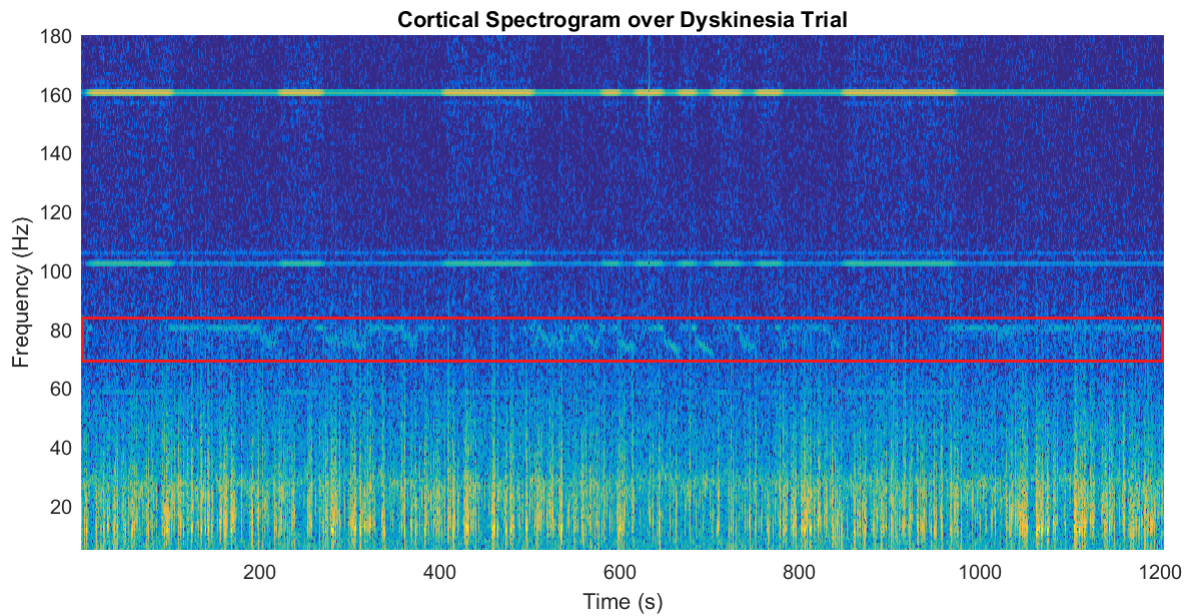


Figure 4.4: Example of variable entrainment of the dyskinesia peak over time. The range of frequency values for the dyskinesia peak are highlighted in red. Note that, for periods when stimulation is HIGH (shown in yellow at 160Hz), when dyskinesia peak is present it remains at 80Hz, or one half the stimulation frequency. However, for periods when stimulation is LOW (shown in teal at 160Hz), when the dyskinesia peak is present it is variable in frequency, moving between 80Hz and another "natural" peak value. These changes appear to the CLDBS algorithm to mean that dyskinesias have subsided, resulting in stimulation updates that ultimately produce oscillatory algorithm behavior.

Table 4.1: Enrolled Parkinson’s disease patient clinical information.

Patient ID	Age	Yrs Since Diagnosis	UPDRS Off Med	UPDRS On Med
P1	65	8	30	14
P2	61	7	29	14

Unified Parkinson’s Disease Rating Scale (UPDRS) scores for each patient, are given in Table 4.1.

The experimental protocol was approved by the UCSF institutional review board (protocol # 13-10878) under a physician sponsored investigational device exemption (IDE # G120283). The study was registered at Clinical Trials.gov (NCT01934296). Informed consent was obtained under the Declaration of the Principles of Helsinki.

4.4.1 *Surgical procedure and DBS parameter tuning*

As described in the Chapter 3, patients were surgically implanted with an Activa PC+S IPG, a cylindrical quadripolar electrode placed in the STN of the thalamus for therapeutic stimulation, and a quadripolar spinal cord stimulation electrode placed over the motor cortex used purely for sensing (additional details of the surgical procedure are provided in [128] and [127]). Stimulation parameters for the IPG were tuned by a clinician and are given in Table 4.2. Patient 1 had bilateral DBS but was only implanted with an Activa PC+S and cortical electrode strip on one side, therefore closed-loop DBS was only performed on one side while continuous DBS was delivered on the opposite side; Patient 2 had unilateral DBS with the Activa PC+S as described above.

4.4.2 *Comparison of stimulation modes*

Patient 1 had three experimental sessions, separated by days or weeks, to compare their clinical scores on subsequently described behavioral assessments for (1) open-loop, continu-

Table 4.2: Clinical programming parameters of Activa PC+S during CLDBS experiments.

Patient ID	Brain Side	Activa Stimulation Contacts	AC-PC Co-ords. of ECoG Recording Contact Pairs	CL Amplitude Range (V)	Pulse Width (μ sec)	OL Amplitude (V)	Freq. (Hz)
P1	R	C+1-	30	1-3	60	3	160
P2	L	C+2-	29	1-5	90	5	130

ous DBS at therapeutic stimulation settings, (2) CLDBS for dyskinesia detection using the algorithm described above (referred to as Nexus D3), and (3) an on-board, fully embedded version of the dyskinesia detection algorithm described above (referred to as Nexus E). The Nexus D3 stimulation mode was assessed for approximately 1 hour; the Nexus E stimulation mode was assessed for approximately 30 minutes.

Patient 2 had two experimental sessions, separated by days or weeks, to compare the performance of (1) open-loop, continuous DBS at therapeutic stimulation settings, and (2) an on-board, fully embedded version of the dyskinesia detection algorithm described above (referred to as Nexus E). Each stimulation mode was assessed for a duration of approximately 10 minutes. Patient 2 was disqualified from participating in the Nexus D3 test due to recording artifacts in the power spectra located in the vicinity (within 5 Hz) of the expected frequency of his dyskinesia peak. In preliminary tests with this patient, these artifacts effectively wiped out any changes in power at the dyskinesia peak frequency. Artifacts were not present in the recording scheme for Nexus E, and since the function of these stimulation modes is quite similar (see clinical and power results for Patient 1 below), it is fair to assume that Nexus D3 would perform similarly to Nexus E if not for the artifacts.

At each experimental session, patients were not informed as to which stimulation mode was being tested, although they were able to self-assess the presence or absence of symptoms and side-effects.

4.4.3 Calibration and pre-test medication

For the Nexus D3 test, the patient was calibrated for the stimulation update threshold at the start of the visit, prior to administration of medication. Calibration took approximately 30 seconds for the average and standard deviation calculations.

After calibration, the patient took his morning medications. After a period to allow the medication to take effect, the closed-loop algorithm testing was started and the periodic behavioral assessments were performed. Medication times relative to the start and end of CLDBS algorithm testing are provided in the last column of Table 4.3. For Nexus E and open-loop testing, both patients were medicated before the assessments with a roughly similar "wash-in" period for medication to take effect as with the Nexus D3 test.

4.4.4 Behavioral assessment

For patient 1, behavioral assessments from the UPDRS and Unified Dyskinesia Rating Scale (UDYS) [44] were conducted at multiple times (approximately every 20 minutes) during open-loop and CLDBS test cases. Specifically, items 20a-c, 21 a-b, and 23a-25b of the UPDRS were administered. Patient 2 did not participate in formal behavioral assessments. Both patients were queried regarding their subjective state at multiple times (approximately every 20 minutes) during the test.

4.4.5 Clinical evaluation

Experimental sessions were video recorded and reviewed *post hoc* by a movement disorder neurologist who was blinded to the test conditions. Patients were also blinded to whether stimulation was open-loop or closed-loop.

4.4.6 Energy calculation

Total energy delivered in one second, E_{1sec} , was calculated as

$$E_{1sec} = \frac{V^2 fp}{Z}(1sec)$$

where V is the stimulation voltage, f is the stimulation frequency, p is the stimulation pulse width, and Z is the impedance [65].

4.5 Results

Results are presented for three aspects of the dyskinesia-mitigation CLDBS paradigms: (1) their total responsiveness, measured in how many stimulation transitions were triggered; (2) their clinical efficacy in terms of both symptom (bradykinesia) reduction and side-effect (dyskinesia) mitigation; and (3) their energy savings relative to open-loop DBS.

4.5.1 Algorithm Responsiveness

The responsiveness of each stimulation mode is presented in terms of the average number of stimulation changes triggered per minute by each stimulation mode. For patient 1, algorithm responsiveness for each stimulation mode is given in Table 4.3. A sample plot of the Nexus D3 CLDBS algorithm's responses over the course of the test period is shown in Figure 4.5. The Nexus E CLDBS mode was the most responsive mode.

For patient 2, the Nexus E CLDBS mode triggered an average of 15.8 stimulation changes per minute. When queried, neither subject reported noticing any stimulation updates during the course of the experimental sessions for any of the stimulation modes.

4.5.2 Clinical Efficacy

For patient 1, relevant clinical scores for bradykinesia and dyskinesia for each test case (open-loop DBS, CLDBS with Nexus D3, and CLDBS with Nexus E) are given in Table 4.3. Increasing scores correspond to more severe expression of each phenomenon. For both the bradykinesia and dyskinesia scores, the scoring neurologist assessed that the difference in clinical scores between each stimulation mode was not significant. That is, all stimulation

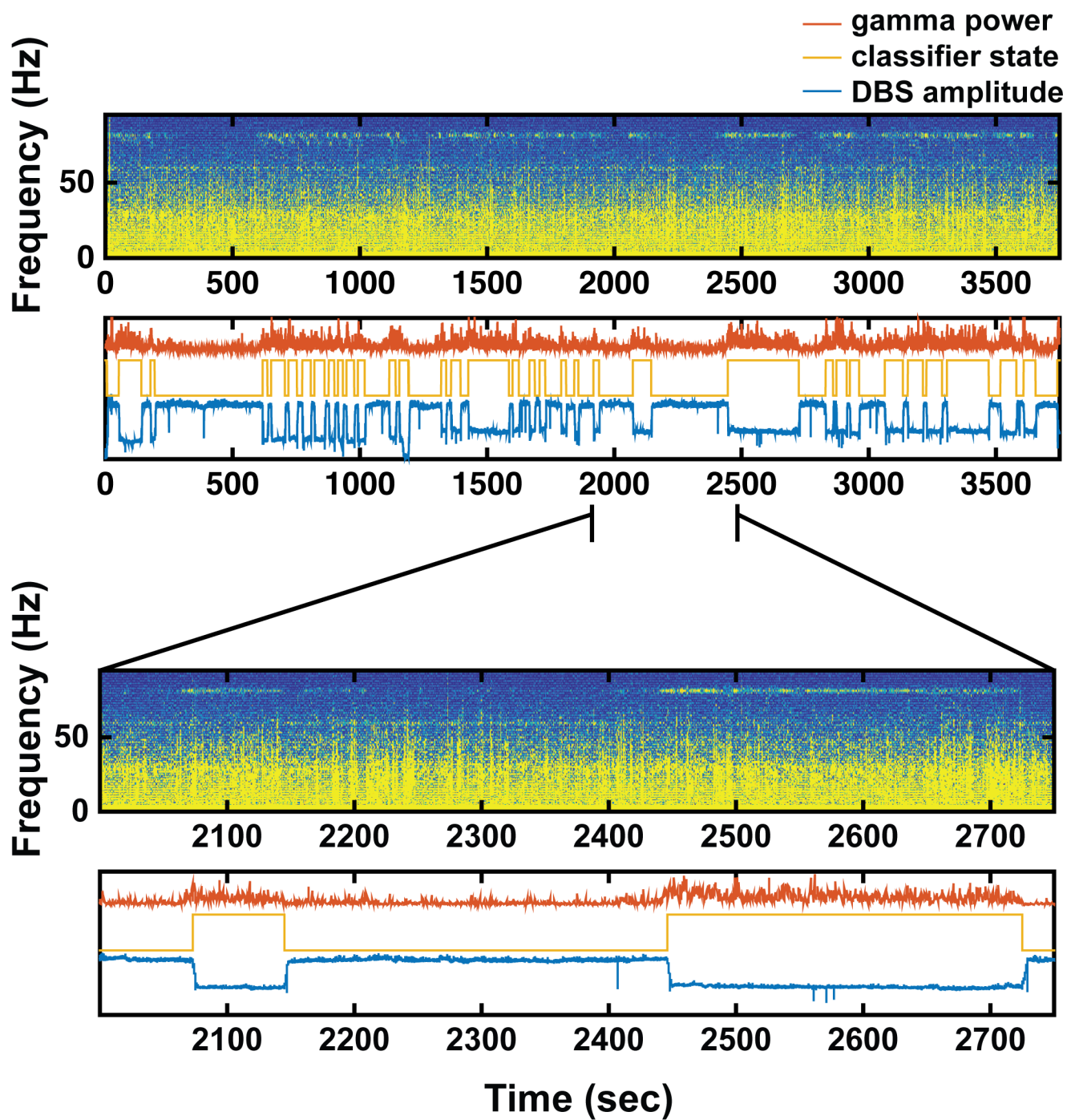


Figure 4.5: Examples of the CLDBS algorithm response

Table 4.3: UCSF Patient 1 clinical scores resulting from tested stimulation paradigms.

Stimulation Mode	Bradykinesia Score	Dyskinesia Score	Total Energy Saved (vs Open Loop)	Avg. Triggers Per Min.	Min. Last Dose	Since Med.
Closed-loop, Nexus D3	14	1.5	38%	1.1	110-175	
Closed-loop, Nexus E	11.83	1.33	45%	16.0	65-110	
Open-loop	12.33	1.667	0%	0	70-110	

modes were clinically equivalent for both bradykinesia and dyskinesia expression for patient 1.

For patient 2, formal clinical assessments necessary for scoring were not performed; however, the neurologist reviewing the experimental videos noted no overt clinical differences for patient 2 between the open-loop and CLDBS (Nexus E) stimulation modes.

4.5.3 Energy Savings

For patient 1, a comparison of energy savings for each stimulation mode relative to open-loop is given in Table 4.3. CLDBS using Nexus E demonstrated the greatest energy savings, but CLDBS using Nexus D3 still had substantial energy benefits compared to open-loop. Patient 2 demonstrated comparable energy savings for Nexus E at 39% energy savings compared to open-loop.

4.6 Discussion

In the experiment described above, I pilot tested a novel, biomarker-based CLDBS algorithm designed to mitigate dyskinesias in PD patients. This research was performed on a fully-embedded Medtronic IPG in two modes, streaming to a laptop computer (Nexus D3) and subsequently using a fully embedded mode (Nexus E). Although the Nexus D3 approach that

I developed could only be tested in one subject to date, the corresponding Nexus E mode that my work enabled was tested in two subjects with consistent results across all metrics. Results were presented for algorithm responsiveness, clinical efficacy, and energy savings.

In assessing the success of the biomarker-based dyskinesia mitigation algorithm that I designed, implemented, and tested, a number of considerations need to be weighed. We ought to determine (1) whether the algorithm achieved the aim of mitigating dyskinesias; (2) whether the attempts to mitigate dyskinesias compromised treatment of symptoms; and (3) whether additional benefits or costs of the new CLDBS algorithm were observed.

There was no significant difference in clinical dyskinesia scores when comparing the traditional open-loop DBS and new CLDBS cases. However, this comparison comes with a caveat—in both cases, the clinical scores were extremely low (less than 2), meaning that few dyskinesias were observed in any of the stimulation paradigms. Our results may demonstrate “floor effects,” where the dyskinesias showed no change because they were already so minimal to begin with. Thus, it is difficult to conclude one way or the other whether our CLDBS dyskinesia-mitigation algorithm was successful in the goal of mitigating dyskinesias.

There was also no significant difference in bradykinesia scores across stimulation modes. This can be seen as a positive for the CLDBS algorithms given that clinical efficacy in symptom reduction was not compromised in an attempt to mitigate side effects. However, it is unclear whether similar performance would be observed in cases where dyskinesias were more severe or pervasive (in other words, when floor effects were not observed). Further testing under circumstances where patients are more dyskinetic is likely necessary to better understand this tradeoff.

There were notable improvements in power savings for both CLDBS stimulation modes compared to open-loop DBS. This result may reflect a secondary benefit of integrating side-effect mitigation into CLDBS algorithms beyond simply minimizing patient exposure to side-effects. Since side-effects in general may indicate that a patient is over-stimulated, using the presence of side-effect biomarkers as triggers to reduce stimulation may decrease energy use without losing clinical benefit.

In this case, since patients were unaware of stimulation adjustments made by the CLDBS algorithms, algorithm responsiveness plays a smaller role in judging algorithm performance—algorithms can instead be judged on clinical efficacy or power savings. Often times rapid responses in classification of dyskinesias may have occurred in response to fluctuations in neural signals that did not correlate with observed behavior or side-effect expression. In some applications of CLDBS, patients are aware of stimulation updates [51] [53], and in these cases differing algorithm responsiveness may have direct consequences for patient experience. However, recent studies in CLDBS for PD have proposed that it is in fact the temporally adaptive aspect of CLDBS that is responsible for the clinical efficacy (perhaps greater than open-loop DBS) observed in CLDBS studies to-date [138]. Side-effects such as paresthesias that have been observed in response to some CLDBS algorithms [53] [51] may therefore pose a direct trade-off with effective CLDBS therapy.

As a first pilot demonstration of a CLDBS algorithm for dyskinesia-mitigation, the present study has several limitations in design, testing, and evaluation. First, the energy results presented here only reflect a fraction of power use during CLDBS testing. Power savings results do not factor in costs for streaming between the laptop and the IPG (in the case of the Nexus D3) and onboard computational costs (for Nexus E). We believe the power savings presented are still significant given that eventually the processing, which is not computationally intensive, would be performed entirely on-board the device (as with Nexus E) thereby cutting power costs for streaming to the laptop³.

As mentioned above, it was difficult to assess the therapeutic effects of the algorithm in terms of dyskinesia-mitigation given that floor effects were observed. This highlights two challenges that permeate CLDBS study design: limited patient populations and limited real-world testing. Few PD patients (less than 20 to our knowledge) receive the Activa PC+S DBS device that enables real-time sensing of neural signals in ambulatory human subjects.

³During discussions with Activa PC+S device engineers at Medtronic, company employees unofficially claimed that power savings of greater than 15% from our closed-loop algorithms would be enough to offset computational costs for onboard algorithm processing including detection and stimulation updates.

Not all patients that receive this device experience dyskinesias. These factors greatly limit possible study sizes. And although both patients in our study report experiencing dyskinesias during everyday life, they may be more dyskinetic under circumstances that could not be fully captured in our clinical test setting. In the future, the CLDBS dyskinesia-mitigation algorithm presented here could be further tested outside of the clinic to better illustrate whether it effectively reduces the frequency and duration of dyskinesias.

The present pilot study opens up a number of avenues for continued research. Provided the underlying neural mechanisms proposed by Starr and Swann are accurate, irregular (variable frequency) stimulation paradigms may be less pro-dyskinetic than constant frequency stimulation modes [128]. Thus, rather than simply reducing stimulation amplitude, a CLDBS algorithm could trigger changes in frequency that may provide better dyskinesia mitigation. Triggering stimulation frequency changes via CLDBS algorithms has yet to be explored.

An additional line of future research that would be useful to investigate are how to intelligently balance symptom reduction and side effect mitigation. In the present study, although symptoms were measured through clinical scores and did not worsen using the CLDBS dyskinesia-mitigation algorithm, symptoms were not explicitly measured and used for feedback in the closed-loop paradigm. It may be impossible to completely avoid aggravating side-effects while maintaining therapeutic benefit, resulting in a necessary trade-off between symptoms and side-effects. Furthermore, the individual levels of side-effect and symptom expressions that a patient will be willing to tolerate may vary depending on the context in which a patient finds herself. Explicitly quantifying this trade-off would be a next step in creating holistic CLDBS therapies that consider multiple, potentially competing aspects of the underlying disorder.

Chapter 5

VOLUNTARILY-CONTROLLED CLDBS: BCI-BASED STIMULATION ADJUSTMENT

Aim 2 of my thesis was to demonstrate a voluntarily-controlled CLDBS system for side effect mitigation. Specifically, I aimed to design a brain-computer interface (BCI)-based system for stimulation adjustment to be piloted with individuals with ET. This chapter describes prior relevant work in BCI development, my experimental setup for evaluating components of a BCI-based CLDBS system, and pilot testing conducted at UW toward the validation of this system. Lastly, I discuss the implications of my results for BCI-based CLDBS approaches and describe future work that ought to be conducted to best expand on my contributions.

Involuntary biomarkers may be difficult to detect or unknown for some side-effects of DBS. For example, there are currently no widely available methods for detecting impaired speech, and prospective methods that rely on the use of processing audio streams on external devices may be difficult to implement in practice as current proposals require transmitting speech to cloud computing resources for processing [54]. Psychological side-effects and changes in affect may be even more difficult to detect with sensors, although some groups have attempted to use voice and image processing [27]. Regardless, there are clearly some side-effects that currently cannot be quantified through LFPs at either the DBS stimulation electrode or at cortical sites.¹

In these cases, it is unclear how to design an involuntary closed-loop system to update stimulation to mitigate side-effects. However, patients themselves are keenly aware of their

¹The same is true for symptom detection; although my focus is on developing methods for side-effect mitigation, an aspect of DBS therapy that has previously been overlooked, the approach I discuss in this chapter would have applications in managing symptoms that lack clearly detectable biomarkers as well.

side-effects, given that otherwise they would not be reported to clinicians.² Additionally, patients maintain an understanding of side-effects relative to changing contexts, which may influence when they would tolerate greater symptom management at the expense of aggravated side-effects (and vice versa). For example, a DBS patient engaged in a demanding fine-motor task may be willing to tolerate greater speech impairment, but these preferences may change if they are suddenly attempting to answer a phone call. These context-dependent changes in preferences may be difficult or impossible for an onboard CLDBS system to perceive given available sensor streams.

An additional potential benefit of giving patients voluntary control over their stimulation is that it may produce better outcomes for some patients regarding their relationship with their DBS device. Some patients have reported that they feel a loss of control after receiving their DBS device [16], possibly resulting in negative perceptions of their therapy and loss of a sense of agency. Autonomous or involuntary CLDBS algorithms may not aid in resolving this problem, since the device is effectively still operating without patient input or making decisions on behalf of the patient. Dr. Sara Goering, who studies issues of agency in DBS, has discussed the idea that giving patients a more active role in CLDBS through may impact feelings of agency [43].

Currently patients may have the ability to use a hand-held “patient programmer” to turn their device on or off. However, this hand-held interface has its drawbacks. Firstly, it requires movement disorder patients to engage in a motor task that may require the use of their affected limb, or to seek the aid of a caregiver to operate. Secondly, for many patients they are forced to choose between a binary on/off for their stimulation settings. Lastly, having to carry around a separate device to make stimulation changes is inconvenient and may dissuade some patients from making changes on a moment-to-moment basis that would in fact improve their personal balance between symptoms and side-effects. Given

²In my own experimental experience with PD patients at UCSF, patients were able to report which side-effects they tended to report with which “group number”—or cluster of stimulation settings—better than clinicians were able to remember or predict simply because they lived with and used these devices every day.

these considerations, it is possible that some patient would prefer a control method that was embedded in their DBS device, that they could operate simply by thinking—in other words, a BCI.

In collaboration with Dr. Andrew Ko at UW Medical Center, I designed, implemented, and piloted the required subsystems for a BCI-based, voluntarily-controlled CLDBS. I used the experimental setup described in Chapter 3 with our enrolled ET subjects³. We tested this system using Nexus D3, where data is streamed from the IPG to the experimental laptop, in multiple ET patients. I summarize results from this pilot testing in subsequent sections, and conclude with noting key problem areas that remain to be solved for future deployment of a full BCI-controlled CLDBS system.

5.1 Implanted ECoG-based BCI Systems in Human Subjects

In this section, I will consider prior work with implanted ECoG-based BCIs in human subjects. The areas that inform my experimental design include (1) the strategies that human subjects use to control BCIs, (2) the feedback that patients are given when using a BCI in order to inform their control and improve performance, and (3) the types of BCI tasks that human subjects perform. Prior research has investigated a number of approaches in each of these categories that inform my own BCI system design. I will also discuss limitations in prior invasive BCI studies that left open research questions which my work addressed.

5.1.1 Training Methods and Control Strategies for BCIs

In order to operate a BCI, users must alter their brain activity in a way that the BCI can recognize. That is, the user’s brain activity must enable the system to differentiate between different corresponding actions that the BCI could take. This involves the user learning an explicit or implicit control strategy that allows them to alter their neural signals.

One design choice to be made is whether the BCI requires users to directly (consciously)

³Note that the system that I piloted could theoretically be used by other patient populations; I tested with ET subjects primarily because they were the population we had approval to work with at UW.

or indirectly alter their neural activity. For example, a user’s control strategy may be to look at a menu of discrete options that are flashing at different frequencies. Depending on the frequency they observe, they will indirectly cause their visual system to produce a steady state visually-evoked potential (SSVEP) which the BCI can process [96]. In other cases, users are more directly focused on controlling their neural signals. This is the case in SMR based BCIs [31], and given that our ECoG electrodes were implanted over motor cortex it was the logical design choice for the systems I engineered. Consciously-controlled systems may require greater mental effort, therefore increasing the chance of user fatigue; however, it is possible that the skills to operate these system could become reflex over time.

A related design distinction is between providing the user with overt control strategies versus operant conditioning [79]. In overt control strategies, the user is provided with cues on how they should try to operate the BCI. For example, in motor imagery control strategies, they may be told to imagine performing certain actions with a particular limb. On the other hand, in operant conditioning, the user is not told a particular method for operating the BCI, and instead learns implicitly through feedback from the BCI how to control the BCI [31] [139]. There have been limited comparisons between these methods in literature, but operant approaches are thought to produce automatic responses akin to reflexes [31], although subjects who initially learn to control a BCI using overt control strategies may eventually cease to use them. In my work, I used overt control strategies for the purpose of reducing participant frustration. My subject population was older and self-described as “simple,” thus I anticipated significant challenges in using an operant training approach. The specific mental strategies used were a topic of my research and will be discussed later in this chapter.

5.1.2 BCI Feedback Types

Another consideration for BCIs is how the interface will convey information about the status of the system back to the user for both standard operation and training purposes. Feedback helps the user understand whether the BCI is doing what they want, and perhaps how

they might alter their neural activity in order to put the BCI in a different desired state. Feedback has been shown to be important for both short term performance gains as well as enabling long-term learning of control strategies [85]. Different forms of feedback have been investigated in prior BCI studies, including visual [96], auditory [90], proprioceptive [94] [106], tactile [26], direct cortical stimulation of somatosensory (S1) areas [30], and more.

My research investigates whether changes in DBS amplitude are a usable form of feedback for the purposes of operating a one-dimensional BCI. To my knowledge, limited prior work has investigated feedback in the form of DBS⁴, although substantial research has investigated side-effects experienced during DBS. Paresthesias, defined as unnatural tactile sensations such as “pins-and-needles,” are a known side effect of DBS for neurological movement disorders [57]. In traditional DBS therapy, paresthesias are experienced only briefly (less than 1 minute) after stimulation is initiated. It has not previously been shown how paresthesias may manifest during CLDBS, where stimulation parameters are modified in real time based on feedback from worn or implanted sensors. Additionally, there is potential for paresthesias to be leveraged as a form of feedback for a BCI system. If users can interpret paresthesias in order to understand the state of their stimulator, it may improve their ability to consciously control their stimulation settings. My work assesses the quality of this form of feedback for the first time.

5.1.3 BCI-Task Design

BCI task design is another aspect of the interface that will ultimately affect user experience and performance. For some studies, the task itself is clinical or therapeutic in nature, such as for stroke rehabilitation [7], in the use of robotic prosthetic limbs for individuals with spinal cord injury or amputation [55], or for communication for individuals with locked-in syndrome [68]. In other studies, BCIs may be used for entertainment such as video games or for personal relaxation in non-clinical settings [82].

⁴A recent poster [124] presents similar results on feedback perceived from thalamic stimulation, although this work has yet to be published in a full paper.

Patient ID	Age	Sex	Clinical Stimulation Settings	Stimulation Contacts	Recording Contacts
P1	61	M	2.5V, 140Hz, 90 μ s	2+0-	8/10
P2	83	M	3.9V, 140Hz, 90 μ s	2+0-	9/11
P3	80	M	3.2V, 110Hz, 60 μ s	2+3-	8/11
P4	69	M	2.3V, 140Hz, 90 μ s	C+1-	8/11

Table 5.1: Enrolled essential tremor patient clinical information.

The application I investigate in my research for CLDBS is clinical in nature but has not been explored in prior BCI studies. However, I draw from prior work in developing one-dimensional BCI cursor tasks. Cursor tasks can be easily used to assess control accuracy with an obvious goal in mind, and provide a “gamified” interface that may encourage the patient to learn competitively. As patients learn increased control, task difficulty can be increased by decreasing target size or increasing the speed of each run. This allowed for comparisons of patient performance across different feedback types and control strategies.

5.2 Methods

BCI-CLDBS experiments were conducted with varying subsets of four male patients prescribed DBS for ET. Clinical data for each patient are given in Table 5.1. Written informed consent was obtained from the patient prior to participation in the study. All aspects of this study were approved by the Institutional Review Board of the University of Washington Medical Center. Approval was received to use the Activa PC+S DBS implant combined with the Resume II electrode strip through an Investigational Device Exemption filed with the FDA. All recorded neural data, test outcomes, medical history, patient testimonies, research notes, and related data were de-identified and stored in a secure location.

5.2.1 Surgical Procedure and DBS Parameter Tuning

Four male patients with ET were enrolled in the study prior to DBS surgery. As described in the Chapter 3, patients were surgically implanted with an Activa PC+S IPG, a cylindri-

cal quadripolar electrode placed in the ventral intermediate nucleus (VIM) of the thalamus for treatment of tremor. In addition to implanting a DBS system, a Resume II strip of 4 spinal-stimulation electrodes were implanted over the right hand area of the motor (M1) and somatosensory (S1) cortices (2 electrodes were placed over each cortex respectively). Placement of the thalamic and cortical electrodes were verified through an intraoperative CT scan. For patients 3 and 4, cortical electrode placement was also checked using the presence of steady-state somatosensory evoked potential measured in the cortical electrodes during electrical stimulation of the median nerve in the contralateral limb. Specifically, the central sulcus was located by observing a SSEP phase reversal in consecutive cortical electrodes. Additional details of the surgical procedure are provided in [53] and [51]. Following implantation and the disappearance of lesion effects, stimulation parameters for the IPG were tuned by a clinician and are given in Table 5.1.

5.2.2 *Determining Patient Control Strategies from Cued Behavioral Tasks*

Cortical activity was recorded months to years after implantation during cued behavioral tasks, including overt movement, motor-imagery, speech, and rest to determine which behaviors might provide usable control strategies for a BCI interface. As an example, if overt movement produced a reliably different signal from resting, a patient could use movement to volitionally turn their stimulator on and rest to turn their stimulator off.

During multiple experimental sessions, patients were prompted to perform each type of cued behavior for approximately three minutes. Cues were given from an external prompt that time-synchronized cues to recorded neural data, and an additional accelerometer was used for ground-truth labeling of behavior periods versus rest⁵. Across all sessions, a time signal was collected from the cortical electrodes at a rate of 422 Hz and time-synchronized with the inertial recordings as described in [52]. As the Activa PC+S can only record signals

⁵During overt movement cues, patients wore the accelerometer. During motor imagery and speaking cues, myself or another researcher moved the accelerometer continuously while the patient engaged in the behavior

referenced between cortical electrodes, the signal was referenced from electrode pairs selected uniquely for each patient and are provided in Table 5.1. Reference pairs were chosen that exhibited the largest beta-band peak recorded at rest in comparison to all other reference pairs for each patient respectively.

Power spectral densities (PSDs) were computed (using Welch’s method with a 1024-point Hamming window, 50% overlap) from the neural data of the cued recordings and averaged by labels derived from accelerometry data into rest or behavioral periods.

5.2.3 *Stimulation Feedback Testing*

A feedback test was used in order to quantify the feedback type that patients might experience while using a BCI-CLDBS system. Patient perceptions of stimulation were recorded during a pseudorandom series of stimulation updates. Stimulation was delivered using patients’ clinically effective contacts, ranging from 0-4 V in amplitude and 0-2.5 V/s in ramping rate. Each test was either a ramp (i.e. moving between two amplitude values at a particular rate) or a hold (i.e. holding constant at a certain amplitude value). Subjects were at rest and blinded to the test conditions. Queries were made immediately after each test was initiated regarding the perceived sensations the patient was experiencing at that moment. The location, strength, duration, and quality of sensations were recorded. An example response would be, “In my right arm I feel weak tingling that fades away after about 2 seconds.” After the experiment, reported sensation strength for each test were coded on a scale from 0 (no paresthesias experienced) to 3 (strong paresthesias experienced).

5.2.4 *BCI-Task Design*

A one-dimensional BCI task was designed to investigate whether BCI tasks could be learned and performed using the novel DBS platform. The BCI task, constructed using the Unity game development platform, was a one-dimensional, fixed-time cursor control task with right-justified targets as in [144]. A screenshot of the BCI task is provided in 5.1. Features were predominantly in beta-band power (16-32 Hz), which have a known correlation of beta-band

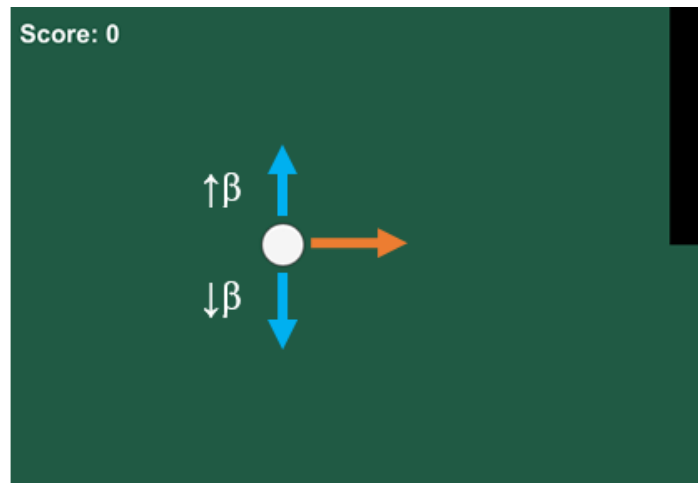


Figure 5.1: Diagram of BCI task, which is a constant-time right-justified box task built using the Unity game development platform. The cursor (white) moves to the right side of the screen at a constant velocity (noted in orange), and the patient modulates beta-band power to control the cursors vertical velocity (noted in blue). The aim of the task is to hit the presented target on either the top or bottom of the screen) (black, upper right corner demonstrated in up position). Score (white, upper left corner) is used to gamify the task.

desynchronization in the motor cortex with both overt movement [102] and motor imagery [86].

Patients controlled the vertical position of the cursor using a binary classifier trained offline on the cued behavior task data (described earlier in the chapter). For classifier training, power spectral density (PSD) features were extracted from cortical data with a sliding, 1-second window using Welch’s method (50% overlap with a 0.5-second Hann window). Frequency bin features therefore had a width of approximately 2 Hz and the frequency range [4,28) Hz was used as features. Features were extracted using this method 5 times per second. Features were normalized to have zero mean and unit standard deviation. Gyroscope data was used as a ground-truth label for behavior versus rest periods. These features and labels were used to train logistic regression classifiers. To prevent overfitting, L2-norm regularization was used, and a grid search method was used to find the optimal hyperparameter for maximizing classifier sensitivity. Features and labels were partitioned into two equal halves

(without shuffling) for cross-validation of the classifiers during training.

At the start of each run, the cursor appeared on the left side of the screen and moved horizontally with a constant velocity such that the cursor reached the right side of the screen 3 seconds after the start of the task. Each trial was approximately 1 minute in duration and consisted of 20 runs with a single target per run, either on the top or bottom of the screen. BCI task trials were separated by 5 minutes each where patients either rested or verbally discussed his impression of the task. Patients performed all of the trials and inter-trial rest periods with his stimulation turned off. Patients had no prior experience using BCIs. Throughout the experimental sessions, qualitative interviews were conducted with the patient regarding his experience using the BCI system. These interviews are discussed in detail in [16].

5.3 Results

Results are presented for three necessary subsystems for BCI-controlled CLDBS: (1) the control strategy that patients might use to volitionally adjust stimulation levels; (2) the feedback that patients receive from stimulation changes; and (3) patient performance on a BCI task using the implanted system.

5.3.1 Control Methods for BCI Operation

PSDs showed reliable differences in power in beta-band between overt limb movement and rest for all tested patients. Other behavioral tasks showed mixed differences across patients.

PSDs for Patient 1 during overt movement are shown in Figure 5.2. Both overt hand and overt arm movement were compared to rest, where overt hand movement was shown to have greatest beta-band desynchronization. PSDs for Patient 1 during imagined movement are shown in Figure 5.3. Much less desynchronization is observed during cued behavior, with only a limited range of high beta-band frequencies showing a small amount of desynchronization.

PSDs for Patient 2 during various cued behaviors are shown in Figure 5.4. Overt hand movement showed notable beta-band desynchronization compared to rest. Motor imagery

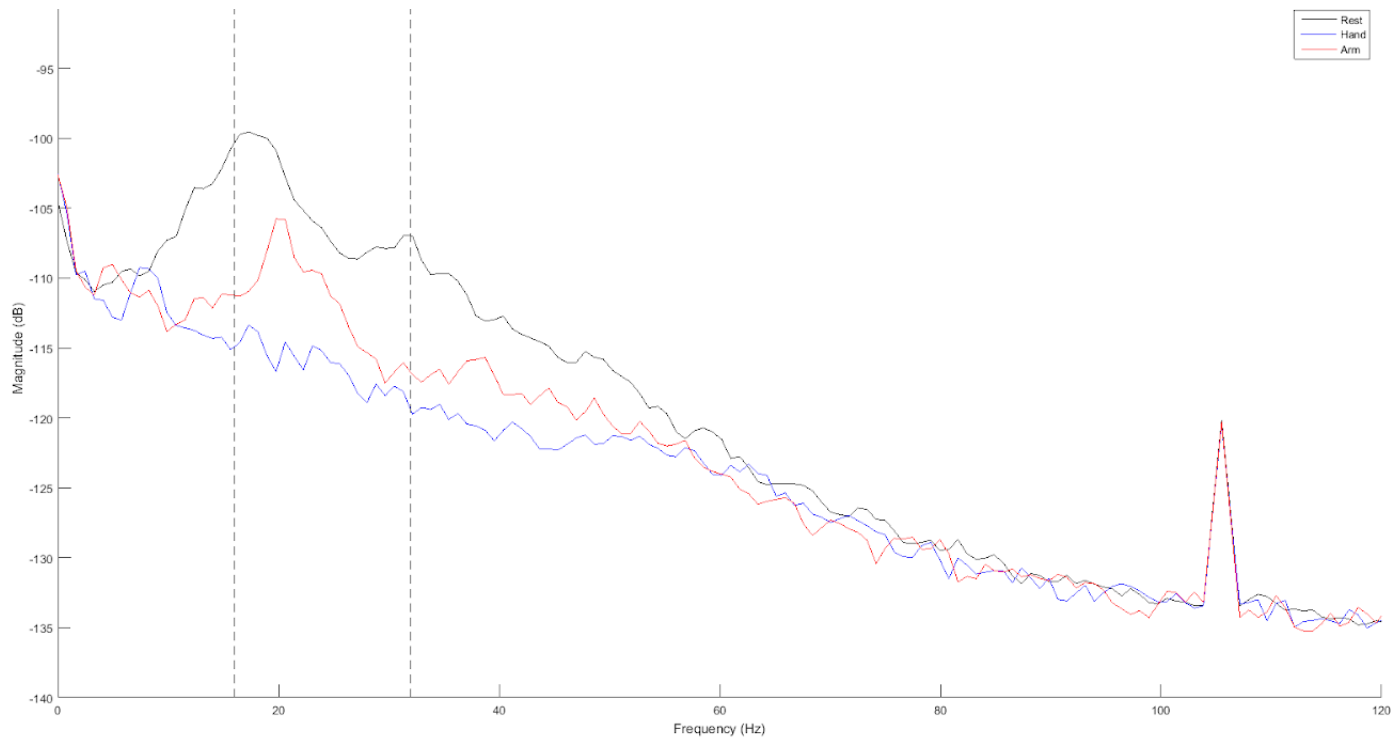


Figure 5.2: UW Patient 1 averaged periodograms during overt hand movement, overt arm movement, and rest. Beta-band frequencies are denoted with dashed vertical lines, and notable desynchronization during both hand and arm movement is observed. A recording artifact is seen at 105 Hz.

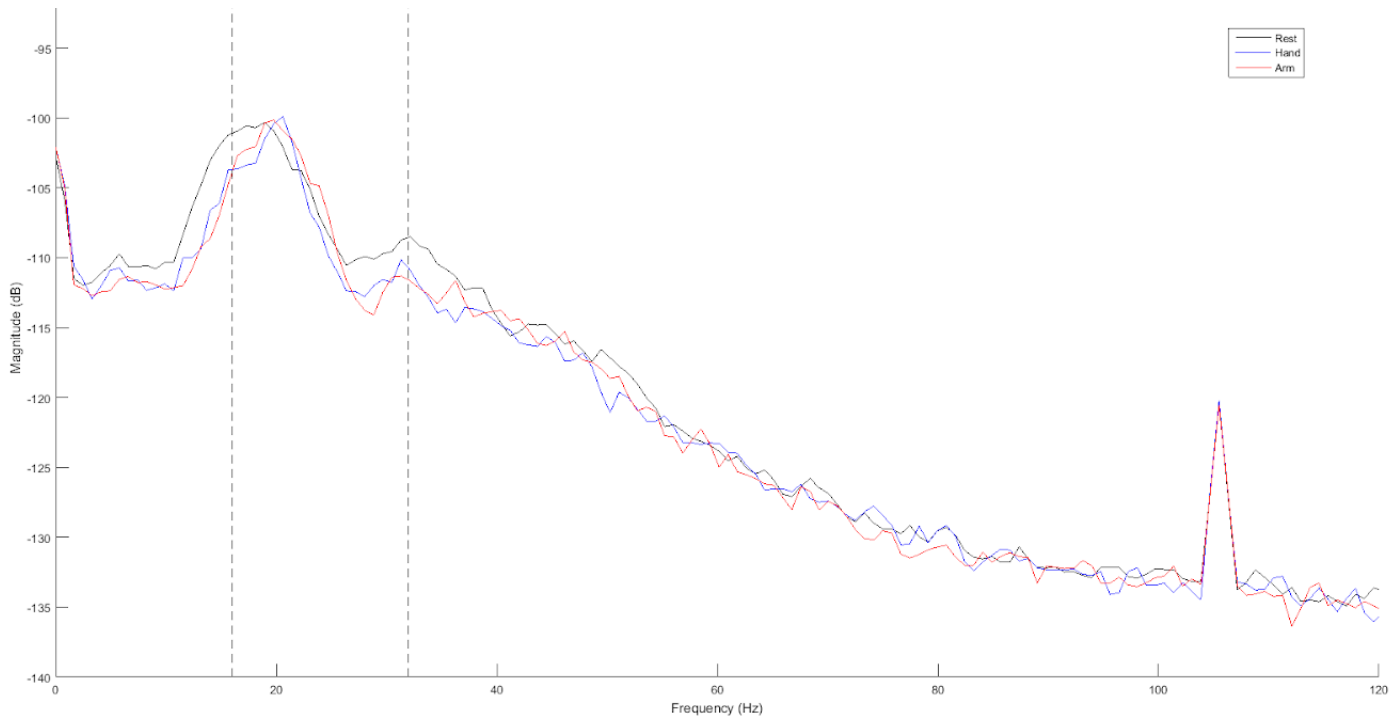


Figure 5.3: UW Patient 1 averaged periodograms during imagined hand movement, imagined arm movement, and rest. Beta-band frequencies are denoted with dashed vertical lines, and limited desynchronization is observed in higher beta-band frequencies during both imagined hand and arm movement. A recording artifact is seen at 105 Hz.

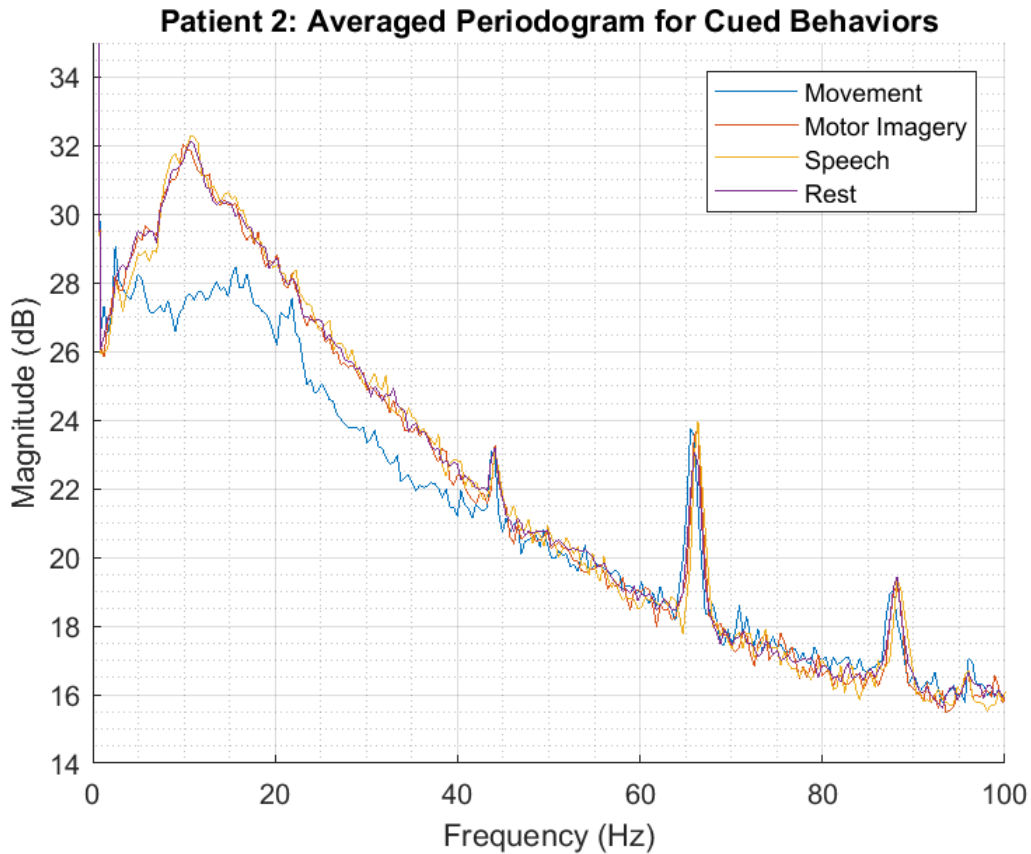


Figure 5.4: UW Patient 2 Averaged Periodograms During Cued Behavior

and speech behaviors were not distinguishable from rest.

PSDs for Patient 3 during various cued behaviors are shown in Figure 5.5. Overt hand movement showed the greatest beta-band desynchronization compared to rest, followed by cued speech and lastly motor imagery, which showed only a small amount of desynchronization compared to rest.

5.3.2 Patient Perception of Stimulation

Paresthesias were experienced in the upper and lower limbs contralateral to the implanted electrode (Patients 1 and 4), in the scalp (Patient 2), and in the contralateral lip and tongue

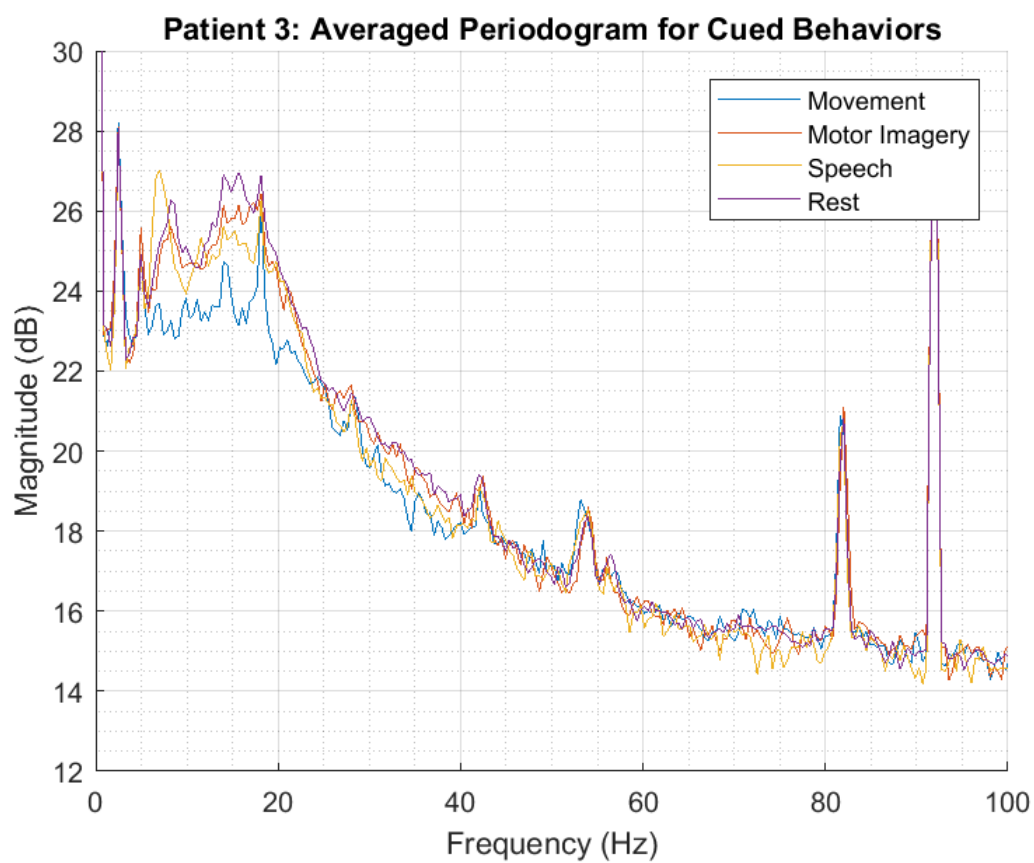


Figure 5.5: UW Patient 3 Averaged Periodograms During Cued Behavior

(Patient 3). Patients described paresthesias as a radiating tingling or “electric” feeling. For two subjects, paresthesias were only experienced during and immediately following increasing ramp periods, and were not experienced during decreasing ramp or hold periods.

Three patients had bipolar stimulation with similar thresholds for sensation in terms of the tested parameters. However, one patient (Patient 4) had monopolar stimulation wherein the cathode is a contact on the thalamic electrode and the anode is the case of the IPG. This patient had a far lower threshold for paresthesias such that paresthesia testing could not be run because he found nearly all configurations too intense to tolerate.

Slew rate, absolute voltage, and total change in voltage all contributed positively to the strength of paresthesias. Figures 5.6, 5.7, and 5.8 show the relationships between final stimulation amplitude, stimulation ramping rate, and evoked paresthesias for patients 1, 2, and 3 respectively. Figure 5.9, 5.10, and 5.11 shows the relationship between stimulation amplitude, stimulation delta (or total change in stimulation amplitude for a given test), and evoked paresthesias for patients 1, 2, and 3 respectively. Figure 5.12, 5.13, and 5.14 shows the relationship between stimulation ramping rate, stimulation delta, and evoked paresthesias for patients 1, 2, and 3 respectively. Across patients, paresthesia strength was remarkably similar under the same test conditions despite differences in location of perceptions. Patients also had identical perception of paresthesias across multiple months of visits when tests were repeated.

5.3.3 Patient Performance in a Visual-Feedback BCI Task

Table 5.2 shows patient performance for two patients who participated in a visual-feedback BCI task. Total task accuracy is given in the right-hand column, and accuracy is also provided by target type. Chance accuracy was 50%. Using the control strategy that provided the greatest spectral separation between rest and cued behavior, both patients performed with better-than-chance accuracy overall on the task. Due to high accuracy on their first trial, patients were not investigated for further learning over time.

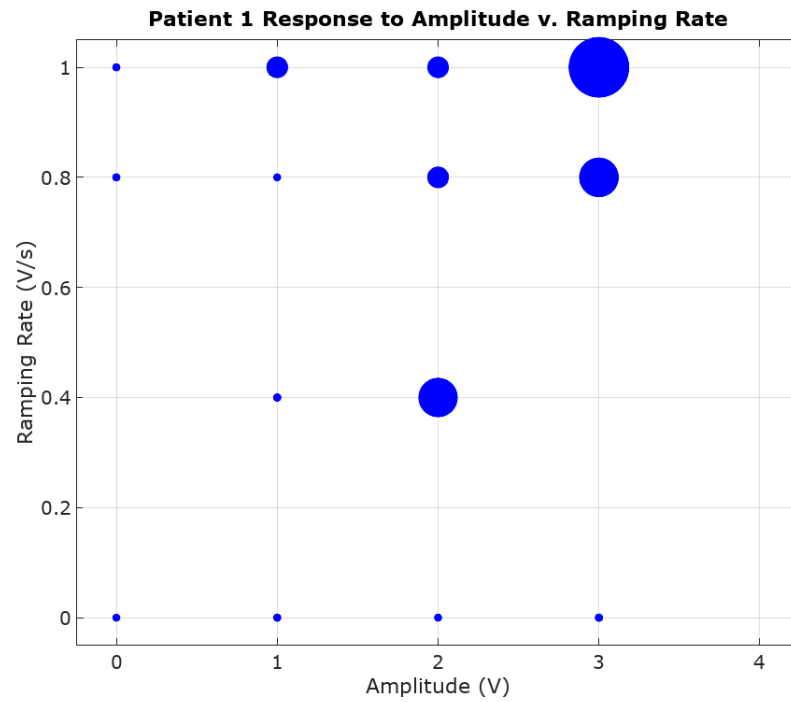


Figure 5.6: UW Patient 1 Perception of Final Amplitude vs. Ramp Rate

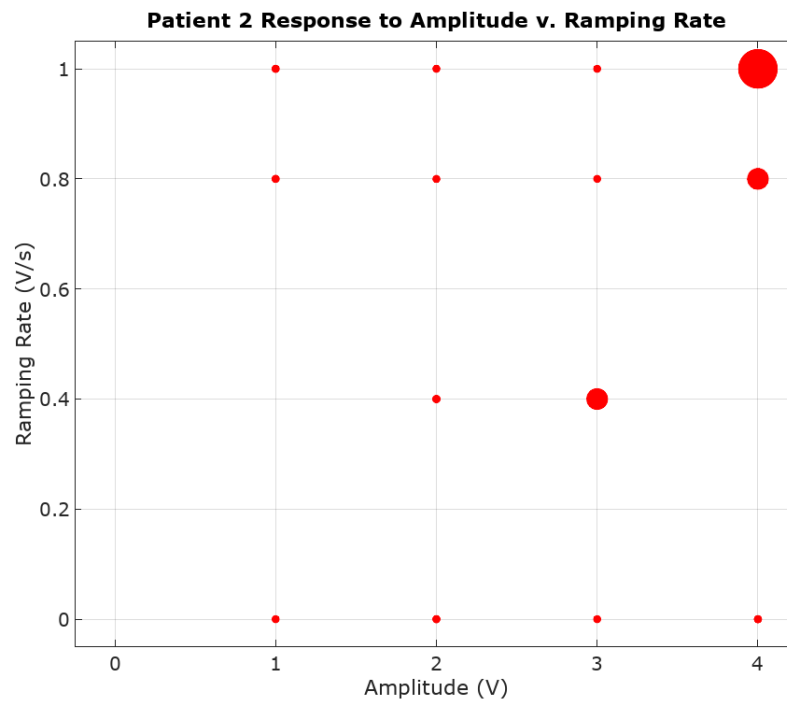


Figure 5.7: UW Patient 2 Perception of Final Amplitude vs. Ramp Rate

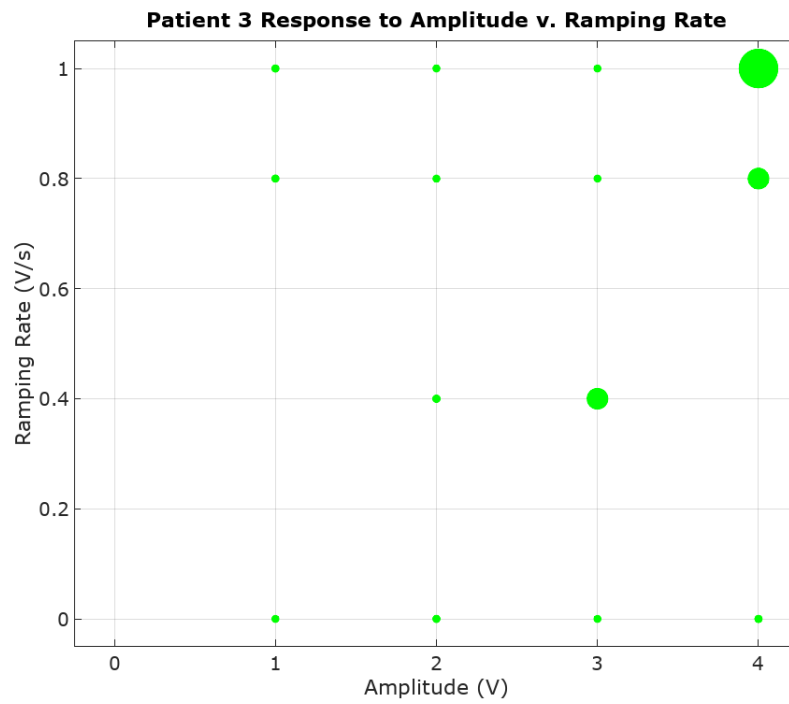


Figure 5.8: UW Patient 3 Perception of Final Amplitude vs. Ramp Rate

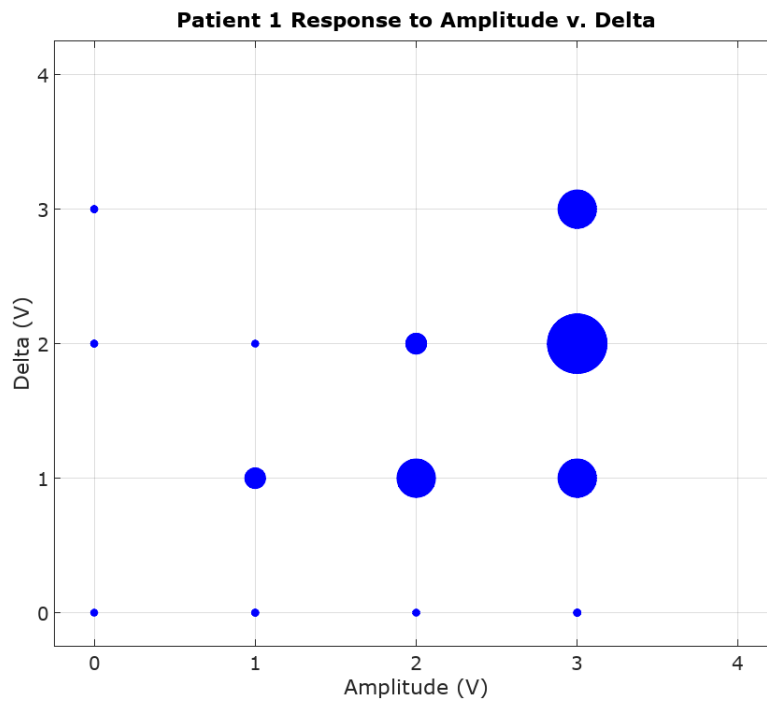


Figure 5.9: UW Patient 1 Perception of Final Amplitude vs. Delta (Amplitude Change)

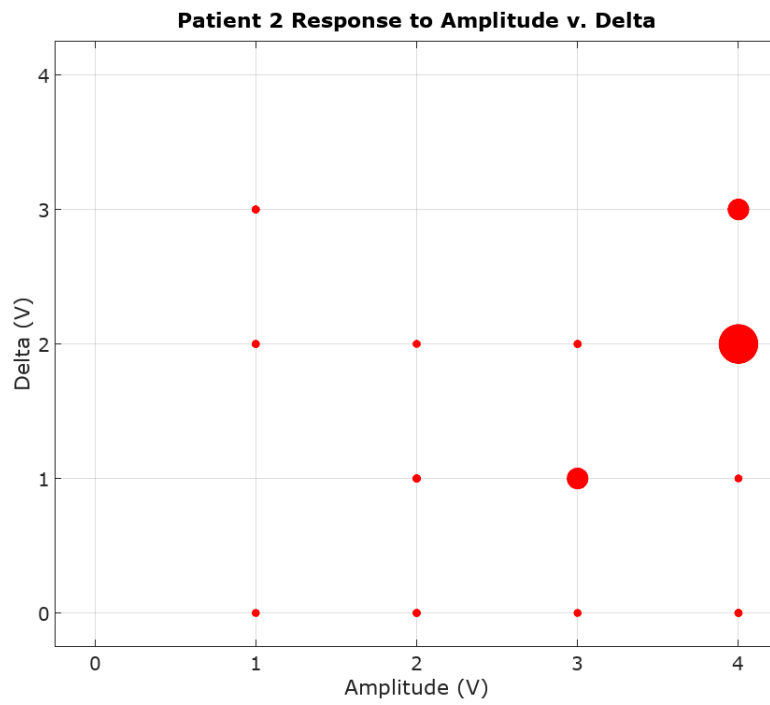


Figure 5.10: UW Patient 2 Perception of Final Amplitude vs. Delta (Amplitude Change)

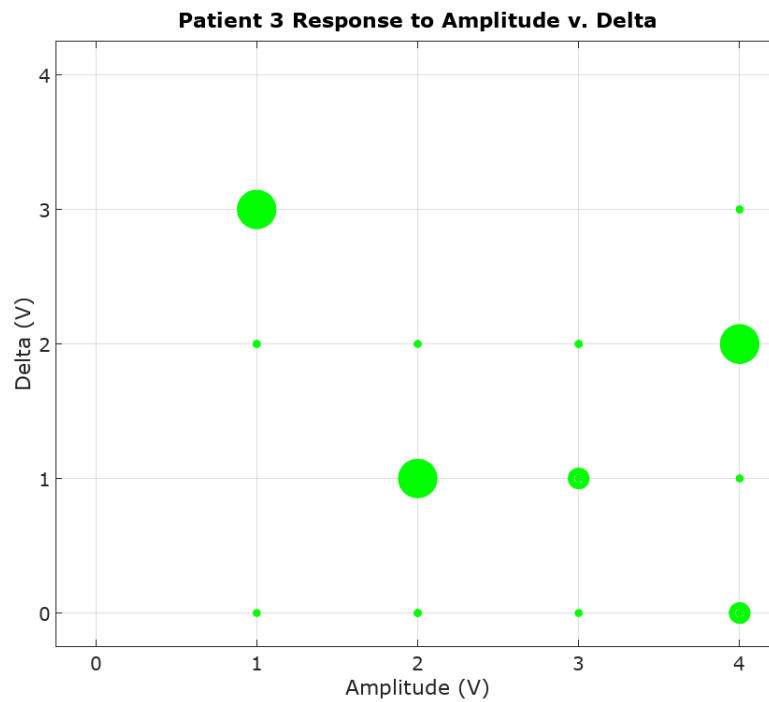


Figure 5.11: UW Patient 3 Perception of Final Amplitude vs. Delta (Amplitude Change)

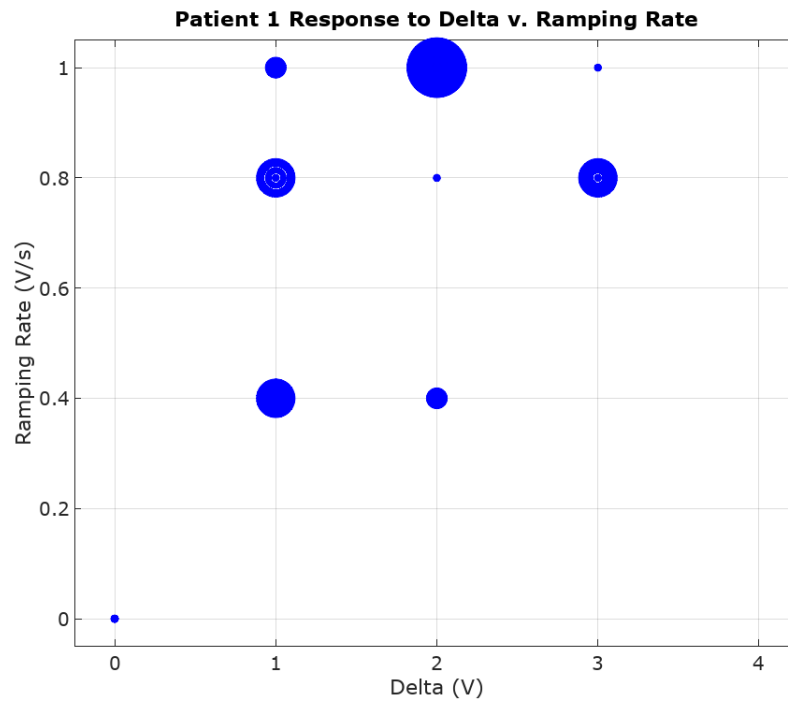


Figure 5.12: UW Patient 1 Perception of Delta (Amplitude Change) vs. Ramp Rate

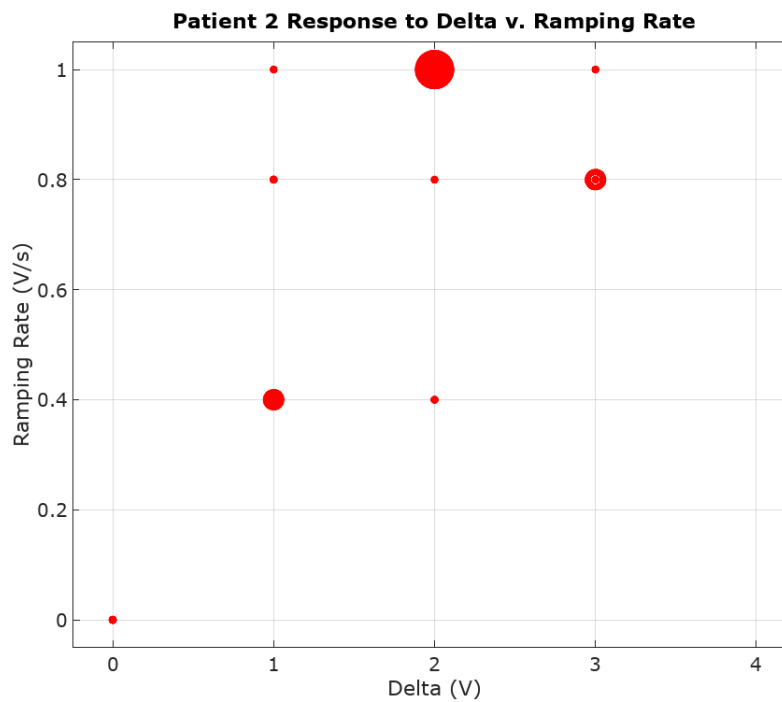


Figure 5.13: UW Patient 2 Perception of Delta (Amplitude Change) vs. Ramp Rate

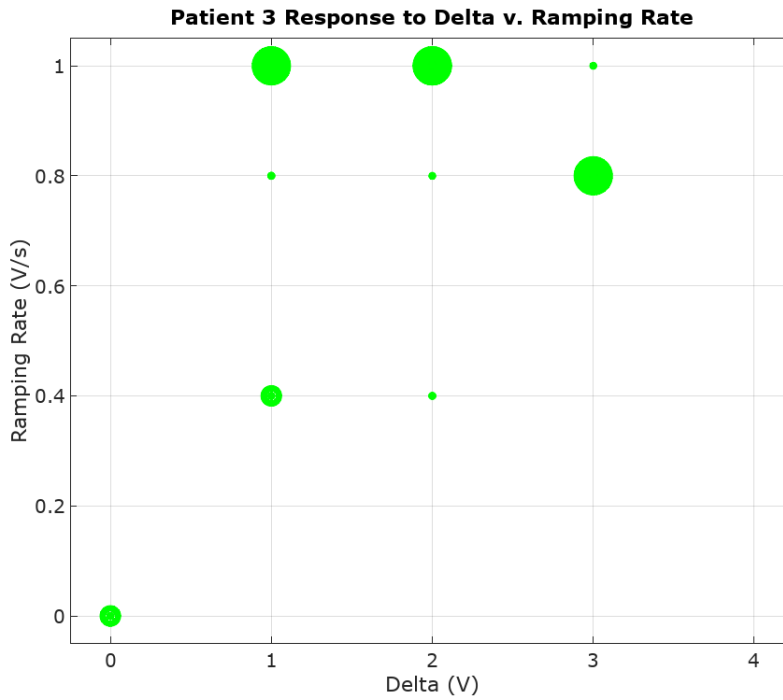


Figure 5.14: UW Patient 3 Perception of Delta (Amplitude Change) vs. Ramp Rate

Patient ID	Control Strategy	Behavior Target Accuracy	Rest Target Accuracy	Total Accuracy
P1	Overt Movement	100%	50%	75%
P1	Imagined Movement	85%	42%	63%
P2	Overt Movement	100%	90%	95%

Table 5.2: BCI task performance for participating patients 1 and 2; Patient 2 did not use the Imagined Movement control strategy due to poor control in preliminary tasks.

5.4 Discussion

Providing individuals with DBS for movement disorders a BCI for control of their stimulation levels could improve their ability to balance symptom and side-effect management, especially in cases where involuntary biomarkers are unavailable or patient preferences may be context-dependent. Such a system also has ethical implications for concepts such as user agency or autonomy as compared to prior, involuntary CLDBS systems. My research is the first step in investigating feasibility and design considerations for BCI-controlled DBS systems.

Towards the goal of understanding how a BCI-controlled DBS system might be implemented, I have worked to design and evaluate a number of necessary subsystems including (1) the control method that an individual would use to update stimulation parameters, (2) the feedback types that an individual receives during operation of the system to inform them of stimulation state, and (3) the type of task that is used to evaluate the system in a clinical setting.

5.4.1 Control Methods for BCI Operation

The first subsystem that I examined was how individuals with BCI-controlled DBS systems might exert control—that is, what mental strategies they might use to alter their brain activity in a perceptible way. Given the placement of cortical electrodes in the hand/arm area of the motor cortex, signals related to overt movement of the contralateral upper limb were easily distinguishable from periods of rest. Furthermore, this sort of activity was distinguishable as power changes in the frequency spectra of these recordings, making them potential candidates for fully embedded processing given capabilities of systems such as Nexus E. Nexus E can only operate classifiers that use power channels, or those that sum power in certain frequency bands. Therefore, using control signals that leverage frequency-domain features increase the ability to transition these systems out of clinic in the near future.

All patients were able to use overt movement of the limb contralateral to the implanted ECoG electrodes to create differentiated outputs for volitional control. This strategy aligns

with the signals we have previously used for involuntary CLDBS for ET. While this demonstrates that a volitionally-controlled BCI can be developed, using overt movement as a control strategy has multiple complications. Regardless of intention, patients would not be able to use their affected limb without triggering stimulation changes, effectively triggering false positives and giving them no way to turn the system off while engaging in activity. Furthermore, patients may want to turn their system on without having to physically move their limb. For these reasons, a control strategy that is distinct from common activities—reducing the risk of false positive triggers—may be desirable. However, given these results, attempted or actual overt movement may be a more promising control strategy for ECoG-based BCIs for other applications, specifically individuals with spinal cord injury.

For our system, other control strategies were limited in their success. For example, motor-imagery is commonly attempted as a control signal for SMR-based BCIs [89] [103]. Our patients found motor-imagery to be challenging to execute; some patients showed no differences in computed PSD between motor-imagery cases and rest, and those with observable differences were smaller than for overt movement. Speech was also attempted as a control strategy with a subset of patients, also with mixed success.

Ultimately, electrode placement and available recording configuration will likely drive which control strategies are available for BCI-controlled DBS systems. Placing electrodes in motor areas as with our system will leverage overt motor control strategies. Future research could examine placement of control electrodes in other locations, such as prefrontal cortex [141].

5.4.2 *Feedback from DBS*

I explored how patients perceive thalamic stimulation and how it might be used as a novel BCI feedback mechanism. Patients are aware of changing stimulation amplitude, such as when stimulation is initially turned on or if amplitude is increased. This awareness is perceived through an unnatural tingling sensation known as paresthesias, which are typically transient and disappear a few seconds after the end of stimulation ramping.

Perceived paresthesias varied in location of perception across patients, likely due to differences in implanted electrode location and programmed stimulation leads. Our single patient with monopolar stimulation also had a notably different experience of paresthesias at far lower thresholds than patients configured with bipolar stimulation. Monopolar configurations typically have lower therapeutic impedances than bipolar stimulation, meaning that at a given stimulation voltage more current will be delivered for monopolar configurations [6], which likely influences the strength of paresthesias experienced.

A design challenge for BCI-controlled DBS systems will be that stimulation does not provide perceptible feedback during all phases of operation. The fact that many patients only perceive their stimulation during ramp-up periods could leave them without knowledge of their stimulation settings during constant stimulation periods or when stimulation is ramping down.

Additionally, the paresthesias received from DBS (which I have here leveraged as a type of feedback for a BCI system) have traditionally been reported as a side-effect of DBS in their own right. As with other CLDBS systems, concerns may be raised over whether patients will tolerate frequent paresthesias during system operation, even if the paresthesias are providing a form information about system state. From self-reports, some patients have very limited tolerance for paresthesias and would not be willing to use such a system on a day-to-day basis. Other patients I queried did not appear to mind paresthesias in our clinical test setting, but further testing will be needed to determine whether they would tolerate such a system when deployed out-of-clinic.

5.4.3 Performance During Cursor Tasks

My research demonstrated that, in principle, implanted DBS systems with cortical sensing electrodes can be used for chronic BCI use. While this demonstration was achieved using a visual-feedback BCI task with Nexus D3 for streaming to an external computer, the classifier was simple enough to be run on existing embedded computation using Nexus E. Provided that a feedback mechanism can be determined, there is no reason that patients could not

control a BCI using the implanted cortical electrodes presented with this system.

The BCI task used was an intentionally simple, one-degree of freedom cursor task. For the purposes of future stimulation control, this task structure should be sufficient given that CLDBS approaches typically only aim to control one parameter, for example stimulation amplitude. However, future work could focus on creating a more engaging task, or one aimed specifically at effective training, especially for patients who experience difficulty.

5.4.4 *Future Work: Realizing BCI-Controlled DBS Out of Clinic*

A major limitation of my experimental setup was the single time-domain ECoG channel which we were able to stream. Most BCI systems—especially those that leverage ECoG for a signal source—rely on multiple channels and exhibit better performance in terms of accuracy and specificity than we were able to achieve [112]. However, given that we have demonstrated proof of operation using a single channel, future work ought to strive for improving on our system with increased channel count. Such an improvement is already within reach using systems such as the Nexus E from Medtronic.

Beyond the ability to leverage the existing four contacts of our system, future work could explore the possibility of using larger (or multiple) cortical electrode strips. Acute ECoG experiments with epilepsy patients often have larger grids electrode grids, but such grids have not been tested chronically in human subjects. Increasing spatial coverage could improve the likelihood that an individual patient could operate a BCI system by increasing the number of control methods.⁶ Using our implanted system, if patients are not skilled at generating hand/arm motor signals on-command, they would be much less likely to perform well on our BCI task due to the placement of our electrodes.

Ultimately, future work in the realm of BCI-controlled DBS must strive to demonstrate successful performance on natural or unstructured tasks such as writing or eating both in and out of clinic. As with BCIs for other applications, demonstrating accuracy on highly

⁶From an exploratory standpoint, increased spatial coverage may also create opportunities for discovering novel biomarkers for non-motor side effects such as difficulty speaking.

structure cursor tasks does not guarantee good performance during continuous unstructured use. Additionally, issues such as inconvenience or fatigue may not present themselves in clinical settings but may quickly render our systems useless out of clinic. I will discuss different approaches to BCI usability in the next chapter, which certainly have applications to this system. While I have had the opportunity to explore and characterize a few aspects of a BCI-controlled DBS system, additional research and development will be needed to move from these first principles to a functional, clinically-effective treatment on par with existing DBS therapies.

Chapter 6

CRITIQUES OF BCI ILLITERACY

Brain-computer interfaces (BCIs) have garnered attention as a potential communication and control interface for individuals with a variety of health conditions, including spinal cord injury, stroke, and autonomic lateral sclerosis (ALS). They are also attractive for commercial applications such as gaming, monitoring personal behavior, and more. BCIs are a general term for technologies that measure a user’s brain activity in order to perform a task. Examples of BCIs include robotic arms controlled by a user’s intention to move, “spellers” that allow individuals with locked-in syndrome to select letters to complete words or phrases that they wish to communicate, and monitors that measure brain activity and provide feedback to promote relaxation. Many BCIs rely on the user being able to voluntarily alter their brain activity in order to differentiate between a discrete menu of options (such as 26 letters on a keyboard) or a continuous range of outputs (such as the range of positions that a robotic arm might take, or a users level of stress).

Under the umbrella of BCI technology, there are different neural mechanisms that may be used as a control signal. For example, in sensorimotor rhythm (SMR) based BCIs, users may imagine moving a limb in order to generate predictable changes in spatial and temporal oscillations of neural populations in their motor cortex. An algorithm that has been calibrated or trained to recognize changes in these recorded signals then triggers a response based on recognition of the user’s brain state. In another example, a P300 BCI may be constructed to utilize a response to an unexpected or “oddball” stimulus that the user is focusing on. This response is a positive amplitude peak that occurs approximately 300ms after the presentation of the stimuli—hence P300. By knowing when an oddball is presented and when the P300 is sensed, the BCI can determine what the user was focusing on. BCIs

can be constructed from other predictable neural responses to auditory, visual, tactile, and other stimuli.

Despite advances in many aspects of BCI performance, a subset of potential BCI users are unable to operate some or all types of BCI despite undergoing the same training as successful users. This phenomenon has been termed BCI illiteracy and framed as a trait possessed by BCI users who do not reach a certain level of performance. Many researchers engaged in BCI research have applied the concept to subsets of users in their respective BCI studies [5] [71] [91] [101] [2] [61] [126] [21] [151] [120]. Some researchers claim that BCI illiteracy affects between 15-30% of people who attempt BCI use, regardless of the type of BCI used [13].

The implications of categorizing users as BCI illiterate may not be initially apparent. It may seem that BCI illiteracy is a benign descriptor of poor performance or even a helpful way to categorize users. However, in using BCI illiteracy as a concept, BCI researchers face a number of scientific and ethical challenges, the outcomes of which stand to directly impact BCI users and the progression of BCI research and development. In this chapter, I argue that BCI illiteracy is an inadequate concept for explaining many cases of poor user performance in BCI systems. The concept of BCI illiteracy relies on poor assumptions and fails to consider key aspects about BCI systems and their relationship to their users.

After reviewing current definitions and examples of BCI illiteracy, I discuss why researchers employ the concept of BCI illiteracy. I then consider how BCI researchers seem to employ the concept of BCI illiteracy (1) to categorize users as poorly performing or “illiterate”; (2) to consolidate groups of users labeled as illiterate so as to study and identify shared causes of poor performance; and (3) to design and implement ways to improve BCIs for users labeled as illiterate. In examining this three-part process, I describe how users are labeled as BCI illiterate in practice, including how proficiency standards are created and justified in BCI studies. I review cited causes for why users might perform poorly on BCIs, including both physiological and skill-based contributors to poor performance. I highlight how the concept of BCI illiteracy places responsibility for the deficiency in BCI system performance on the user rather than the BCI platform. I discuss how researchers have attempted to

use BCI illiteracy to improve BCI design. Lastly, in light of these considerations, I propose improvements and alternative concepts to BCI illiteracy for researchers seeking to improve the process of BCI research.

6.1 Definitions of BCI Illiteracy and Notes on Terminology

BCI illiteracy is a proposed condition wherein users of BCI technology fail to reach proficiency in using a BCI in a standard training period. Through their experience across a variety of BCI studies, researchers estimate that 15-30% of BCI users could be labeled as BCI illiterate [13] [142]. Such difficulties are seen across multiple BCI types that rely on different neural signals; in fact, it is possible for an individual to be considered BCI illiterate with one form of BCI while being able to reach proficiency on another [4]. BCI illiteracy as a concept relies on comparing the performance of an individual user to a norm which may vary with each BCI system. These norms have two key features. First, the norm sets a performance threshold representing proficiency. Second, the norm sets a finite time period during which users are expected to reach proficient performance. Users may be classified as illiterate if their performance with the BCI does not meet this norm: they do not reach a certain level of performance, or they do not reach it fast enough within the confines of the study and its training period.

In light of the norms used to determine how users are labeled, discussing BCI illiteracy often encourages the use of normative terminology towards prospective users, such as proficient or successful users in contrast to deficient, unsuccessful, or illiterate users. As I critique the concept of BCI illiteracy, I strive to separate myself from such normative phrasing, as the norms used to define BCI illiteracy are themselves encompassed in my criticisms. However, at times this language is difficult to avoid; when I use such terms, I mean them relative to and entangled with existing norms used in BCI research rather than as independent, self-sufficient categories.

The term BCI illiteracy evokes comparisons between learning to use BCIs and written or

spoken language acquisition¹. To avoid conceptual snares in how BCI use may or may not relate to language acquisition, some researchers have chosen to use the terms BCI inefficiency, BCI aphasia, or normative descriptions of performance [4]. My criticisms of BCI illiteracy relate to the concept and its function in BCI research rather than the particular terminology used. I will continue to use the phrase BCI illiteracy, as it is by far the most popular of these terms, but from this point forward my arguments will apply to any concept similar to BCI illiteracy regardless of the specific terminology used.

6.2 Motivations for Categorizing Users as BCI Illiterate

To my knowledge, BCI illiteracy has not explicitly been defended as a helpful concept in the field of BCI research, but neither has it been challenged by BCI researchers. Potential benefits to using BCI illiteracy may be outlined through consideration of how researchers apply the concept in their research processes. Researchers want to identify which users perform poorly on their BCIs, understand why they perform poorly, and determine how they may alter their BCIs in order to improve performance. Currently, using BCI illiteracy as a paradigm, they may identify which users perform poorly by labeling these users as BCI illiterate relative to a certain proficiency norm; they may examine groups of users labeled as BCI illiterate for explanations or commonalities of why these users performed poorly; and they may make modifications to the BCI system (including hardware, software, and training protocols) in an attempt to improve performance for those users².

Researchers may want to group users who they label as illiterate in order to examine the commonalities between these users and to highlight the differences between users who operate their BCIs as intended and users who do not, thereby informing how researchers may best improve their BCI systems. For example, a group of users labeled as BCI illiterate when using a P300 BCI system may all be unable to generate a typical P300 signal like

¹A more detailed discussion of the similarities or differences between BCI skill and literacy, and the accuracy of such terminology, is provided in [4].

²Individual BCI researchers may not go through all of these steps—some just stop at labeling, some only propose to design BCIs for illiterate populations, etc.

successful users. In this case, efforts to improve signal-processing algorithms to identify P300 peaks may be misguided, since the critical content (the P300 peak) is missing from the recorded signals. A better solution may be to use a different type of BCI which relies on a fundamentally different neural signal phenomenon that the user is capable of generating. This example demonstrates how researchers may want to employ BCI illiteracy as a tool to identify causes of poor system performance and produce tailored solutions to address those causes.

In addition to understanding why some users do not fit well with BCI technology, using BCI illiteracy in a predictive sense could identify BCI users who would likely perform poorly and prevent them from receiving devices or systems that they are unable to use. Imagine a scenario where a potential user is prescribed a BCI by their clinician, but upon receiving the device and going through a traditional training protocol they are unable to use their device reliably. This scenario becomes more disturbing if the recipient had to undergo a costly or risky surgery in order to receive their ineffective device. Using the concept of BCI illiteracy may seem in this light to be an explanatory or even preventative measure to avoid pairing users with devices and systems they could not successfully operate. This use of BCI illiteracy would seem especially effective if there were ways to screen patients for this characteristic ahead of time. Several studies have already been undertaken to develop predictors of BCI illiteracy [3] [2] [13] [126], though there is currently no definitive way to screen for any type of BCI illiteracy on a patient-by-patient basis.

While employing BCI illiteracy as a tool in BCI research may sound straightforward, I argue that multiple challenges arise from how the concept is framed and used in practice. Prior work by Brendan Allison and Christa Neuper (in their chapter “Could Anyone Learn to Use a BCI?”) identifies multiple issues with BCI Illiteracy, including inconsistent thresholds for proficiency, poor differentiation of the numerous causes for poor BCI performance, and more. They have taken these issues as opportunities to make BCI illiteracy more rigorous as a category, for example by producing standards for proficiency levels and outlining categories of causes of illiteracy [4]. I will counter that there are more fundamental issues at play in

the way that BCI illiteracy is used. Specifically, BCI illiteracy relies on the assumption that prospective users ought to be able to use a given BCI system. In cases where they are unable to operate a BCI system, labeling these users as BCI illiterate clearly places the locus of deficiency on the user. BCI illiteracy reflects and affects the way that we design BCI systems, and it may be misguided to approach it as a well posed idea that needs only to be standardized. Instead, we ought to critically examine the way that the concept of BCI illiteracy affects the BCI systems that we produce and consider alternative concepts that may better serve a wide variety of BCI users.

6.3 Labeling Users as BCI Illiterate

In the BCI research process, the first step at which BCI illiteracy is often employed as a concept is in the identification or classification of users who are not compatible with the BCI system. A user might be labeled as BCI illiterate after participating in a BCI study if their performance was not considered proficient on that particular BCI system. As outlined above, proficient performance is a norm with two components: an accuracy level that users are expected to achieve, and a finite window (generally the length of the experiment) within which users are expected to achieve this accuracy.

The way that this norm is determined remains largely unjustified in BCI studies and, as noted by Allison and Neuper, may be inconsistent between studies [4]. To verify that they are in fact exerting control over the BCI, users are expected to perform above chance accuracy; beyond this criterion, the choice for proficiency thresholds may in reality be relatively arbitrary. For example, in a two-target task where chance accuracy is 50%, the level for proficiency (and the distinction between proficient and illiterate users) may be cited as 60% accuracy [46] or 70% accuracy [83]. The decisions for these thresholds are made by researchers but are not necessarily justified when results are presented. The McCane study, which demonstrated a communication BCI for ALS patients, set their proficiency threshold at 70%, citing a prior source that this was necessary for “acceptable communication”; yet the previous study only noted that “while accuracy levels less than 60% provide substantial

bits/selection, the time needed to produce useful communication might be unacceptable” [115]. Other studies do not provide any overt justification for their performance thresholds and may instead rely on trends from other research studies.

Manipulating proficiency thresholds, for example from 60% to 70%, can substantially change the population of users labeled as illiterate. Allison and Neuper examine one such case:

[one study] refers to the 6.7% of subjects who attained less than 60% accuracy in a two-choice ERD task as ‘marginal.’ The article assumes that the 93.3% of subjects who attained better performance would be effectively literate. Had a threshold of 70% been used instead, the number of ‘marginal’ (aka illiterate) subjects would have increased to 48.7%. [4]

Without explicit justification, the researchers chose a proficiency threshold that portrayed the number of illiterate users as similar to, or even less than, other studies. While a careful reviewer might question the 6% proficiency threshold, 6.7% failure rate sounds like a mostly-good BCI that only fails a few users; on the other hand, a 48.7% failure rate sounds like a design flaw in the BCI that would be difficult to attribute to users.

Recent work in metrics for evaluating BCI performance has looked for methods of comparing performance more effectively across studies [132]. These efforts would seem to answer criticisms such as those raised by Alison and Neuper that the thresholds used for BCI illiteracy are not standardized across studies [4]. But I argue further that standardized thresholds, while important for comparisons, are not enough. In addition to being standardized and among other possible criteria, performance thresholds should be justifiable; researchers ought to be able to support, beyond simple comparisons to chance accuracy, why they believe that level of performance is necessary.

Justification for performance thresholds could be derived directly from the users that BCIs are expected to serve. Notably, user input on this aspect of BCIs is almost entirely absent. The accuracy levels chosen for proficiency are not explicitly validated as acceptable to BCI recipients, just as lower accuracy values have not clearly been deemed unacceptable. Depending on the recipients in question—whether they are able-bodied, familiar with

technology, etc.—the desired level of accuracy may vary. It may not be possible to find a universal standard for performance, but understanding the differing needs of various user populations could improve efforts to produce specialized BCIs.

Aside from direct user input, proficiency levels could be drawn relative to alternative existing solutions that BCIs are meant to augment or replace. There are few existing comparisons of desired performance levels—in terms of communication rate, accuracy, ease of use, etc.—between BCIs and other systems. For example, BCIs for communication could compare communication rates to manual selection systems for individuals with locked-in syndrome. Until a justified standard for acceptable performance—which may vary depending on the BCI system, the use case, and the user population in question—is determined, the performance thresholds set by BCI researchers remain speculative.

We may consider the impact of BCI illiteracy as a classification mechanism on two separate scales: that of individual users and that of populations of users. For individuals, there is currently little consequence for being labeled as BCI illiterate outside the confines of the research study. Users may not even be explicitly aware of their label, as these terms may be applied only in summarizing the results of the study. It has been noted in some studies that users who experience difficulty in operating a BCI system wanted more time to become proficient in using that system [45]—that is, they commented on one aspect of the norm being used to determine literacy. The impact for individual users could change as BCIs become more prevalent, or particularly if screening measures for BCI illiteracy were used in practice in determining who receives a given BCI. If BCIs are used more frequently by the general public in the future, then individuals who cannot receive a usable BCI may be separated from important resources that others could commonly access including assistive devices for communication and control, entertainment opportunities, and more.

Beyond the problems posed by classification for individual users, the process of labeling populations of users as proficient or deficient has implications for future BCI research efforts. Because proficiency thresholds determine which users will be identified as BCI illiterate, researchers using poorly justified thresholds may reach specious conclusions about populations

of BCI illiterate users. This process is in its early stages, but some researchers have undertaken efforts to study how demographics such as age, gender, and other factors correlate with BCI performance [4]. Although BCI illiteracy predictors may be implemented with the intent “to avoid the frustrating and costly procedure of trying to establish BCI control” [13], issues of representation could arise in future BCI studies depending on how such demographic correlations are used. Studying user groups who experience difficulty using BCI systems is a good undertaking, but researchers should think carefully about how they define this group of users so as to avoid missteps in identifying supposed causes for poor performance during BCI use, and how they use this information to influence representation in BCI studies.

6.4 Identifying Causes of Poor User Performance in BCI Systems

A subsequent function for BCI illiteracy as a concept may be to attempt to identify common traits—so-called causes of poor performance—in users who have not successfully operated a given BCI system. Once a group of users has been identified who fall below the performance norm for a given system, researchers are interested in understanding what characteristics of these users may have contributed to their performance. Analyzing features of these users collectively may seem to aid in identifying relevant correlations. If there are three users labeled as illiterate in a study, for example, each user may share a single trait that was linked to poor system performance in all three cases, or they may have a diversity of reasons why the BCI system was unsuitable for them. BCI researchers wish to understand causal traits (which they presume the users to possess) that result in user performance below their study’s threshold.

In grouping and studying users labeled as illiterate, researchers may suspect these users to share causal traits. But these users may only share in common the ratio between their performance and the proficiency threshold set by researchers. If this ratio doesn’t track some phenomena in the user or some feature of the interface, it is hard to justify its use at all. Information developed around shared traits of these poorly performing users—predictors and screenings, underlying neuroscientific attributes, and more—would then seem suspect.

To illustrate possible categories of causes for poor user performance during BCI use, it is helpful to return to the two examples of BCIs mentioned earlier. In the first example, SMR BCIs, the individual may be asked to move or imagine movement in a specific limb. A user lacking the specified limb may or may not be able to generate the desired signal, depending on the robustness of their memory of the experience of moving their limb. But able-bodied individuals may still not generate the correct signals to control SMR BCIs; imagined movements can be difficult to train someone to execute given that the experience is relatively subjective. Even the aspect of movement being imagined matters, such as whether you are imagining visually (what it looks like to move) versus kinesthetically (what it feels like to move), imagining your own body or a generic body, etc.³ [89]. It may be hard to disentangle whether the user simply needs a different set of instructions to help them learn the task, or if a more fundamental difference in their neurophysiology is the cause.

We can also consider the second example of P300 BCIs. The user views images (in many cases alphabet letters) as they are varied in an attempt to evoke an expected signal, the P300. Users who have visual impairments would clearly not be able to use such a BCI; similarly, a user with attention deficits may not focus on a letter long enough to generate a P300. But these users are unlikely to be classified as BCI illiterate; they would likely have been excluded from joining the study in the first place. This is due to the obvious, known mismatch between the user's apparent capacities and the requirements of the interface; prior to engaging with the BCI system, researchers could likely predict that these users may experience difficulty. It may be similar to expecting someone whose limbs are paralyzed to operate a standard automobile—an unmodified, commercially available car is clearly and predictably not designed for that person's needs.

Barring the subject's inability to view or focus on the task at hand, it is possible that their brain simply does not respond to the stimuli in the expected way. For example, approximately

³Neuper et al. found that imagining movement kinesthetically rather than visually resulted in more consistently localized spatial patterns in cortical signals [89].

10% of subjects⁴ do not produce a robust P300 signal [4]. These are the users who would likely be classified as BCI illiterate, because there is no anticipated mismatch between their known capacities and the design of the interface. Furthermore, until it is determined that the user in this case cannot produce a P300, there are no obvious differences between users labeled as illiterate and those who are able to operate a BCI. Given that P300s are not generally measured apart from use in specific BCIs, the user likely would have no way of knowing that they did not produce a P300 signal until they were asked to engage in a BCI task that uncovered this feature.

The described state of BCI illiteracy is actually a label for a number of underlying causes. There may be physiological causes, like a fundamental mismatch between the users' capacities and the requirements of the BCI interface. This mismatch may be obvious, such as when an individual is blind and the BCI system uses a visual interface, or it may be less obvious, such as when a BCI system uses P300 signals but a user does not generate such signals. Aside from a decisively physiological cause, a user may not acquire the necessary skills to operate the interface if the control method is challenging or cognitively taxing, or if the training protocol is not effective. In the following subsections, I will explore these causes in more detail in order to call into question certain intuitions and assumptions underlying BCI illiteracy which have not previously been examined by researchers who employ it as a concept.

6.4.1 Physiological Causes of Poor Performance

As I have illustrated, some cases of user difficulty which have been labeled as BCI illiteracy may stem from a mismatch in the user's physiology and the demands of the BCI system. We could call this group of causes neurophysiological. A neurophysiological cause of BCI illiteracy would be one where, for a given patient, the BCI system is incapable of detecting the appropriate neural signals for reasons that may or may not be obvious to researchers.

⁴These subjects are described as “seemingly normal”—that is, they have no apparent difference in cognitive function as compared to subjects who do produce a typical P300 signal.

An intuitive distinction is that, regardless of the effort or skill exerted by the user, they are theoretically incapable of operating that BCI (either temporarily or permanently).

Users who would likely be labeled as BCI illiterate—who have been included in a BCI study because they have no obvious excluding impairments—are not immediately differentiable from successful users based on obvious external physical or cognitive symptoms. When BCI illiteracy is employed as a label, it is often the case that we do not have a good explanation for why the BCI in question did not work for a subset of users. The differences in brain structure that could lead to BCI illiteracy may not be to the extent that they inhibit other functioning. For some individuals, their brain signals may be difficult to read through their scalp, for example if the relevant neural populations are located in folds of the brain (sulci) where surface electrodes cannot record from [4]. A noninvasive BCI which relies on recording signals from the scalp would likely not provide a usable interface for such users. Such physiological differences may only be discovered after a user has enrolled in a BCI study and has failed to achieve proficiency on a BCI. Furthermore, it is possible that such physiological differences would only be discussed theoretically and never verified on a user-by-user basis.

Physiological contributors to poor performance in a BCI system are not necessarily permanent features of the subject. One simple example of how users can move in and out of the category of BCI illiteracy is to consider how transient factors, such as changes in attention level, fatigue, or frustration [88], or social factors, such as emotional responses, interactions, and social cues experienced during BCI training or use [116], may cause a users brain signals to change such that they operate their BCI less successfully. Such confounding factors are often referenced as reasons why BCIs that have been tested successfully in a laboratory setting could fail to work as well when tested outside of a controlled environment in the “real world.” There is no guarantee that the individual labeled as BCI illiterate would be unable to use the same BCI on a day when they have altered their caffeine intake, had more or less sleep, or somehow altered their activity in another way. These effects are not necessarily reflective of some permanent, deficient state on the part of the BCI user. Similarly, there’s no guarantee that a proficient user may not later exhibit an illiterate level of performance.

An individual with a progressive disease may be prescribed a BCI that they can initially operate, but later lose the ability to use it with proficiency because of changes in their mental or physical health.

BCI illiteracy has not been constructed to handle these transient factors, and researchers who wish to maintain their use of the concept will need to clarify how they are labeling their users with respect to temporary changes in their performance levels. Are users labeled as BCI illiterate during the hour after they have had a coffee, but not other hours? On days when they have had too little sleep, but not other days? Can previously proficient users suddenly acquire the label of illiteracy? Answers to such questions regarding transient factors that render a user more or less literate could impact the way that we conceptualize problems in BCI design.

6.4.2 Non-Physiological Causes of Poor Performance

Suppose researchers cannot find a temporary or permanent biological explanation—in brain structure or function—to explain a user’s poor BCI performance. In this case, the user is theoretically capable of controlling the BCI, but may lack the skill needed to operate the system or they may not fully understand the instructions given by researchers. Researchers may then turn to factors such as training protocols, user effort, and other non-physiological contributors that could explain deficient performance.

Research in the field of BCI supports the idea that many instances described as BCI illiteracy may be due to the structure of current BCI training protocols. In a recent study, researchers asked individuals to perform a simple, non-BCI motor task (drawing circles and triangles on a tablet screen). The training approach that participants were given to learn the task were designed to mimic those given in most BCI studies; for example, training schemes were not adapted to individual users and users were given limited autonomy in their own training. Their study found that, even in the case of a simple motor task which participants were theoretically capable of executing, approximately 15% of participants who were physically capable of performing the drawing task did not successfully learn to draw

circles and triangles that the system could differentiate at desired times [59]. This percentage is similar to the ratio of individuals who fail to reach proficiency in BCI tasks with similar training schemes, suggesting that the training protocols (rather than some complexity of the BCI system) may contribute to instances of BCI illiteracy.

In addressing the shortcomings of BCI training schemes, Lotte et al. references specific training literature to understand how to improve BCI training protocols. For example, current BCI systems may only show a user whether they have successfully hit a target (whether their signals were accurate) with no feedback about how they might improve their control efforts (for example by imagining a different type of movement, imagining a different sensation, etc). Instead, feedback should explicitly inform the user how to correct their output signals, rather than just whether their signals were accurate. Further, goals should be explicitly stated; the user's goal, when clearly stated, may be to generate brain signals with certain qualities or characteristics rather than hit a target with the cursor [79]. Improved BCI training schemes should be of particular interest to BCI researchers because they could increase the number of users who are able to reach proficiency without the need for costly improvements to hardware or signal processing.

Intuitively, when considering contributors such as training protocols or user effort, it may be helpful to compare BCI skill acquisition with how individuals learn to use other new technologies. Labeling users as BCI illiterate may reflect an erroneous assumption that current BCI systems are optimized to be simple to learn and use. BCI is a relatively young technology that in most cases is unintuitive to learn. Other emerging technologies were also unintuitive to learn when they were first commercialized, such as automobiles and computers. For example, examining the case of early automobiles, Car and Driver lists the steps to start a Model T as

1. Pull the choke adjacent to the right fender while engaging the crank lever
2. Get into the car. Insert the ignition key Adjust the timing stalk upward and pull back on the hand brake
3. Return to the front of the car. Use your left hand to crank the lever... (if the engine backfires the left arm is less likely to be broken). [20]

Whereas early automobiles required a complex and possibly dangerous series of tasks to start and were regarded as unreliable, modern models have been redesigned such that they can be started with actions as simple as the turn of a key or even the press of a button. In addition, efforts were made to improve how individuals learned to operate their cars. While original automobile drivers had to learn to operate their vehicles from either the seller or a written user manual, modern naïve automobile operators may take Driver’s Education courses which are regulated by the government to ensure a quality curriculum. Returning to the case of BCIs, it is presumptuous to believe that current BCI systems are inherently intuitive to use or that we have designed the best possible training protocols. Instead, researchers ought to acknowledge that today’s BCIs may be similar to original automobiles in their relative level of complexity of operation.

6.4.3 Challenges in Inferring Causes from Users Labeled as Illiterate

Current approaches by BCI researchers to develop a body of knowledge regarding causes of BCI illiteracy, methods for illiteracy prediction, and solutions for the condition, could be referred to as the biologization of BCI illiteracy as a descriptive category. We could understand the category “BCI illiterate” as a human kind described by Ian Hacking; it is a socially constructed category for sorting humans around which we might try to develop knowledge. Hacking describes a common push to biologize these socially constructed human kinds for example, scanning criminals to research what brain activity is correlated with violent or criminal tendencies [48]. Language surrounding BCI illiteracy reflects the process of biologization, such as the paper titled “Towards a cure for BCI illiteracy,” implying that BCI illiteracy is a condition to be treated and cured [142]. Research in this vein implicitly assumes that there are underlying user features, whether structural or functional, to be discovered that will explain BCI illiteracy—although such features may not exist. If such features could be identified, researchers would aim to develop fixes that address the underlying features in order to improve existing BCIs or create new BCIs that are better suited to the problematic variations in physiology.

Developing a body of knowledge around the perceived condition of BCI illiteracy poses a challenge. In the creation of knowledge about BCI illiteracy, researchers study a sample of users that have been labeled as BCI illiterate. This labeling occurs through interaction with an imperfect BCI system, including comparing the users to a proficiency threshold which may not have been determined from a compelling basis. Even if the performance threshold is well justified, the process of identifying user traits based solely on the correlation of a performance metric is ill-defined, especially if those traits are only transient. Understanding the causes of BCI illiteracy is difficult because the inclusion of users under such a label is messy even with rigorous performance standards.

6.4.4 Challenges in Framing the Cause of Poor Performance

In addition to relying on questionable methods for gaining understanding of user populations, BCI illiteracy as a concept relies on the assumption that the user “owns” the problem of poor performance. I am not the first BCI researcher to notice these implications. For example, Allison and Neuper note that, “it is also unclear whether ‘BCI illiteracy’ reflects a failure on behalf of the subject or BCI, and whether this distinction is meaningful,” but also acknowledge that from a framing perspective, “‘BCI illiteracy’ implies that failure to use a BCI results from inadequate effort by the user, which is generally not true some subjects could never learn to use a particular BCI” [4]. Yet even if we claim that BCI illiteracy is not meant to blame the user for poor performance, the reality remains that BCI illiteracy is a label applied to the user rather than the BCI system. The locus of deficiency, regardless of intention, is placed on the user.

This distribution of deficiency is not novel; it mirrors a similar the conflict between medical and social models of disability. These models pose two alternative frameworks for the “locus” of disability as well as proper responses to perceived problems. As philosopher Anita Silvers explains,

...the medical model takes disability to be a problem requiring medical intervention—
and as both the prerogative and the responsibility of medical professionals to fix—the

social model understands disability as a political problem calling for corrective action by citizen activists who alter other peoples attitudes and reform the practices of the state. [122].

That is, the medical model of disability assumes disability to be a trait possessed by the disabled individual. The social model views disability as a societal factor resulting from a mismatch in an individual's abilities and the environment that they must interact with. If we adopt a medical-type model of poor BCI performance, where the user possesses some temporary or permanent condition that inhibits them from successfully operating their BCI, then the concept of BCI illiteracy may seem appropriate. This inhibition may be perceived to be biological, such as in the case that users cannot generate appropriate signals at the electrode recording site; or it may be perceived to be cognitive or psychological, such as if they cannot properly follow a training protocol to learn to manipulate their generated signals successfully. If, however, we adopt a social-type model of these same scenarios, then the problem lies in the lack of fit between user and BCI paradigm, not necessarily in the individual user. We could reframe these scenarios and say, instead, that a BCI system is flawed if it failed to meet the needs of its intended users. For example, a BCI may have been designed with inappropriate electrode sites for certain users, or a BCI training protocol may be too complicated for a subset of individuals.

Similar intuitions have been raised in other fields of technological development. Describing their approach towards developing effective security frameworks that required the participation of human operators, the People-Centered Security Lead for the National Cyber Security Centre (NCSC) of the UK recently noted that “if security doesn't work for people, it doesn't work” [23]. In response to problems of framing presented by BCI illiteracy, a similar mentality might be applied to BCI platforms which are meant to serve in assistive or commercial applications. If a BCI doesn't work for its users, it doesn't work.

6.5 Does the Concept of BCI Illiteracy Allow BCI Researchers to Improve BCIs?

A last step in the BCI research process where BCI illiteracy may be employed as a concept is in the improvement of BCI systems. Having labeled a group of users as illiterate, and having studied this group for potential causes of illiteracy, researchers may wish to close the developmental circle by applying changes to BCI systems that “cure” cases of illiteracy. There is not enough evidence in the field of BCI research to suggest that this step of the process happens effectively. Furthermore, taking this approach to improve BCIs is at the sacrifice of alternative approaches, which may result in better outcomes for BCI users.

Practically speaking, the users labeled as illiterate in one BCI study may not be available for a follow-up study in which improved BCIs are tested. Although I have outlined three general steps where BCI illiteracy may be applied as a concept in the research process, often an individual research team is not engaged in all three of those steps. Some focus on design of their own BCI and simply label users who perform poorly within their study (step 1) without further investigating the causes that led to this poor performance; other groups are focused on developing predictors of illiteracy divorced from a particular BCI system (step 2). Thus, assessing whether insights gained from studying illiterate-labeled individuals actually manifest in effective improvements is challenging. Few groups have claimed to accomplish the aim of designing BCIs that reduce the occurrence of BCI illiteracy. As an example, one group applied machine learning techniques to improve performance of SMR BCIs, and noted that these techniques improved performance for illiterate users such that they were above a 70% proficiency threshold [142]. Despite these improvements, the users’ performance levels for the illiterate-labeled group at the end of the study were still below that of users initially labeled as proficient.

In the example above, it is unclear whether the changes made to the BCI designs were driven by an understanding of the needs of illiterate users. It is relevant to consider the relationship between which aspects of BCI design are the most researched versus the pre-

viously discussed possible causes for BCI illiteracy. Surveys of the field have noted that most of the efforts to improve BCI design have focused on changes to signal processing and algorithms and have been implemented through offline studies—that is, those that are run without users [97]. While these efforts may make use of limited face-to-face time with end-users and avoid the challenges of developing novel hardware, they have their limits. Such efforts do not answer highlighted problems with BCI training protocols, and they do not improve the incorporation of other user feedback into BCI design. This disconnect between identified issues contributing to BCI illiteracy and the improvements actually pursued by BCI researchers suggests that knowledge developed from the concept of BCI illiteracy may not be driving real improvements in BCI design.

Ultimately, developing BCIs under the framework of BCI illiteracy not only places the locus of deficiency on the user of the system, it also reflects a research process in which a system is designed by researchers and its effectiveness for users is later assessed. While such an approach does not preclude considering user needs in the initial design of the BCI system, it certainly does not seem to prioritize involving users at all stages of design. Deriving BCI system requirements and metrics directly in partnership with user populations may be preferable rather than from the concept of BCI illiteracy applied after a BCI design has already been implemented. BCI illiteracy is one approach to the goal of developing effective BCI systems, but there is reason to question whether it is the most straightforward or effective approach.

6.6 Alternatives to BCI Illiteracy

Nowhere in the published BCI literature is the idea of BCI illiteracy defended as a valuable way to label potential users. During early BCI studies, as researchers identified groups of individuals who were unable to effectively use their BCI systems, the concept arose organically without explicit consideration for its effects. BCI researchers were simply attempting to explain a phenomenon that they had witnessed in their experiments. Yet the concept of BCI illiteracy as it is currently structured obscures further scientific investigation into

reasons for poor performance in BCI systems. Furthermore, the concept used to explain this phenomenon, whether named “illiteracy,” “inefficiency,” “aphasia,” or others, places the problem inherently on the user of the BCI system. Even if researchers are interested in developing BCIs with better performance, they do so while framing the problem as a trait which poorly performing users possess, rather than framing it as a failure of the BCI system. Further standardizing BCI illiteracy as a category does not address this fundamental problem of framing.

BCI illiteracy is not the only possible approach to characterizing, understanding, and solving problems of poor performance on BCI systems. Rather than using the conceptual framework of BCI illiteracy, researchers could incorporate BCI users throughout the design process so that they help to define the standard to which BCI systems must adhere. One potential paradigm for this incorporation is user-centered design (UCD). UCD focuses on usability, or “how well a specific technology suits its purpose and meets the needs and requirements of the targeted end-users”; in standards for UCD, usability is defined in terms of effectiveness, efficiency, and user satisfaction [70]. In the UCD framework, users would suggest a minimum level of usability which the BCI system needs to meet. By leveraging UCD principles to identify usability as a priority or even as a design constraint—that is, a criterion that a final BCI design must satisfy for a given population—researchers would not leave room for concepts like BCI illiteracy. BCI systems that do not meet a minimum level of usability for their intended users will be revised or rejected as a failure in design rather than a failure on the part of the user. This is not to say that a single BCI must work for all users, but rather that any usability issues stem from limitations in the BCI rather than the users who interact with it.

Although uncommon, this approach to BCI development is not without precedent. Prior work includes studies where researchers used tailored approaches for different subjects, including flexibility about visual versus auditory modes of feedback [114] and flexibility about possible control schemes depending on which was most effective on a user-by-user basis [41]. Other studies simply aimed to design a speller system for “layman use” that offered a simpler

interface than prior spellers [62]. In another example, Kbler et al. applied UCD principles to discuss BCI usability with 19 prospective users. Participants readily provided feedback that could inform performance thresholds, such as “five times faster would be acceptable,” or “with my own AT I can write 90 characters per minute” [69]. These statements provide a kind of justification previously lacking in performance thresholds chosen by BCI researchers. Notably, the studies that take this approach do not make references to concepts such as BCI illiteracy.

A UCD approach does not require a BCI system to function perfectly “out-of-the-box” with no training time or effort on the part of the user. Some users could enjoy learning to use their BCI, provided the training was designed in a way that users found meaningful and fulfilling. As in the case of determining other BCI development priorities, potential end users should be the ones to dictate how much of a “user training burden” is acceptable in a fully designed, commercial BCI system.

A final caveat is that a UCD approach may identify some users that feel other technologies are a better fit for their needs, such as eye-tracking devices for individuals who are not fully locked-in [98]. BCI researchers ought to be frank about the limitations of their technologies. BCIs, especially those that are fully implanted, are currently an expensive technology that may be inaccessible to many potential users. Wearable, noninvasive BCIs are generally less effective, or users may find them inconvenient or embarrassing to use in public. Under a UCD approach, it is especially critical that potential recipients of assistive technologies be integrated in the design process from the very start to ensure that we produce BCIs not just because they are an impressive technology that researchers feel potential users should want, but rather because they are serving a need.

6.7 Beyond BCI Illiteracy: Guidelines for Improving BCI Research Efforts

If we were to move away from concepts like BCI illiteracy, how would our research processes change? Recent efforts to incorporate UCD approaches into BCI research align intuitively with the idea of reframing the BCI system as the locus for improvement. BCI requirements—

necessary accuracy and speed of communication, ease of calibration and training, comfort and required effort, etc.—would be driven directly by user needs, and systems that did not meet these needs would be seen as deficient. These approaches have only been applied in a handful of studies [62] [41] [114] [69], and much remains to be discovered about how we might improve our incorporation of users throughout BCI development. Even the process of eliciting such feedback from prospective users with severe impairments such as locked-in syndrome may be an area for research [100]. Researchers may also face challenges in trying to design BCIs to serve diverse populations with conflicting needs, and methods to balancing such perspectives in the specific case of BCI systems would also be an area for investigation.

In addition to these preliminary efforts, I propose the following guidelines for navigating situations in the BCI research process where it is tempting to use BCI illiteracy:

1. Define and understand the user population(s) your BCI system aims to serve. Use the needs of these populations to inform BCI design. Aim to understand whether subpopulations have heterogeneous needs that may result in different design considerations for different individuals.
2. When evaluating the performance of BCI systems, justify metrics and the thresholds used to define success based on user input, which may be derived directly or in comparison to user feedback on alternative technologies.
3. Define poor performance in terms of shortcomings of the BCI system. For example, a P300 speller BCI is not a suitable for users who do not generate a standard P300 response to oddball stimuli. A BCI that doesn't work for its users doesn't work.

6.8 Conclusion

BCIs have shown promise for a variety of applications, from assistive technology to personal use or as entertainment platforms. For all of the excitement surrounding BCIs, most researchers in the field would agree that fundamental issues remained to be solved. Many

BCIs are not reliable enough for use outside a controlled experimental setting, or they are more cumbersome than they are assistive. There are clearly opportunities for improvement in the design of BCI systems.

It should come as no surprise that, in addition to improvements to BCI design, there may be areas to improve the research processes that generate BCIs. BCI illiteracy is just one example of a conceptual framework that may not be optimal for understanding or developing BCI systems. Though initially employed to understand how users interact with BCI systems, there are clear drawbacks to BCI illiteracy as a concept. These drawbacks include limited conceptual rigor, such as poorly justified performance thresholds or a variety of underlying causes that may be conflated. More fundamentally, BCI illiteracy assumes a problematic framing that the user possesses a state or quality of deficit that may be discovered through their interaction and poor performance on a BCI system. As researchers tasked with developing usable BCI systems, we should take pause at the notion that we are defining our users in terms of their ability to use these systems.

Users face legitimate difficulties in operating BCI systems. Focusing research efforts on addressing these difficulties is an important pursuit for BCI researchers. But the conceptual approaches used to frame and investigate these difficulties are not a foregone conclusion, and BCI illiteracy is not the only possible approach. Critiquing concepts such as BCI illiteracy and seeking alternative frameworks will not necessarily result in more usable BCIs or better incorporation of user views in BCI development; but exploring and revising how we frame the users of BCI systems is an opportunity for improving our research process that could provide rich returns and should not be overlooked.

Chapter 7

FRAMEWORKS FOR IMPROVING EMBEDDED ETHICS COLLABORATIONS

Many of the challenges we face today, whether environmental, political, or medical, necessitate novel cross-disciplinary solutions. Single-domain expertise may not provide the necessary tools to define, approach, or solve problems. Approaches that do not integrate a variety of diverse perspectives may overlook key issues; for example, a novel treatment for a medical disorder may be technologically impressive, but morally problematic if developed by parties focused solely on technological advancement. This example highlights a particularly challenging cross-disciplinary exchange that of understanding ethical considerations in scientific and technological fields.

Integrating ethics expertise into scientific and technological research efforts is rarely straightforward. While researchers with basic science or engineering backgrounds may have intuitions regarding ethical issues in their research projects, they may have competing interests, blind-spots, or gaps in knowledge that prevent them from fully elucidating or addressing these concerns. On the other hand, seeking input from experts trained in philosophy or ethics disciplines presents alternative challenges. Research teams may be hesitant to accept input on ethical considerations from outsiders, especially if they feel the ethicist lacks full understanding of either the technical details of their project or the first-hand experience of conducting scientific research. The question of when to seek input in the research and design process—sometimes discussed in terms of upstream, midstream, or downstream engagement [37]—also poses a challenge in formulating effective applied ethics approaches.

In this paper, we discuss our team’s approach to investigating ethical considerations in our research. Specifically, our “embedded ethicist” functioned as another member of our

engineering research team over the past four years by: attending team meetings, occupying a desk in our lab space, and aiding in the design, execution, and analysis of our technical experiments. We believe this fully embedded approach is unique from prior applied ethics efforts that we have surveyed. Although we worked specifically on a neural engineering project, and so the ethical findings from our collaboration are most relevant to the field of neuroethics, we argue that our general collaborative approach could be applied in a wide range of scientific and technical domains with similar success. In the following discussion, we compare our approach to prior published accounts of applied ethics. These include embedded approaches that are similar to ours in form, but noted greater levels of tension between collaborators than we experienced [33] [105] [39]. We then evaluate our work through a number of theoretical lenses, including the concept of trading zones [42] and alternative modes of collaborative socio-technological integration [38]. We describe unique aspects of our approach that may have contributed to our success. Lastly, we address common concerns for our approach including the worry that engineers would simply co-opt their embedded ethicist, and the possibility that interdisciplinary team members would have trouble developing an intellectual and professional identity.

7.1 Our experience with the embedded ethics model

Our collaboration began through the support of the Center for Sensorimotor Neural Engineering (CSNE), a National Science Foundation (NSF) Engineering Research Center (ERC)¹ that aims to engineer neuroplasticity for the purpose of rehabilitating individuals with stroke and spinal cord injuries. As per NSF specifications for ERCs, the CSNE pursues several research thrusts, or areas of fundamental knowledge, in the interest of supporting new neural technologies for restoring health and function. In addition to its scientific research thrusts,

¹According to the NSF website (https://www.nsf.gov/funding/pgm_summ.jsp?pims_id=5502), the ERC program goal is “to integrate engineering research and education with technological innovation to transform national prosperity, health, and security.” ERCs provide funding for up to 10 years for a consortium of researchers across multiple institutions to collaboratively tackle engineering challenges in various domains.

the CSNE supports a Neuroethics Thrust to investigate ethical questions arising in the development and use of neural technologies.

A research project was initiated by CSNE members leadership from the medical device manufacturer Medtronic Inc. and members of University of Washington's Biorobotics Lab (BRL) to investigate new adaptive deep brain stimulation (DBS) technologies. During the early stages of their project, the CSNE's Neuroethics Thrust created a neuroethics predoctoral fellowship program, whereby humanities Ph.D students (predominantly from the philosophy department) are tasked with conducting neuroethics research, observing laboratories associated with the CSNE, and raising awareness about neuroethical problems relevant to CSNE's membership through workshops and outreach events. One such fellow (TB) was assigned to observe the BRL. The lab's engineers, however, saw an opportunity to gain insights about the lived-experiences of people using the adaptive DBS technologies they were investigating. TB expressed an interest in this possibility, and began to build a sustained collaboration using an embedded ethicist approach.

In our embedded ethics approach, we work as a team on a series of related projects and experimental platforms, with at least one member, MT, interested in technical research questions (in our case, developing or improving novel approaches to DBS) and at least one member, TB, interested in ethical research questions (in our case, questions arising in applied neuroethics for DBS technologies). Other researchers including scientists, engineers, legal scholars, and philosophers are or have been involved in the collaboration at one time or another, with varying degrees of interest in the technical, legal, or ethical aspects of the projects.

In order to accomplish our personal and shared research goals, our team collaborated in acquiring the resources to execute our project through grants and other support; in crafting, practicing, and executing experimental protocols that would simultaneously investigate technical and ethical research questions; in taking on tasks that were outside the scope of our respective disciplines when required; and in analyzing and presenting research results through collaborative publications. These tasks required team members to contribute time,

monetary resources, and expertise over a sustained period of time, and at times had to be weighed against other commitments in terms of their value to individual team members and to the collaboration as a whole. Further, these tasks often stacked on top of individual members' obligations to their own respective departments and professional organizations.

In addition to substantial collaboration on core research efforts (revising research questions, crafting and executing experiments, and analyzing and presenting results), our collaboration had more mundane aspects. Our team shared laboratory space located in the Electrical Engineering Department at UW, and engineering team members were assigned desk space in the laboratory by default when joining the graduate program. TB was not a member of the department, but a desk space in the lab was assigned to him once the project was initiated. TB made this space his main working space on campus, and noted that this allowed him to witness and participate in impromptu laboratory activities and discussions instead of finding out about them after the fact. MT also noted that being able to initiate spontaneous discussions with TB (rather than having to draft emails or wait for regular meetings) allowed for greater exchange of ideas in a more organic fashion.

In addition to our shared lab space, we mutually participated in mundane tasks and lab roles such as website management, meeting scheduling between individuals and the whole research group, and more. We felt this close contact was a key feature of our approach; although, theoretically, we may have been able to conduct successful research without this level of contact, we found in practice that sharing day-to-day space and effort resulted in a rich collaborative experience as well as a high level of empathy and understanding between team members.

The phrasing "embedded ethicist" focuses on the difference between the ethicist and the rest of the team the expectation being that the ethicist, once embedded, will serve as an expert for other lab members who lack ethics expertise. In our experience, however, our collaboration quickly developed into a bidirectional exchange. Each team member approached the project with a personal set of research questions, the focus of which spanned our respective fields and required diverse methods of investigation. An engineer on the team may

have initially approached the project with the question, “which algorithm provides the best performance in terms of processing neural signals?” In contrast, an ethicist on the team may have initially wanted to ask, “do the side-effects of DBS pose a threat to the users sense of identity?” After engaging with the project, our shared collaborative experience resulted in complications, additions, and revisions to our original research questions—these changes reflected research interests we came to share over time. MT became interested in ethical questions surrounding the assessment of user performance in brain-computer interface tasks and the concept of BCI illiteracy [4]; TB became interested in the ethical dimensions of giving either users or algorithms different forms of control over stimulation parameters.

This bidirectional exchange involved individual team members gaining expertise and training in domains that their respective graduate training would normally not encompass. In investigating the concept of BCI illiteracy, MT joined a neuroethics journal club that met weekly, took a formal course in neuroethics, drafted a paper discussing ethical challenges in BCI performance assessment, and sought feedback from the neuroethics group at the CSNE during one of their weekly meetings. TB became familiar with laboratory equipment used during clinical DBS experiments and learned signal processing and machine learning concepts that were specific to the algorithms being tested while he interviewed study participants. These examples illustrate attempts from both parties to gain a certain level of fluency in the foreign disciplines’ language, concepts, and methodologies.

At this time, our collaboration is ongoing. However, given that the collaboration has been primarily driven by graduate students on the project, we anticipate either a resolution or a substantial shift in the collaboration following our respective dissertation defenses depending on the interests of incoming graduate students in our departments and in the CSNE. In the discussion that follows, we will consider not only the research accomplishments resultant from the project, but also the skills and competencies that we as individual researchers have gained from our participation in the project which we will take forward to future roles and project teams.

7.2 Survey of other approaches/general embedded ethics and related applications

To understand the benefits or limitations of our embedded ethics approach, it is helpful to consider other common methods to applying ethics in scientific research teams. Although it is not an exhaustive list of prior efforts, we compare our method to research ethics consultations, ethics inventories, and prior team-based embedded ethics efforts. The latter embedded ethics efforts may be most similar in structure to our approach, but we identify several key differences between our methods.

7.2.1 Research Ethics Consultation

The first format we compared for applying ethics to research teams is the research ethics consultation. An illustrative example of this format is presented by Cho et al. from their experience conducting consultations at Stanford University. The stated goal of these consultations is “maximizing the benefits and minimizing potential harms of research to society.” This goal may be achieved by providing short-term advice to project researchers, or through broader discussions sparked by project content. In practice, consultations bring a range of expert perspectives from other disciplines to understand a project from a broader perspective. A consultation is initiated at the request of the research team/project in question or through an external referral. When a consultation is initiated, a determination was made as to the scale of the consultation; in the Stanford model, a hybrid approach is used in which some standard consultations were managed by a single consultant while more involved consultations drew together a team of consultants with relevant backgrounds [25]. Other groups have engaged in similar research consultation efforts [84] [118] [104].

The research ethics consultation, in contrast to our embedded ethics experience, is focused on providing a service. This focus has the benefit of being easily packaged as a standard part of the research process [25]. Whereas adding a full additional team member in the form of an embedded ethicist for the duration of a research project may not be practical for all

research teams, scheduling one or more ethics consultations can be easily accommodated into a project timeline in the same way as technical research milestones. By the same token, consultations are more limited in scope than our approach. For example, while a thorough consultation could provide benefits such as written recommendations for the research project, it is unlikely that an ethics consultation would result in a level of depth to produce a collaborative publication. Furthermore, consulting services that attempted to conduct academic ethics research in projects on which they consulted could become conflicted in terms of where they allocate resources—for example, which projects they choose to consult on [25]. For this reason, especially at institutions that already have an ethics consultation process in place, it may be wise for the ethics consultant(s) to recommend initiating embedded ethics collaborations in special cases where a research project appears to have sufficient ethical depth, and sufficient resources, to foster such an approach.

Our approach also addresses a concern raised against ethics consultations that consultants may not have enough expertise for the research projects they are assessing [25]. Although this problem may exist in the early stages of an embedded ethics collaboration, it was our experience that our embedded ethicist quickly understood the technical details necessary to contribute not only valuable ethical considerations, but additionally to assist in technical aspects of the design and implementation of the experiments. We would also propose that a successful embedded ethics collaboration serves as a valuable training ground for both the ethicists and technical researchers on the project. Individuals with these types of collaborative experiences could be especially valuable as future members of consulting teams.

7.2.2 Ethics Inventories

Some engagement approaches ask collaborators on research teams to self-assess the ethical issues or even the philosophical assumptions they bring to the project. An example is the Toolbox approach for philosophical dialogue presented by Eigenbrode et al. They identify a number of challenges to interdisciplinary research that they link to epistemological and metaphysical differences between disciplines. One challenge is that collaborators on research

projects are instilled with their own conceptual schemes, which include epistemological and metaphysical assumptions, through their specialized disciplinary training. Eigenbrode et al. present a set of questions—the Toolbox—that can be used by respective collaborators to self-evaluate the differences and similarities between their respective conceptual schemes [35].

In contrast to the other approaches we survey, ethics inventory approaches may not require the participation of expert-trained individuals or groups (although the creators do recommend assigning a facilitator whose purpose is to keep discussion focused rather than to provide uniquely positioned expert input). Rather, the expert contributions in this approach are provided in crafting the questions included in the Toolbox. Although this may be beneficial in cases where it is difficult to find expert input, for example on projects that do not have the resources to sustain an embedded ethicist or at institutions without established consultation programs, it is possible that this approach would not yield the same benefits in terms of recommendations for resolving differences discovered through the toolbox. In teams that tested the toolbox, a few researchers noted that they doubted its effectiveness for this reason [35].

Another difference is that some ethics inventories may be conducted independently of the research project that collaborators are engaged in. In the case of the Toolbox approach, self-assessment is concerned with the conceptual schemes that collaborators hold based on their own training and experiences rather than the ethical content of the project at hand. This is also in contrast with typical research ethics consultations, which are typically project-oriented.

Eigenbrode et al. claim that it is preferable to identify differing assumptions in a structured way—such as through a conversation facilitated by their Toolbox methodology—than to rely on unstructured conversations [35]. We argue, contra Eigenbrode and in line with our experiences, that relatively unstructured conversations can be instrumental in fostering deep collaborations. We acknowledge that Eigenbrode et al. have laid out a useful framework for identifying pressure points where disciplinary differences may pose challenges for cross-disciplinary collaborations, and we agree that a structured approach may be suitable

for many research teams. However, we disagree that structured conversations are always preferable. Our collaboration was successful in overcoming these disciplinary differences without this structure for a number of reasons. First, we often discovered these differing assumptions in a more exploratory fashion, and in a more organic way than an inventory-style approach. For example, our differing methodologies were clearly highlighted when designing and reviewing our interacting research protocols. When differences in methodology were discovered, we felt comfortable questioning and discussing these differences openly. In such cases, we examined differences in our confirmation and validation of evidence through reviewing and critiquing our co-authored publications that were bound for journals in our native disciplines. We feel our approach has given us the type of insights advertised by an ethics inventory—but through a series of exploratory experiences rather than through a series of structured investigations. In other words, we saw these differences functionally during the day-to-day execution of the collaboration.

7.2.3 Embedded Ethics Approaches: Ethicists as Co-Investigators

Embedded approaches to applied ethics, where ethicists join research teams of scientists and engineers as co-investigators, are yet another model for understanding ethical dimensions of technological research projects. Such approaches may have initially arisen as social scientists aimed to study scientific culture and knowledge production using ethnographic approaches; mirroring the role of an ethnographer, the social scientist would study scientists in their “native environment” of the laboratory [33]. In other versions of this approach, such as our own, ethicists join research teams in order to consider the ethical challenges of the project at hand. As such, the goals for an embedded approach may be diverse but could include studying the practices and processes of scientists and engineers, analysing ethical challenges present in the particular content or output of a research project, or even providing recommendations for how the results of a project might be implemented.

Multiple prior attempts at embedded ethics collaborations noted that collaborative methodologies were not predefined, and at times were determined organically and implicitly. Fitzger-

ald et al. noted that in their case, “there were no obvious processes for ongoing assessment or mediation ... nor did there seem to be an accounting for the quality and process of collaboration” [39]. Doubleday described a similar experience at the onset of his collaboration [33], and our own experience was similar in that we did not explicitly discuss how our collaboration should unfold.

Despite producing positive research outcomes, prior approaches have cited tensions between ethicists and technical team members during embedded-style collaborations. In some cases, tensions arose around conflicting views of the roles of each member of the collaboration. Viseu notes that technical collaborators assumed that social scientists would be able to predict ethical problems in their project prior to collaborative research, and argues that this moves the social scientist to the role of public mediator rather than an ethnographer of laboratory culture. Doubleday moves further to claim that this assignment of roles allowed technical scientists to remain separated from public engagement, back at the laboratory and therefore “able to continue with their research” while simultaneously noting that these expectations cause the ethnography projects to suffer [33]. It is implicitly assumed that an outcome of social scientist involvement will be an educated public that would be more accepting of the nanotechnology the scientists produced. An analogous experience in our collaboration may have been an emphasis on “end-user acceptance” of neurotechnology as a positive and expected outcome of neuroethicist involvement.

In some cases, social scientists’ research activities were viewed as antagonistic. For example, Viseu notes that technical staff were cautioned regarding their interactions following a presentation in which Viseu discussed ethnographic findings [33]. Worries were also aired about personal [39] or collaborator qualifications [33], most often from technical team members concerned about the technical knowledge possessed by humanist collaborators. Taken together, these experiences point to a deeper conflict regarding the perceived primacy of technical aspects relative to humanist aspects of embedded collaborations. As Fitzgerald et al. explain of their own collaboration, which included elements from neuroscience domains,

the neural was often unconsciously positioned as the thing to be understood, and the social as a mildly querulous constraint upon it—even in avowedly transdisciplinary collaborations like ours, some knowledges have to interject and insist on their own usefulness; others have the privilege of taking their universal utility for granted. [39]

While we did not tackle this type of conflict explicitly, our collaboration exemplified a mutual respect for “foreign” disciplines—in our willingness to engage with publications, methodologies, and even disciplinary politics—that may have avoided such pitfalls. We discuss this mutual commitment further below.

A general challenge discussed in many embedded ethics accounts was how to assess the success of a collaboration. Doubleday and Viseu noted pressures to produce content from their collaborations that was quantifiable in the short term, such as a video about social/ethical issues in nanotechnology or a web portal, rather than supporting less quantifiable long term goals [33]. We ran into this pressure a few times when interacting with the broader research community at the CSNE’s; at one point, TB was asked by another graduate student in a technical field to create a “Buzzfeed-style” summary of key publications in neuroethics, and it was suggested to other neuroethicists at the CSNE to devise a list of recommendations for ethical neural engineering. But in general we were supported without these pressures: we received financial support for TB’s role for 4 years without stipulating that short-term outcomes needed to be produced. This provided us the time and freedom to develop an effective collaboration which sparked multiple co-authored publications and new perspectives for design of neural interfaces.

Considering some of the tensions described above, Fitzgerald et al. discussed in detail that, in lieu of structured communication methods, their collaboration thrived in ambivalence and uncommunicated tension between collaborators; they go so far as to hypothesize that these features were responsible for their collaborative success [39]. Our experience was markedly different in that we routinely discussed pressures that we were feeling or problems that we were dealing with. For example, we had candid discussions regarding who would benefit most from first-authorship on different publications based on disciplinary standards; we discussed together when we felt implicit assumptions were being made regarding our

roles in the project, especially as minorities in our fields (a woman in electrical engineering and a person of color in philosophy); and simply when we had too much on our plates and needed to take a step back from the collaboration to satisfy external requirements such as program exams. This continuous line of communication helped develop shared empathy and understanding that made it easier to air conflicts as the collaboration progressed. Both authors felt high levels of responsibility and commitment, and few feelings of ambivalence, to the project.

Fitzgerald et al. present the mundane aspects of their collaborative experience as a challenge to what they see as prior idealized schemas for how interdisciplinary research ought to operate [39]. In our experience, the mundane aspects of our collaboration served to support our grander research efforts, though not at the expense of theoretical explanations which we will tackle in the next section. For example, being in close proximity with one another—insofar as we shared the same office space and attended the same events—made it easier for us one another updated on the status of our work together. Daily labors which did not directly support the research (like maintaining the lab website or hosting lab tours) still served to affirm our commitment to the collaboration in a way that we feel strengthened our outcomes overall.

7.3 Theoretical Lenses for Understanding Our Approach

In addition to placing our collaboration as unique relative to prior accounts of applied and embedded ethics approaches, we aim to understand our collaboration through existing theoretical lenses. These include definitions of interdisciplinarity; the concept of trading zones and interactional expertise; and possible modes of socio-technological integration.

7.3.1 Defining Cross-Disciplinary Subtypes

A number of terms have been employed to describe different subtypes of cross-disciplinary collaboration; generally, these terms describe a ranging degree of synthesis of methods and

concepts that collaborators². For example, *multidisciplinary* may simply mean “a conglomeration of disciplinary components” where research is “cumulative or additive rather than integrative by nature.” [58]. *Interdisciplinary* describes “a more synthetic attempt of mutual interaction” [58], one where “collaborators accept, understand, and sometimes apply one another’s disciplinary methods and approaches” [35]. *Transdisciplinary* collaborations may go a step further because the problems being addressed “cannot be captured within existing disciplinary domains,” necessitating unique epistemological perspectives that the contributing disciplines cannot offer [35]. The term *antidisciplinary* has also been used to describe collaborative approaches that transcend single disciplines, but unlike transdisciplinary work may not seek to establish institutional or official novel disciplines [63] [147].

Our project, situated between the electrical engineering, neuroscience, and philosophy departments at UW and producing research relevant to the fields of neural engineering and neuroethics, was interdisciplinary in nature. Although our approach synthesized techniques and concepts from our respective disciplines in unique ways, we do not feel that we were creating a novel discipline or generating outcomes that could not be appreciated from existing disciplinary perspectives. We acknowledge this positioning with the understanding that collaborative approaches such as our own may be more effective for certain cross-disciplinary subtypes, although these applications remain to be investigated.

7.3.2 *Trading Zones*

The concept of a *trading zone* was introduced by Galison in his study of research cultures of physicists. The term describes how researchers trained in different disciplines or subfields may overcome barriers in communication, methodology, or other aspects to produce meaningful collaborative exchange. For example, researchers in such a trading zone may establish a contact language or interlanguage in order to facilitate such an exchange of concepts that

²The present set of definitions appears to be the most common formulation, but other prior work may deviate from this description (for example, using the term “interdisciplinary” to describe all types of cross-disciplinary work).

may have different functions in each respective discipline [42]. Collins et al. extends on Galison's definition to include other types of trading zones where an interlanguage does not develop, using two differentiating axes: collaborative vs. coerced and homogenous vs. heterogenous trading zones [29]. Within this framework, it is possible for a trading zone to shift between these characterizations over time due to varying strength in relationships, collaborative output or success, institutional support, etc.

It is clear to us that our collaboration constitutes a trading zone. Although the authors did not face explicit problems with communication in the sense of the conflict reported in other embedded collaborations, our collaboration did compel us to learn new terms, concepts, and research methods from one another in order to successfully interact. Where TB had to familiarize himself with neural engineering research broadly, MT had to familiarize herself similarly with neuroethical research. By collaborating closely, we found we were able to serve as guides to each other's respective research. Further, our work together required the synthesis of new terms that accurately describe the technologies developed in our lab, as well as new concepts that capture the possible moral problems that come with said technologies.

The concept of trading zones, and more specifically the spectrum of homogenous vs. heterogenous zones [29], interacts with a logistical challenge we faced in our collaboration, which was creating separate and shared academic identities. We entered the collaboration with our own disciplinary affiliations: TB as an ethicist and philosopher, and MT as an electrical engineer. Over time, and especially as we discussed the outcomes of our collaboration with other researchers in our own disciplines, it became clear that our intellectual identities and roles had been shifted and altered. Although we may have become more homogenous within the context of our own collaboration as we built understanding together, we became simultaneously distanced from the experiences of many researchers in our native disciplines. As a result, our collaborative work required we perform a type of translation of our own interlanguage, experience, and outcomes for researchers in our own fields.

A key feature of trading zones is that the meaning that a particular group assigns to an object of trade may differ from the meaning that another group assigns. Despite these differ-

ences in meaning, an exchange is still possible. As an example, TB introduced concepts such as user agency to describe one aspect of the experience of using a neural prosthetic. In many discussions, most researchers from a technical background would implicitly wield the idea of increasing user agency for the purpose of increasing end-user acceptance, a move that ethicists are not quick to make. Thus, “user agency” holds different meanings and associations for technical audiences than it does for ethicists. Only through our sustained collaboration did we uncover (and in some ways unpack or lessen) these differences in meaning, and researchers external to our collaboration.

Actions that we took in setting collaborative norms, especially early in our collaborative experience, may have helped to foster deeper collaboration and to improve our respective interactional expertise. For example, we wrote a theoretical, forward looking collaborative publication during the first academic quarter that TB was embedded in the lab [15]. Creating this publication required that we hold regular meetings, develop an understanding for how ideas or drafts would be shared, develop an understanding of foundational literature in one another’s disciplines, and more. By engaging in this process early, we took an active role in shaping the quality of the trading zone that we were in.

7.3.3 Modes of Socio-Technical Integration

Fisher et al. have proposed frameworks for “mapping the field” of collaborative approaches to socio-technical integration by comparing methods and goals [38]. Of note, they define socio-technical integration as “distinct from ... related approaches primarily insofar as it involves close, transformational interaction with scientific and technical experts.” Our collaboration seems to fit this definition well.

One way they aim to characterize such collaborative approaches is based on their *forms*, *means*, and *ends*. They take the *form* of an approach is “how it is related to its domain of inquiry along two dimensions: (1) how it conceptualizes the relationship between the societal contexts it focuses on and the practices it engages, and (2) how it organizes the relationship between its own practices and those it engages.” They define the *means* of an approach as

“the methods and standards an integration approach employs as it operates.” Lastly, they specify that the *ends* of an approach are “the values and norms that motivate and justify an approach’s activities” [38].

From an understanding of how collaborative approaches may be characterized by their form, means, and ends, Fisher et al propose a two-dimensional mapping of each approach based on its *values* and *capacities*. *Values* are combinations of ends and forms, and range from “native values,” where ends and forms seek to enhance existing goals and commitments of the focal expert practices, to “alternative values,” where ends and forms introduce new goals and commitments. *Capacities* are combinations of means/forms, and range from “native capacities,” which seek to enhance latent resources and capacities, to “alternative capacities,” which seek to introduce additional knowledge, content, and resources [38].

The two dimensional mapping of native to alternative values and capacities generates four quadrants into which collaborative approaches may fall. Fisher et al. label each quadrant as a mode of collaboration. Approaches with both native values and capacities *facilitate*; approaches with native values and alternative capacities *augment*; approaches with alternative values and native capacities *problematize*; and approaches with both alternative values and capacities *reform* [38].

The addition of an embedded ethicist to the research project supplied a number of alternative capacities, from novel concepts (such as how a neural interface might impact user agency and autonomy) to novel methodologies (there had been no prior plans or structure for conducting interviews with participants during our experiments). TB also received the benefit of conducting his work in a technical experimental context that enriched his ability to interview participants about experiences as they were happening rather than after the fact. Thus, our collaboration often served to augment the individual capacities of collaborators.

At the onset of the project, both authors entered the collaboration with their own values which were likely influenced by their respective disciplinary experience. Over time and throughout the collaboration, these values were examined organically and alternatives were considered. For example, after designing, testing, and evaluating neural interfaces side-

by-side with TB, and after engaging with literature from other disciplines, MT developed critiques of how researchers in her field framed user performance. Thus, although the collaboration did not begin with the intention of reform, this mode of integration presented itself over time.

7.4 Unique features of our collaboration

We identified a number of unique features of our collaboration that may have contributed to our success. These include the neural engineering project that we collaborated on; our prior experiences and our status as early-career researchers; and our mutual commitment of resources.

7.4.1 Neural engineering and neuroethics as collaborative spaces

Our project falls under the already interdisciplinary umbrellas of neural engineering and neuroethics. In these fields, it is commonplace for researchers from different engineering and scientific disciplines to collaborate; furthermore, researchers and the general public alike seem to carry an intuition that there are unique social and ethical challenges in neural engineering that warrant special investigation [108]. Prior embedded ethics approaches such as Fitzgerald et al., which was a project based in neuroscience, have recognized this interdisciplinary makeup, commenting that

contemporary neurosciences are already made up of a host of (sometimes competing) disciplines and perspectives; there is a kind of multidisciplinary cosmopolitanism inherent to the formation of the ‘new brain sciences’ that may make the presence of epistemic difference a lot less jarring for the typical neuroscientist, and a lot easier to live with [107]. [39]

However, this account places the humanists on the project in contrast with the neuroscientists in terms of their ability to tolerate epistemic difference despite the fact that the entire project was based in this interdisciplinary field. It is unclear why TB, our project’s ethicist, did not share the somewhat alienating experience of Fitzgerald et al., but it is possible that the

fact that the project was explicitly neuroethical in nature prepared us to undertake an interdisciplinary approach.

7.4.2 Our prior cross-disciplinary experiences

Prior to this collaborative effort, both of the authors had experience engaging in projects—both academic and personal—outside of their graduate program disciplines. As an undergraduate student, MT received her B.S. in Engineering from Harvey Mudd College, a liberal arts college whose mission statement is “to educate engineers, scientists, and mathematicians well versed in all of these areas and in the humanities and the social sciences so that they may assume leadership in their fields with a clear understanding of the impact of their work on society” [28]. As an undergraduate student, she conducted a qualitative research survey project in collaboration with a relationship psychology faculty member. On the other hand, despite pursuing a graduate program in philosophy, TB has maintained an interest in computer skills and hacking from a young age. In summary, both of the authors admittedly had an existing appreciation for the types of non-native ideas and methodologies that they would later encounter through this interdisciplinary collaboration, which may have made them more comfortable engaging with approaches that would not have usually appeared in their graduate training.

7.4.3 Our status as early-career contributors

The authors, who were the main researchers involved in the day-to-day workings of this collaboration, were both graduate students in doctoral programs at the time of the collaboration. It is possible that their early career status worked favorably in that they were not as bound by expectations or conceptual schemes imposed by their native disciplines. Although the need for interdisciplinary training and the potential for experiential interdisciplinary encounters to act as valuable training grounds for early-career researchers have both been recognized [14] [80], the idea that early-career researchers may be particularly poised to conduct interdisciplinary collaborations has received less attention. Graduate students and

early-career faculty may have received comparatively less specialized disciplinary experience, allowing them to collaborate more flexibly with researchers from other fields. Given our collaborative success, we suggest that this is an area worthy of future investigation.

7.4.4 Mutual commitment of resources

A final feature present in our collaboration, which we did not encounter in many of the prior cases that we reviewed, was an increased level of commitment from technical collaborators such as MT. Prior work noted that humanists often felt burdened to understand technical aspects of their projects without an equivalent effort from scientists or engineers to understand the theory or methodologies from humanities fields [39]. On the other hand, despite finding detailed accounts of social scientists' experiences in embedded ethics collaborations, we found fewer case studies from the perspective of technical collaborators in embedded ethics collaborations. Similarly, publications of such accounts were almost always in social science journals rather than science and engineering technical journals.

In our case, such an imbalance was not present. MT read papers from humanities journals, completed a course in neuroethics, guest lectured in subsequent neuroethics courses, included neuroethics based goals in her dissertation proposal, and was the primary author on two ethics focused publications (including this one) about the project. The collaborative success is partly due to a truly mutual commitment of resources—in time, logistical and intellectual effort, and funding support—from MT, TB, and their respective graduate advisors.

7.5 Additional considerations and limitations

Although we observed substantial benefits from our collaboration on both personal and project-level scales, we acknowledge that our approach requires certain consideration. In this section, we discuss potential issues and limitations that might give pause to groups considering similar implementations of embedded ethics collaborations.

7.5.1 Issues of resources

We acknowledge that our approach requires a higher level of resources, in terms of both time and money, compared to alternative applied ethics schemes. It is not necessarily feasible for every research team to find full financial support for an embedded ethicist. In some cases, the ethical questions that a project presents may not be interesting enough for an ethics research to commit their full time to the project. Before employing our approach, a research team ought to look critically at the resources available as well as each members personal interest in the project to ensure that this level of commitment is warranted. Caution should especially be taken if imbalances in resources may be exacerbated by political pressures such as institutional mandates for “interdisciplinary research.” In such cases, some social scientists may be compelled to pursue such collaborations in order to secure limited humanities funding while their technical collaborators are not held to such pressures [39]. In assessing whether an embedded ethics collaboration is feasible, it is possible that our approach could be suggested as a result of a less-resource intensive approach (such as through an ethics consultation) once it is apparent that rich ethical questions exist within the project and that the technical team under consideration can contribute mutually to the collaboration.

7.5.2 Issues of finding and maintaining an intellectual identity

Both engineering and ethics researchers in our collaboration have noted challenges in forming individual intellectual identities that encompass their respective research interests while withstanding scrutiny from disciplinary standards. This is particularly relevant for early-career team members, specifically graduate students who needed to defend their work in the form of academic papers and dissertations. For example, MT had concerns about whether their ethical questions would seem technical enough if presented as dissertation chapters for her electrical engineering doctoral program. Similarly, TB had to consider whether applied ethics work would be valued in his department, whether multi-author publications from the collaboration (in contrast to solo-author publications) would weaken his portfolio, as well

as whether his more empirically-informed work would be considered as rigorous or focused as his more theoretical work. These concerns became magnified when considering how to present themselves as candidates during a job search. Although learning interdisciplinary skills was certainly valuable for our collaboration, it is not easy to convey the value of these collaborations or describe the products produced through them to the outside observer, especially if these outcomes do not conform to the disciplinary norms of our respective fields. We observed and discussed these pressures during our collaboration, and would recommend other teams do the same in order to build sensitivity to and support for each individual collaborator's needs.

7.5.3 Issues of Co-Opted Ethicists

A frequent concern expressed in prior literature and in our own conversations with other researchers is that of the compromised, or “co-opted,” ethicist. This concern is almost always posed in the direction of the embedded ethicist—rarely are concerns raised that a scientist will be co-opted by ethicists. But there is a worry that an ethicist who is tied to a single research project over a long period may not remain a neutral party, and implicitly there is therefore an assumption that they should maintain neutrality and preserve a certain critical distance in order to remain impartial enough to identify and raise moral concerns about the research and the conduct of fellow researchers.

Our response to this concern is multifaceted. First, it is important to distinguish the aims of the embedded ethicist, or their role in the team, from other forms of ethical oversight. The embedded ethicist is not expected, nor should they try to fill the role of regulatory bodies such as the IRB or FDA for the team on which they are embedded. Furthermore, they have no greater or lesser responsibility than any of the engineers or scientists on their team to raise concerns over perceived misconduct. Further, it is not clear that academics trained in ethics are particularly well-positioned to serve in this role. That is, it is not clear that having conducted ethics research in the past prevents the ethicist from committing harms of their own. Embedded ethicists do not necessarily serve as some sort of deployed “ethics

police,” and being upfront about this distinction is important. On the other hand, if they raise observations or criticisms of team practices they may risk being seen as antagonistic even if their commentary is valuable [33]; creating a collaborative environment where such critiques are valued and integrated is undeniably challenging.

The implicit belief that social scientists with critical distance are more closely aligned with public concerns around technology [39] comes hand-in-hand with the assumption that scientists or engineers are inherently worse at examining the ethical dimensions of their projects. We found this to be generally untrue. For example, MT initially identified issues surrounding assessment of user performance on neural interfaces and brought ethicists to the table to improve and refine the discussion. Thus, although ethicists often bring unique domain knowledge and methodologies that can assist in understanding ethical challenges, it is not valid to say that their critical distance in itself is what enables them to identify and elaborate on ethical challenges, or that a decrease in critical distance would make them worse at this task.

Lastly, it is valuable to consider whether ethicists face the issue of co-optation more so than other research team members. There are certainly pressures to produce results that validate lines of research that a team has been pursuing, especially if funding pressures mean that researchers may not pursue alternative approaches. If, for example, collaborating with a neuroscientist would legitimate lines of research for a group of electrical engineers, co-optation issues still exist. Furthermore, negative results, though a part of the scientific process, are not typically thought to win grants. We would argue that all members of the team face unique pressures to conduct research in certain ways that may be at odds with producing ethical science or technologies.

7.6 Conclusion

Interdisciplinary research collaborations are vital to solving some of the most difficult problems we face today, but they can present conceptual and logistical challenges for researchers involved. This may be especially true when attempting to collaborate across disciplines

with vastly different methodologies, such as between engineering and ethics. Prior interdisciplinary efforts to bring ethics to science and engineering fields have engaged different levels of resources, from team-driven inventories and expert-led consultation services to fully embedded efforts where social scientists join technical project teams as “labmates.” Each approach presents different benefits and limitations based on the level of commitment involved.

In this paper, we presented our experience in an embedded ethics collaboration where both an ethicist (TB) and an electrical engineer (MT) committed a high level of their intellectual and material efforts. Although the format of our collaboration was similar to some prior embedded ethics efforts, we noted unique aspects to our collaboration as well as less conflict between researchers of different disciplines than prior efforts had reported. Through documenting our efforts, we aim to guide future interdisciplinary research teams towards the possibility of more effective ethics collaborations. Although we recognize that embedded ethics approaches may not be feasible or appropriate for all interdisciplinary research projects, we also reject the idea that such an approach is out of reach for many interdisciplinary teams that would otherwise find such a project intimidating. Instead, we feel the rich benefits of embedded ethics approaches warrant consideration and further study from interdisciplinary teams in the future.

Chapter 8

CONCLUSION

My dissertation research has developed and tested novel methods for side-effect mitigation in CLDBS. I have also examined neuroethical challenges surrounding assessment of user performance in BCI systems and provided recommendations for teams engaged in embedded ethics collaborations. In conclusion, I summarize my major research contributions to these fields. With each research contribution, I cite relevant publications that I have authored or co-authored. I also discuss possible future research directions in the fields of CLDBS, ECoG-based BCI, and neuroethics, that will leverage my research accomplishments and bring the technologies and recommendations that I have presented closer to real-world use.

8.1 Research Contributions

8.1.1 Aim 1: Pilot Testing of Safety and Feasibility of a Biomarker-Based Dyskinesia Mitigation System

In Aim 1, I piloted a novel methods for dyskinesia side-effect mitigation in CLDBS for PD patients [129]. Having demonstrated a baseline level of feasibility for this method, and following subsequent efficacy studies, this approach has the potential to be deployed in future real world systems through the help of collaborators at Medtronic and other researchers and developers in the field of DBS.

8.1.2 Aim 1: Validated CLDBS Algorithm Performance between Nexus D & Nexus E Platforms

In implementing the dyskinesia side-effect mitigation system for Aim 1, we tested algorithm implementation with both Nexus D (Medtronic’s streaming interface between the Activa

PC+S and the desktop application I had written) and Nexus E (Medtronic’s fully embedded classifier system). Our results indicated remarkably similar performance in terms of clinical scores and power savings across both implementations, suggesting that algorithms pilot tested on Nexus D may perform similarly on Nexus E. The Nexus D streaming system provides easier visualization and prototyping than Nexus E since the latter requires data downloads after each test in order to investigate performance. My work helps to validate prototyping on Nexus D given that we saw reasonably similar performance once our algorithm was ported to Nexus E.

8.1.3 Aim 2: Investigated Subsystem Design Considerations in BCI-Based CLDBS

In Aim 2, I investigated how human subjects interact with multiple subsystems crucial to the design of a BCI-based CLDBS system, including subsystems for signal processing, control methods, feedback, and stimulation mapping [129]. My research into these subsystems have highlighted key considerations when implementing a full BCI-based CLDBS system.

8.1.4 Aim 2: Characterization of Parasthesias Evoked during CLDBS for ET

In Aims 1 and 2, I piloted two novel methods for side-effect mitigation in CLDBS [129]. Having demonstrated a baseline level of feasibility for these methods, and following subsequent efficacy studies, they have the potential to be deployed in future real world systems through the help of collaborators at Medtronic and other researchers and developers in the field of DBS.

8.1.5 Aim 2: Demonstration of Chronic ECoG for Neuroprosthetics

Given that Aim 2 leverages a chronic fully-implanted ECoG-based BCI, my research provided insight into design of fully-implanted BCIs which had previously been confined to animal models. I published data verifying that signals recorded from our system remained stable multiple years after implantation, confirming that ECoG-based systems would have long-

term viability for use in CLDBS systems and BCIs in general [136] [51] [56].

8.1.6 Aims 1 & 2: CLDBS Systems as Tools for Improving Neuroscientific Understanding

The CLDBS systems that I engineered and tested also allow us to learn more about the underlying neuroscience of PD and ET, which could have impact beyond the nominal goal of side-effect mitigation. For example, in testing the dyskinesia-mitigation system from Aim 1 we discovered a minimum stimulation voltage between 1–2V was necessary for entrainment of the dyskinesia peak at half of the stimulation frequency. This feature of the dyskinesia peak was previously unknown and discovered only through interaction between the patient and the CLDBS system. It is possible that other phenomena of the underlying disorders will be discovered through further development and testing of the CLDBS systems that I have piloted in my dissertation.

8.1.7 Aim 3: Improving Characterizations of BCI User Performance

Aim 3 of my dissertation included developing critiques of BCI illiteracy, a concept BCI researchers have developed to characterize user performance in BCI systems. I saw key shortcomings in BCI illiteracy and the framing of BCI users that it reflects. These shortcomings stand to negatively impact recipients of BCI systems. Through my critiques of BCI illiteracy, I produced recommendations that will have direct influence over how researchers characterize patient-system success in BCI studies. I improve upon prior discussions of BCI illiteracy by challenging the notion that it is simply a concept in need of standardization. My recommendations provide alternatives to BCI illiteracy by applying user-centered design principles to BCI user performance characterization for the first time [134].

8.1.8 Aim 3: Recommendations for Improving Future Embedded Ethics Collaborations

Aim 3 of my dissertation also produced recommendations to improve ethics collaborations in the field of neural engineering and beyond. My research in novel side-effect mitigation

methods for CLDBS was conducted within an embedded ethics collaboration with philosophy graduate student Timothy Brown. Brown investigated ethical issues in CLDBS including effects of novel algorithms on patient agency. Our team received numerous questions from other scholars interested in how we executed our collaboration successfully, and Brown and I noted that prior accounts of embedded ethics collaborations often cited significantly more conflict than our own. We wrote an account of our collaboration and explored reasons for our success in order to produce recommendations for improving embedded ethics collaborations. Technical research teams that are interested in exploring ethical issues present in their projects can benefit from our recommendations for embedded ethics approaches [135].

8.2 Future Work

8.2.1 Aim 1: Testing Clinical Efficacy of Dyskinesia Mitigation System

While my dissertation research developed crucial pilot tests for safety and feasibility of two novel CLDBS systems for side effect mitigation, out-of-clinic tests or a full clinical trial of either system were outside the scope of my work. These studies would be needed to further investigate clinical efficacy of these novel systems in a larger patient sample size than what was available for my research. Furthermore, testing out of clinic is important to verify that system behavior is not substantially different in a natural environment that may be hard to replicate in purely in-clinic tests.

8.2.2 Aims 1 & 2: Optimization of Symptom and Side-Effect Trade-off

Integrating side effect mitigation into existing closed-loop algorithms for symptom reduction and finding optimal solutions for balancing these competing needs was also beyond the scope of my research. In Aim 1 I tested a system that solely prioritized dyskinesia mitigation. Realistically, the patient has multiple competing needs surrounding symptoms that they would likely be treated as well as side effects that they would like minimized. Future research could rigorously quantify these trade-offs to ensure a holistic CLDBS approach.

8.2.3 Aims 1 & 2: Understanding Patient Preference for Automation vs. Voluntary Control

Additionally, while I was able to make theoretical comparisons of the two methods (involuntary biomarkers vs. voluntary BCI-control) across a small number of patients, I was not able to draw strong conclusions as to which methods patients prefer or for which contexts they prefer them. It is likely that individual patients have differing needs that may influence how much control they desire over their stimulation levels on a moment-to-moment basis. Researching these needs and how they influence desired control would be an important follow-up to ensure that patient input is properly considered in system design.

8.2.4 Aim 3: Expanding Critiques of BCI Illiteracy

Although the third aim of my thesis initiated a conversation around BCI illiteracy as an ethical challenge in BCI research, further dialogue after my initial critique would improve upon the points that I raised. Marion Boulicault, a philosophy graduate student at MIT who is affiliated with the CSNE, has expressed interest in expanding upon my critique of BCI illiteracy through her own dissertation and has presented a seminar to CSNE graduate students summarizing how her work will expand upon my own. Her research will bring further attention to the work I have done and expand the scope of the critique that I have initiated, and will likely draw the attention of philosophers whereas my work was aimed at engineering audiences. This interdisciplinary problem will require expertise from multiple disciplines to address, so my work will be enriched by researchers such as Marion joining the conversation.

8.2.5 Aim 3: Implementing Recommendations for Improving Embedded Ethics Collaborations

Similarly, while my collaboration with Timothy Brown will develop a preliminary list of recommendations for future embedded ethics collaborations, the efforts to expand and implement these recommendations on future teams will be left to future researchers. Our

recommendations are based on an initial comparison of the circumstances, structure, and functional aspects of our collaboration relative to other reported embedded ethics collaborations with greater or lesser success. However, it remains to be seen whether other teams could successfully replicate our collaborative success using our recommendations. It is possible that additional factors (in terms of team composition, project area, institutional support, etc.) beyond those that we have considered can have significant influence on the success of these types of collaborations. These additional factors may be discovered by other teams as they begin to build on our collaborative model, further enriching our understanding of how and when to implement successful embedded ethics collaborations.

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