To Linda Shute, Patrick Hogg, and Kayla Shute
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Tourette syndrome (TS) is a complex neuropsychiatric disorder characterized by multiple motor and vocal tics. Numerous therapeutic options exist for patients with TS, but in some cases there is no relief. Deep brain stimulation (DBS) is a newly emerging therapy for patients with severe intractable TS. Over 100 TS patients have been implanted with DBS, but the most efficacious way to deliver DBS to this population has not been established.

Modern experimental deep brain stimulators are equipped with stimulation as well as recording capabilities. These devices allow for researchers to investigate the brain rhythms underpinning neurological disorders. To better understand TS and the most efficacious ways to deliver DBS, we studied the brain activity collected from two patients with TS who were implanted with DBS. In our investigation, we studied the neurological correlates of tics, the response of the brain to the delivery of therapeutic brain stimulation, and tested chronic closed loop stimulation. Our results uncovered potential approaches to improve DBS for TS patients and some of the mechanisms that may give rise to the disorder.
CHAPTER 1
THE HISTORY OF DEEP BRAIN STIMULATION AND TOURETTE SYNDROME

Introduction

Understanding the brain is a task that requires a multilevel investigation ranging from the subcellular scale to human-human interactions. The dynamics of the system are likely more complicated than anything known to man and currently we do not even know how much we do no know. Lyall Watson put it best when he said, “If the brain were so simple we could understand it, we would be so simple we couldn’t”\(^1\). The process of investigating the brain draws on the philosophical and scientific dilemmas that give life meaning, and sometimes the knowledge that we obtain only brings up more questions. The tools necessary to truly make sense of this abstract machine do not currently exist, but for now… we can make do.

Early Electrical Therapies

Our initial knowledge of the brain primarily stems from experiments with electrical stimulation in the brain and cases of brain trauma or lesions. Electrical stimulation first emerged as a therapeutic approach to treating external ailments\(^2\). The use of electrical stimulation as a therapeutic modality extends long before the discovery and characterization of electromagnetism\(^3\). As early as ~50 AD, physicians suggested that their patients rub their skin with animals possessing natural electric properties (even though they were ignorant of electricity and the mechanism of their prescription)\(^4\). These primitive electric therapies were used to treat physical ailments, such as paralysis\(^5\). As time went on, the number of disorders treated with this approach was widened to include mental disorders\(^6\) and became one of the earliest developed therapies for
epileptic populations\textsuperscript{7}. The reasons for these early successes were unknown at the time.

By the rise of the 19\textsuperscript{th} century, scientists had uncovered substantial evidence that the human brain was an electrical organ\textsuperscript{8}. Experiments by Giovanni Aldini on deceased criminals demonstrated that stimulation of the brain surface could elicit grotesque facial contortions in a dead human being\textsuperscript{9}. These early tests suggested that proper control of brain stimulation might be a useful tool for treating neurological disorders\textsuperscript{10}. The 20\textsuperscript{th} century and the early 21\textsuperscript{st} century were marked by a slew of experimental stimulation studies that acted as the stepping-stones towards understanding the basic layout of the brain and the potential for developing brain therapies\textsuperscript{11}.

Early stimulation trials, as well as serendipitous accidents, shined light on the unknown nature of the brain’s architecture. Anatomically, the brain grossly consists of various deep structures (called nuclei\textsuperscript{12}), a wrinkled surface (called the cortex\textsuperscript{13}), and the fiber tracts for subcortical-cortical and cortico-cortical connections\textsuperscript{14}. The cortex, or the wrinkled surface of the human brain, is broken down into two facets: sulci and gyri\textsuperscript{15}. The sulci are the deep grooves of the surface and the gyri are the wrinkles on the top. Wilder Penfield, a surgeon, studied the cortex of his patients’ brains by electrically stimulating a sulci called the central sulcus and found that the mapping of the brain was relatively consistent between individuals\textsuperscript{16}. In particular, Penfield noticed that control of certain parts of the body was associated with similar regions of the central sulcus across patients. Using data from multiple patients, Penfield created a “map” of body parts associated with various portions of the central sulcus. This map became popularly known as the homunculus\textsuperscript{17}. This was some of the early evidence that demonstrated
that specific areas of the brain are involved in specific functions (also known as the structure-function relationship\textsuperscript{18}).

**Ablative Techniques Take Over**

Neurosurgical resection of brain tissue emerged from the early concepts of the structure-function relationship\textsuperscript{19–22}. Resecting brain tissue associated with tumors was\textsuperscript{23,24}, and still is\textsuperscript{25,26}, commonly practiced, but the medically accepted resection of tissue specifically to modify function did not emerge until the basic groundwork for the structure function hypothesis was taking hold\textsuperscript{27}. In the early 1940’s, lobotomies, or removal of a brain lobe, was a regularly practiced form of brain surgery\textsuperscript{28}. At this point in time, more focus was placed on the cortex of the brain. Deep nuclei of the brain were known to be involved in some basic functions\textsuperscript{29,30}, but the potential benefits of deep nuclei surgery were not yet established.

The identification of a disorder described as “the shaking palsy” set the world of neuroscience down a path that would eventually show the grave importance of the deep nuclei of the brain. In 1817, Dr James Parkinson described a series of individuals in a park who presented with a set of symptoms that he called “the shaking palsy”\textsuperscript{31}. In time the understanding of this disorder would be further refined and would eventually be called Parkinson’s Disease (PD)\textsuperscript{32,33}. PD is a complex neurological disorder that impairs movements, effects cognition, and ultimately results in death. Post-mortem investigation of individuals with PD revealed a striking deficiency in a deep region of their brains called the substantia nigra (SN)\textsuperscript{34}. The SN, which means black substance in Latin, is a region of the brain with a dense population of melanin containing neurons\textsuperscript{35}. The melanin in these neurons makes them appear black to the naked eye, hence the name of the SN. The SN of patients with Parkinson’s disease post mortem was nearly
nonexistent. This was some of the earliest evidence of a disorder primarily characterized by damage to a deep nucleus of the brain.

Investigation of deep brain nuclei connectivity led to the understanding that the SN was highly involved in the control of a group of nuclei in the brain called the basal ganglia. Emerging evidence from multiple sources demonstrated that movement was partially controlled by the basal ganglia and that disruption of the basal ganglia could cause deficits or impairments in movement. The study of PD and the basal ganglia eventually revealed that lesioning, or damaging specific nuclei of the basal ganglia could benefit patients with PD. The dysfunctional SN of patients with PD set the basal ganglia out of balance and destroying certain regions of the basal ganglia could help reestablish equilibrium.

Lesioning deep regions of the brain proved to be a complex task. In contrast to lobotomies or cortical lesioning, the deep regions of the brain are not easily accessible. Two British scientists, Horsely and Clarke, realized that lesioning a specific deep nuclei would require a coordinate system and a targeting approach. A frame was developed that attached to the skull of the patient and provided the surgeon with a series of coordinates and references points. This coordinate system allowed the surgeon to estimate the location of the brain nuclei using images collected with MRI and X-Ray before the surgery even began. Once the target was determined, a hole was cut into the skull and a rod with an electrode at the tip was mechanically advanced through the brain tissue until it reached the target. Although surgeries were planned in advance, the exact position of the deep brain nuclei were not exactly known and more precise
methods of assessing brain structure were necessary\textsuperscript{46}. This additional information came from analysis of single neuron activity\textsuperscript{47}.

The neuron is the basic processing unit of the brain\textsuperscript{48}. Neural communication occurs via electrical impulses called action potentials\textsuperscript{49}. A neuron receives input from surrounding neurons and if the inputs pass a certain threshold, the neuron will produce an action potential\textsuperscript{50}. Electrical measurement of an action potential is possible when an electrode is placed in close proximity to the neuron producing the potential\textsuperscript{51}. Neurons are associated with functions and mental processes\textsuperscript{52,53}. Changes in function or mental processes will change the rate at which neurons produce action potentials\textsuperscript{54}. The structure-function relationship of the brain indicates that neurons in some regions will be associated with function A and then neurons in another region will be associated with function B\textsuperscript{27}. After various animal and human studies, researchers developed maps of the expected neuronal firing patterns of various deep nuclei of the brain\textsuperscript{55–57}. During human surgeries, the electrical activity at the tip of the rod was played back as a sound wave to the physicians in the operating room\textsuperscript{58,59}. Surgeons and staff were able to improve their understanding of “where in the brain” they were by listening to the characteristic firing patterns of the brain\textsuperscript{58}.

Once the target region was reached, the tissue was lesioned via ablation. A high-powered electrical current was injected into the target region of the brain to heat the tissue and destroy the cells\textsuperscript{60}. Following ablation, some of the disease manifestations of PD (such as tremor) were immediately corrected\textsuperscript{61}. This procedure was revolutionary in that it offered immediate symptom relief, Unfortunately the effects of the ablation were not permanent, tremors would return after some years went by, and the ablation did not
directly treat the disorder\textsuperscript{62}. After ablation was performed, there were few options available to the patient for future surgeries. Destruction of the nucleus was permanent and any deficits or complications that occurred as a result of the surgery were generally uncorrectable\textsuperscript{63}.

**Deep Brain Stimulation Emerges**

All of this changed in the year 1991 when Alim Louis Benabid released his seminal article describing a procedure that eventually became known as deep brain stimulation\textsuperscript{64}. Physicians had previously shown that high frequency stimulation of deep nuclei could reduce tremor in PD patients, but these tests were only performed in the acute setting\textsuperscript{65}. Benabid changed the course of history by instead suggesting the chronic use of low amplitude high frequency stimulation, as opposed to ablation. The technology necessary to take this therapy from principal to practice was not clinically approved and it would take until 1997 for the Food and Drug Administration (FDA) to approve a fully implantable, stand alone, brain stimulator.

Medtronic created the first FDA approved deep brain stimulator\textsuperscript{66}. The commercially available deep brain stimulator is essentially an electrode, cables, a battery, and some small electronics. The device itself was created by modifying the already FDA approved cardiac pacemaker\textsuperscript{67}. The housing of the modern deep brain stimulator is the same housing that holds the pacemaker. Acquiring FDA approval is a complex and expensive task, so Medtronic utilized the previously approved device housing to lessen the financial and temporal burden of gaining approval\textsuperscript{68}.

One of the major advantages of deep brain stimulation is its reversibility\textsuperscript{69}. Unlike ablation, DBS does not destroy nuclei\textsuperscript{70}. The application of low amplitude high frequency stimulation provides an ablation effect that is reversible; in general, the
benefits of DBS are only observed while the device is active\textsuperscript{71}. Therapeutic benefits are not sustained if the stimulator is turned off\textsuperscript{71}. In addition to this, side effects of DBS are transient\textsuperscript{72}. Altering the parameters of stimulation can help to mitigate side effects. Side effects of DBS can include sensorimotor or psychological disturbances\textsuperscript{73}. The tradeoff between side effects and benefits are balanced by the application of specific DBS settings: pulse width, voltage, and frequency\textsuperscript{74}. Identifying the ideal stimulation settings is a complex problem that is currently solved by assessing how a patient responds to each individual setting\textsuperscript{75,76}.

**DBS as a Learning Tool**

One of the major questions underlying DBS is “how does it work”. The mechanism behind the therapeutic effect of DBS is not understood, but various hypotheses exist. The four primary hypotheses are: disruption of pathological network activity\textsuperscript{77}, synaptic depression\textsuperscript{78}, synaptic inhibition\textsuperscript{79}, and blockading depolarization\textsuperscript{80}. The disruption of pathological network activity hypothesis suggests that the neural signals contain information that is inherently disruptive of normal functioning. The “content” of the neural signals is flawed and the intended message is being obscured by some undesirable message. In this case, DBS is effective by disrupting this undesired message and allowing normal functioning to occur. This is inherently different than the other hypotheses because it is based in the notion that DBS actively changes the content of brain signals, while the other hypotheses suggest that DBS is more of a disruptive “temporary lesion”. The minute differences between the hypotheses boil down to the ultimate questions of “what does DBS do to the cells of the brain”.

Researchers have evaluated the activity of neurons local to the deep brain stimulation electrode and neurons far away from the electrode to try and understand
how stimulation impacts their behavior. High frequency stimulation reduces the neuronal firing of a nucleus local to the deep brain stimulation. It is hypothesized that the high frequency of the stimulation disables the normal functioning of the voltage-gated proteins in the cellular membranes of the neurons; neurons cannot produce action potentials without the use of voltage-gated proteins. Recordings from neurons far away from the electrode shows that the effects of stimulation partially depend upon how close the electrode is to fiber tracks. Stimulation modeling predicts that high frequency voltages will activate fiber tracks descending/ascending from nuclei. This means that the effect of the stimulation will depend upon the original characteristics of the fiber tracts.

Depending on the cells and neurotransmitters present in a nucleus, its fiber tracts may be excitatory, inhibitory, or both. A balance of excitatory and inhibitory action potentials controls the extent to which various regions of the brain are activated. If the DBS electrode is placed close to fiber tracks from an excitatory nucleus, the effects of DBS are expected to be excitatory, and vice versa. Another complexity in the mechanism of DBS is antidromic action potentials. Under normal physiological conditions, a neuron produces an action potential at a region called the axon hillock and the signal is then transmitted down its axon to another neuron where it forms a synapse. Action potentials travel unidirectionally when they are produced by a cell. Stimulation allows for bidirectional action potentials because it can trigger an action potential in the middle of the axon. At the site of the stimulation, an action potential is sent towards the synapse and the axon hillock. Changes in cellular dynamics as a result of antidromic stimulation are not understood. Clearly, there are many complexities at
play in the mechanisms of DBS. One further complexity is the lack of understanding of neuroplasticity. The immediate effect of DBS is one complicated question, but there is also the question of what the stimulation is doing to the brain in the long term. Few studies have effectively addressed this question and it is currently a hot topic of research\textsuperscript{90,91}.

**Expanding the Reach of DBS**

Following the application of DBS to PD, physicians looked outwards to other diseases that might be treatable with this approach. Essential tremor, a disorder characterized by excessive tremor when an individual has the intention to move, was the first obvious choice\textsuperscript{92}. At rest, individuals with essential tremor do not have a tremor\textsuperscript{93}. When the intention to move emerges, such as the desire to pick up a cup of coffee, the hand begins to tremor. PD and essential tremor are fundamentally different disorders with different associated pathologies\textsuperscript{94}. PD is a degradation of the SN, while essential tremor is a cerebellar disorder\textsuperscript{95}. The ideal location for stimulating the brain in PD patients is not the same as the ideal area for stimulating the brain in essential tremor patients\textsuperscript{96,97}. To treat a new disorder with DBS, the ideal target needs to be established or the therapy may be unsuccessful.

The number of disorders treated with DBS continued to grow after the successes of PD and essential tremor. Dystonia, a disease of continual muscle locking and inability to move, was next to be treated with DBS\textsuperscript{98}. But the effects of DBS on dystonic patients was different than PD and essential tremor\textsuperscript{99}. In these other two disorders, an immediate reduction in symptoms was observed when DBS was turned on. Dystonia patients, however, did not show improvement for multiple months after stimulation was
first turned on. The long latency between stimulation onset and benefit was, and still is, a major complication in the understanding of how DBS works.

DBS was further extended as an experimental therapy for many major neurological disorders. While FDA approval is required for implantation of most major medical devices, some exceptions do exist. For patient populations that are implanted less than 4000 times per year, the FDA allows for a Human Device Exemption (HDE). The HDE is a label that allows for specialized medicine which is approved for one indication to be applied to another indication if the number of individuals to be treated is sufficiently small. The reason for the HDE is that the cost of acquiring FDA approval is millions of dollars and this pay wall could potentially prohibit small populations from ever receiving the medical treatment that they need. Under the HDE and other exception criteria, DBS has been applied to disorders such as Obsessive Compulsive Disorder, Depression, Addiction, Obesity, and Tourette Syndrome (TS). The study of DBS in TS is the primary focus of this dissertation.

**Tourette Syndrome**

The clinical hallmark of TS is involuntary, sudden, repetitive, yet fluctuating movements and vocalizations with varying degrees of intensity, frequency, and durations. The course of tics is unpredictable and varies across patients. Common simple motor tics include eye blinking, head, neck or limb jerking, sustained mouth opening or shoulder rotation, and examples of complex motor tics are touching, hitting, gyrating, bending and copropraxia (gesturing and touching of genitalia). Common vocal tics are grunting, squeaking, coughing, sniffing, snorting and throat clearing. Although coprololia (shouting obscenities or profanities) is popularly considered to be a cardinal feature of TS, only 10-19% of individuals with TS exhibit this
symptom$^{107}$. In the appropriate context, many tics would appear as non-pathological behaviors. It is the lack of context, the urge to do the motion, and the repetitive nature of the motion that makes it a tic$^{106}$. The social environment and other triggers may influence how many tics the individual feels the urge to express$^{108}$. In some cases, high levels of stress have been seen to magnify the number of tics$^{109}$. Although these risk factors can affect symptomology, the disease is not of psychogenic origin. Evidence of this stems from the clinical effectiveness of neuroleptic drugs in many TS cases$^{110}$.

TS is an early onset disease, with an average age onset of 6-7 years old$^{111}$. The criteria for diagnosis of TS is that the patients must have 1) a combination of chronic motor and phonic tics, and these must 2) occur several times a day for at least 1 year. 3) The symptoms must have an onset before the age of 18 years of age and 4) these must not be explained by other medical/neurological conditions (Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) and the International Classification of Diseases, tenth edition criteria)$^{112}$. It is common for individuals with TS to suffer from comorbidities such as obsessive compulsive disorder (OCD), attention-deficit/hyperactivity disorder (ADHD), impulse control disorder, and other behavioral disorders$^{113}$. For many cases (about 50%), the symptoms of TS decrease as individuals enter adulthood$^{114}$. In others, symptoms may worsen and introduce complications to relationships, employment, and physical safety$^{115}$.

A number of treatment options exist for TS. Habit reversal using psychotherapy has been effective in reducing tics in some cases$^{116}$. Haloperidol and pimozide are FDA-approved antipsychotics for the treatment of TS$^{117}$. Other non-FDA approved medications for treating TS, such as guanfacine, are under investigation$^{118}$. Many of
these medications have shown promise in reducing symptoms of TS during clinical trials, but some patients are non-responsive to these therapies or their tics are so severe that they have difficulty functioning normally even with medication\textsuperscript{110}. This small portion of the TS population is deemed treatment refractory. For patients in this category, invasive procedures are the next best treatment option.

Surgical interventions for high severity treatment refractory TS have been developed over the last six decades. Frontal lobotomies and leucotomies were performed on TS patients as early as 1955\textsuperscript{119}. Surgical lesioning of the cingulate cortex, midline thalamus, intralaminar thalamus, ventrolateral thalamus, dentate nucleus and others have been investigated and turned up mixed results\textsuperscript{120}. Amidst the vast number of attempted surgical targets is growing evidence of the pathophysiology of TS and the key brain regions involved in the disorder\textsuperscript{86}. Functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS) have shown an increase in excitation of the primary motor (M1) cortical areas in TS patients\textsuperscript{121}. Evidence suggests that the basal ganglia, a network of subcortical structures within the brain, is involved in motor program selection\textsuperscript{122}. Pathological firing patterns within the basal ganglia may give rise to undesired motor programs that interfere with normal motor program selection downstream in the motor cortex\textsuperscript{86}. The basal ganglia are connected to thalamic nuclei that than project onto motor cortices, which then feed back into the basal ganglia\textsuperscript{39}. Improper functioning of the thalamo-cortical-basal ganglia (TCBG) loop is one of the major hypotheses behind the pathophysiology of TS\textsuperscript{86}. To further investigate the pathophysiology of TS, the following research was proposed at the time of the qualifying exam.
Specific Aims
Specific Aim 1. To Determine the Electrophysiological Markers of Tics in TS.

Pathophysiological neural data is assessed by investigating the changes in brain activity when patients have tics. Some patients exhibit the ability to suppress their tics for a period of time, allowing for acquisition of a tic free movement free baseline. Acquiring a tic free baseline in patients who cannot suppress tics will require knowledge of when the tics are occurring within the neurological data. To achieve this, we employed several recording modalities to quantify movement and activity. Neurological data, EMG/accelerometer, and video data were acquired simultaneously and synchronized. A low powered, clinically safe, stimulation was generated from the deep brain stimulator at the beginning and end of each recording. This internal stimulation is detectable on the external EMG electrodes. Synchronization of the EMG and neurological data was achieved by aligning the stimulation pulse detected in the EMG signals with the stimulation pulse present in the neurological signals. A connection between the EMG system and the camera allows the EMG and video data streams to be synchronized. As a result, the EMG, video, and neurological data can all be viewed in the same timeline. A neurologist examined the video data and identify periods of time in which the patient was ticing. Analyzing the neurological data and EMG at these times will allow for observation of the frequency specific features present within the motor cortices and thalamic regions at the time of tic. This high precision time localization of neurological data related to tic allowed us to investigate causality between brain structures, the origins of tic, and predictability of tics.

To date, we have implanted two patients with Medtronic Activa PC+S Neurostimulators. Analysis of intraoperative data reveals features of tics within thalamic
regions in both patients. Data for two patients is shown in Figure 1-1. The patients were asked to perform a series of tasks in interleaved trials. The conditions were left hand movement, right hand movement, ticing, and baseline (no movement or ticing). An $R^2$ (coefficient of determination) analysis was performed to identify spectral and spatial features of each condition. Only statistically significant results ($p$-value < .05) are shown in Figure 1-1. High frequency activity within the contralateral motor cortices was observed during movement (e.g., the left motor cortex displays increased high frequency activity during right hand movements). No thalamic activity was observed during volitional movements. Low and high frequency activity was observed in the contralateral thalamic and cortical regions during tic. The spectral and spatial distinction between volitional movements and tics suggests that detecting tics from brain activity is possible.

The high frequency features are not observed in the post-operative data. Low frequency features, in contrast, were still present in post-operative data (Figure 1-2). The activity of the thalamic and cortical signals in these low frequency bands was compared with the times in which tics occurred (as specified by a neurologist). A strong relationship between tic onset and low frequency signals in thalamic and cortical electrodes was observed. An offline threshold detection method utilizing the instantaneous variance of the 1-10 Hz bandpassed cortical and thalamic data was developed for the first patient. The method was evaluated by its sensitivity and specificity. Sensitivity was defined as the percentage of tics that were detected. Specificity was defined as the percentage of detections that occurred during an actual tic. A sensitivity of 85% and a specificity of 83% across 4 months of tic data were
obtained. Further analysis is necessary to improve detection rates. This aim is addressed in Chapter 3.

**Specific Aim 2. To Uncover the Effects of Acute and Chronic DBS Stimulation on Thalamo-Cortical Circuits in TS.**

At each follow-up visit, patients were given a new set of clinically defined “therapeutic” settings. High frequency stimulation tends to provide therapeutic benefit. To assess the response of the brain to the therapeutic settings we performed a series of experiments. To assess therapeutic stimulation from arbitrary stimulation, we tested against a power-matched low frequency version of the patient’s therapeutic stimulation setting. These power matched, low frequency settings will be referred to as the “non-therapeutic settings”. A “no stimulation” baseline was also be collected. The patient was blinded to whether they were receiving high frequency stimulation or low frequency stimulation. Video footage was recorded during all trials. The patients were asked to refrain from any volitional movements during the trial and to remain awake. A baseline recording, without any stimulation, was first collected from all channels. Then the therapeutic stimulation settings, or non-therapeutic stimulation settings were activated in the deep brain stimulator. Stimulation was provided for 10 minutes. Data collection began when the stimulator has been on for 8 minutes. Four minutes of data will be collected at 800 Hz. Therefore, two minutes of stimulation ON and 2 minutes of stimulation OFF will be collected. This data will be statistically analyzed to investigate the physiological implications of deep brain stimulation.

In our first subject, we investigated changes in phase-amplitude coupling (PAC) during periods without, during, and after nontherapeutic/therapeutic stimulation. Consistent PAC within conditions across multiple months in electrodes over the primary
motor cortex were observed. PAC was driven within the alpha-phase gamma-amplitude range post-therapeutic stimulation. PAC within the same range was observed during the tic-free, movement free baseline condition. No PAC was observed post-nontherapeutic stimulation. During tics (not shown), no PAC was observed. A visual trend was observed between the PAC and YGTSS scores of the patient. This may indicate that PAC in cortical electrodes is a marker for therapeutic stimulation settings. Further investigation will clarify these findings. No consistent patterns in PAC were observed within thalamic electrodes. This aim is addressed in Chapter 4.

**Specific Aim 3. To Test the Effectiveness of Responsive Stimulation in the Acute Setting.**

Responsive brain stimulation techniques have been hypothesized to have potential advantages compared to continuous DBS. These advantages include 1) the provision of a better and specifically tailored approach for individual patients, 2) the ability to address the paroxysmal nature of the symptoms of TS, 3) a long-term strategy that may prevent or limit tolerance to the stimulation, 4) decreased side effects, and 5) increased battery life. We assessed the effectiveness of responsive DBS in reducing tic severity in the acute setting. Data recording sessions with no stimulation will be interleaved with stimulation trials as a control. Multiple trials of each method will be performed in randomized orders. Neurological data, EMG, and video will be captured during all trials and a trained neurologist will assess the YGTSS.

The Medtronic Activa PC+S (specifications and device limitations available\(^{123}\)) was designed for stimulation, recording, and detection of real time events. Real time detection is triggered using the power channels. A built-in online support vector machine classifier can be used to detect changes in state. The classifier is generated offline from
the power data during two different conditions. After the classifier is built, it is uploaded to the neurostimulator. The neurostimulator creates time stamps that mark when an event detection occurs. Using an external communication device called Nexus-D, it is possible to trigger stimulations. As mentioned earlier, real-time tic detection will be evaluated in the acute setting during follow up visits. Once tic detection reaches high accuracy, an acute stimulation will be provided at the time of tic detection. Various stimulation settings and durations will be tested across multiple trials. This aim is addressed in Chapter 5.
Figure 1-1. Movement and Tic related Activity. A) Subject 1 brain model and electrode implants. B) Bipolar raw data collected from Medtronic Activa PC+S from the motor cortex (top; in black) along with its spectrogram normalized to baseline (bottom; in log scale) around tic onset. C) Raw data from thalamus time aligned with cortical data in B. D-E) Raw data and spectrograms during voluntary hand movement over hand motor cortex and thalamus. Raw activity in thalamus shows distinct patterns during tics compared to voluntary movements. F) Subject 2 brain model and electrode implants. G-H) Raw data and its spectrogram in subject 2 during tics and movement.
Figure 1-2. Cortico-cortical phase amplitude coupling patterns during baseline and following stimulation. Phase amplitude coupling is a measure of interactions between low frequency phase (long range) and high frequency amplitude (local). Recent studies have shown that PAC is modulated during stimulation in Parkinson’s Disease. Here we show modulations in PAC following therapeutic stimulation that differ from non-therapeutic stimulation across 3 months. The Yale Global Tic Severity Scale (YGTSS) is a quantification of tic periodicity. A reduction in YGTSS scores indicates an improvement in symptoms. The YGTSS scores for this patient decreased with treatment.
CHAPTER 2
IMPLANTATION OF DBS ELECTRODES

Delivering therapeutic DBS is a complex task that involves multiple stages of vetting, planning, surgery, and post surgical follow up visits. Even with the correct placement of a DBS electrode and a skilled team of medical staff, some patients may not receive benefits from DBS therapy\(^{124}\). The reason for this is partially because some physical manifestations may appear to be one disorder, but the underlying pathology is actually a different disorder\(^{125}\). In addition, even if the underlying pathology is correctly identified, the symptoms that can be effectively managed via DBS therapy are not always the most debilitating elements of the disorder\(^{126}\). Therefore, choosing a patient for DBS therapy requires an understanding of the patient’s quality of life with their disorder.

At the University of Florida, a multidisciplinary team of psychiatrists, psychologists, speech therapists, neurologists, and neurosurgeons meets with patients who have been referred by external doctors for DBS therapy. Based upon the patient’s indication, a profile is generated to propose implantation of a DBS electrode into a specific region of the brain. The profile of the patient will include a complete medical history, video examples of the patient’s disorder, and the results of several neurological and physiological tests. Each member of the multidisciplinary team works with the patient individually and generates a report of their impression of the patient. Later, a meeting is held with all members of the team and a discussion is had to share the information and expertise of the various members. The culmination of this meeting is the decision to move forward with implantation or to reject the patient for DBS.
When a patient is selected for DBS implantation, the layout of the patient’s brain must be digitally scanned into 3-dimensional space using imaging technology. Computed tomography (CT)\textsuperscript{127} and magnetic resonance imaging (MRI)\textsuperscript{128} scans of the patient’s head are collected. The CT scan is sensitive to the density of tissue and this information is used to appropriately model the skull and architecture of the head. The CT does not have sufficient resolution to delineate between brain structures. The MRI is sensitive to the amount of hydrogen in a material and can be used to delineate between various structures within the brain and on the surface of the brain. The MRI and CT scans are fused together\textsuperscript{129,130}, via a process called coregistration, to form a complex image that uses the advantages of both modalities. Coregistration is the process of rotating and scaling 3-dimensional images so that specific key points, called fiducial markers, in both images are aligned\textsuperscript{131}. A coregistered set of images can be directly overlaid and easily compared because the 3-dimension coordinates of both images are identical. The fused MRI-CT scan allows for identification of key brain regions within the scope of the coordinates of the brain/skull in the real world.

To locate the target region of the brain for DBS, neurologists and neurosurgeons must start by identifying key landmarks of the brain. The anterior commissure (AC) and posterior commissure (PC) are some of the most easily visible fiber tracks in the brain due to their size\textsuperscript{132}. A line is drawn that intersects the AC and PC, and this is known as the AC-PC line. With the AC-PC line as a reference, the expected coordinates of the target brain region can be identified\textsuperscript{133}. The slices of the brain thought to contain the target region are then inspected. The MRI-CT is fed into a system that compares the data of the current patient’s brain to an “atlas” of brain regions\textsuperscript{134}. The atlas is
essentially a set of expertly labeled human brain images that are compared with a new brain image. The atlas attempts to automatically label the specific regions of the brain in this new patient's brain image. With the labeled MRI-CT scan, the neurosurgeon chooses a target location for the electrode. Then, following analysis of the entire brain image, the neurosurgeon plots a trajectory from the exterior of the skull to the target region. This trajectory must be expertly planned; the trajectory cannot intersect with major vasculature or a bleed, complication, or death may occur. After all planning and preparation is complete, a patient is cleared for surgery.

The surgical suite for DBS is designed with a specialized layout and set of tools. The configuration of each operating room may vary from site to site. The following details regarding the operating room pertain to the configuration at UF Health. The first major difference between DBS implantation surgery and most other surgeries is that the patient is usually awake. Implanting electrodes into the brain can have many unforeseen complications and currently there is no reliable technique available to detect motor or psychiatric deficits that might occur during a surgery if a patient is not awake. Due to the patient's consciousness, they will breath on their own. A freely moving and freely breathing patient presents complications with the maintenance of a sterile field. In many non-DBS surgeries, a patient's body will be covered with a sterile drape and only the relevant portion of the body will be exposed. DBS surgeries typically include a divider in the room that separates sterile from sub-sterile. Most of the patient's body is in the sub-sterile field and the patient's scalp is in the sterile field. On the sub sterile side of the surgical suite resides the neurologist, nursing staff, anesthesiologist, DBS device
experts, and engineers. The sterile side of the surgical suite includes the neurosurgeons and any staff necessary to assist them during the surgery.

The surgery begins with the mounting of the head ring. The head ring is a metal device locks the patients head into a fixed position and places it in the same coordinate system as the co-registered MRI-CT scan. Next the relevant portion of the patient’s scalp is sterilized and local anesthetic is applied to the scalp. Incisions are made into the skin the reveal the skull and retractors, or skin clamps, are put in place to hold the skin back. The neurosurgeon then carefully drills into the skull to in order to reveal the brain and surrounding dural tissues. The brain does not contain pain receptors, but the tissue immediately above it, called the dura mater, does contain pain receptors. Once an adequate portion of the skull has been removed, the dura mater is exposed to open air. The neurosurgeon applies an anesthetic to the dura mater and then bisects the dural tissue to reveal the brain. At this point, the implantation of the electrode can begin.

Implantation of a DBS electrode requires machine level precision and accuracy, combined with human intuition and guidance. A robotic apparatus is used to advance the electrode through the brain tissue along the trajectory planned by the neurosurgeon before the surgery. The apparatus, under the neurosurgeons control, performs a large portion of the electrode placement automatically, until the electrode is about 30mm away from its target. Then, the neurologist temporarily takes control of the DBS electrode implantation.

The neurologist holds in his hand a small device with an analog wheel that he can use to advance the DBS electrode deeper or shallower in the patient’s brain. The
exact target location the DBS electrode typically cannot be resolved using imaging alone. A more precise localization of the target brain region is determined by analysis of the single neuron activity\textsuperscript{29}. The neurologist analyses the single neuron activity, advances the electrode a bit, analyses the activity again, and repeats this process until the patterns of neuron firing suggest that the desired location has been reached. In addition to this, a series of tests may be performed to elicit changes and validate implantation. One example of this is: indirect detection of the optic tract. The globus pallidus is a brain nuclei that is sometimes a target for DBS\textsuperscript{97}. The globus pallidus is located beneath the optic tract\textsuperscript{139}. The optic tract is a fiber bundle that carries information directly from the retina of the eye to the back of the brain\textsuperscript{137}. When an individual sees a bright light, a large signal is sent through the optic tract to the back of the brain. A change in the signal coming from the globus pallidus after a light is flashed in the patient’s eyes can help validate the location of the electrode. For other types of electrodes, such as electrocorticographic (ECoG) electrodes\textsuperscript{140} that rest subdurally on the surface of the brain, a separate set of techniques are employed to validate electrode location.

For some DBS cases, such as the DBS cases described in this document, electrodes are placed on the surface of the brain as well as deep inside the brain. The placement of ECoG electrodes involves initial planning based upon the MRI-CT scan as well as intraoperative testing. Electrodes in this study were placed over the premotor and primary motor cortices. The motor cortices are gyri on the surface of the brain that are responsible for the processing and generation of movement\textsuperscript{141}. The motor cortices are located anterior to the central sulcus, a divide in the brain that separates motor
processing from sensory processing\textsuperscript{137}. Locating the motor cortices intraoperatively is a complex task because there is no standard device utilized for placing ECoG strips between the dura and the brain tissue.

To circumvent this difficulty, techniques have been developed to identify the location of the central sulcus intraoperatively. A procedure called the evoked potential phase reversal technique\textsuperscript{142} is effective for identifying the location of the central sulcus. Electrodes are placed on the surface of the patient’s hand and an electrical stimulus is periodically delivered. The electrical activity from the ECoG strips that are suspected to be near the central sulcus are recorded and time aligned to the delivery of the stimulus. A large positive deflection in neural activity is observed in the motor cortices when the electrical stimulus is delivered to the hand. Conversely, a large negative deflection in neural activity is observed in the sensory cortices when the electrical stimulus is delivered to the hand. Depending on whether the ECoG strip is before or after the central sulcus, the deflection will be either positive or negative. The neurosurgeon moves the ECoG strip multiple times and measures the evoked response. Using the deflections as feedback, the neurosurgeon can more confidently say that the electrodes are placed on the motor cortices, as opposed to the sensory cortices.

Beyond the phase reversal technique, additional approaches must be employed to verify the location and function of the tissue beneath the ECoG strips. The motor cortices are complicated structures that have a highly organized somatotopic structure\textsuperscript{17}. The regions of the motor cortices that process information regarding the hand are different than the regions that process information regarding the throat. The functional mechanisms of the tissue beneath the ECoG strip are identified by a process
called real time functional mapping (SIGFRIED). SIGFRIED is a computation technique that utilizes Gaussian mixture models on top of gamma activity measured from multiple ECoG contacts in an effort to identify relationships between specific contacts and patient activity. Gamma activity is a specific range of frequencies from the electrical signals of the brain that are highly localized. Research has shown that the gamma activity of specific brain regions can be used to predict various human functions such as movement and speech. During a SIGFRIED task, a patient is asked to remain still, move their hands, and mimic a kissing motion. A computer collects the data during these different conditions, builds a model, and reports which contacts are on top of areas of the brain that control specific functions. The performance of this algorithm has been tested against the gold standard of stimulation based functional mapping and a strong correlation between the results of both tests has been observed. Following SIGFRIED, the patients were asked to perform another series of tasks. These tasks are described in chapter 3 in the intraoperative recording section. Additional details regarding the specifics of the implantation in the patients described within this document is also available in Chapter 3.

Following DBS electrode and ECoG strip implantation, the patient’s scalp is closed and the patient is anesthetized. In the case of elderly patients, this may be the end of the surgery, but younger patients may undergo all portions of the DBS surgery at one time. After DBS electrodes are in place, the pulse generator must be implanted. The pulse generator is the device that provides the electrical stimulation to the DBS electrodes. The pulse generator is typically implanted in the distal tissues of the chest above the breast and beneath the clavicle. A pocket to hold the pulse generator is
bisected into the chest tissue and the device is placed in the pocket. Then a cable connecting the DBS electrodes to the pulse generator is tunneled through the patient’s neck. The devices are connected and initial tests are performed to validate that the connection is successful. Any remaining open tissues are then closed and the patient is sent to recovery. In many modern cases, patients may go home the night of the surgery or the next day.
CHAPTER 3
TIC DETECTION

Introduction

Tourette syndrome is a neuropsychiatric disorder characterized by multiple motor and vocal tics\textsuperscript{148-107}. Tics are involuntary or partially voluntary movements that complicate daily tasks and frequently result in social embarrassment, leading to decreased quality of life\textsuperscript{115}. Tics generally begin in childhood and subside or lessen during puberty, however in approximately 20% of cases tics persist or even worsen\textsuperscript{103}. Numerous pharmacological and behavioral therapy options exist for Tourette syndrome\textsuperscript{104,149,150}, but in severe cases there may be little or no relief\textsuperscript{151}.

Deep brain stimulation (DBS) is an emerging therapy for severe intractable cases of Tourette syndrome and is yet to be approved by the FDA for this indication. It is reserved as a last line of therapy after other pharmacological and behavioral therapies fail\textsuperscript{152–154}. It is estimated that approximately 120 Tourette syndrome patients worldwide have been treated with DBS since 1999, and almost all 48 published studies report some degree of motor tic reduction\textsuperscript{155}. While initial trials have been promising, the mechanisms underpinning the success of DBS treatment in Tourette syndrome remain unknown. Current models of Tourette syndrome pathophysiology have hypothesized that thalamocortical basal ganglia dysfunction is as a key component leading to many of the symptoms in Tourette syndrome\textsuperscript{86,122}. Inhibitory input from basal ganglia structures directed toward thalamic nuclei likely plays a role in suppressing unwanted motor patterns while activating desired motor patterns. It has been hypothesized that dysfunctional striatal activity decreases inhibitory projections from basal ganglia structures resulting in excessive disinhibition of thalamic nuclei. This excessive
disinhibition in turn leads to the production of undesired motor patterns, also referred to as tics. To test this hypothesis, the electrophysiological correlates of tics must be studied. Presently, the available literature reports increases in low frequency (2-13 Hz) local field potential (LFP) activity within the centromedian-parafascicular nucleus of the thalamus (CM-PF) \textsuperscript{156} and a reduced mean frequency and irregular grouped firing during single neuron recordings from the globus pallidus internus (GPI) \textsuperscript{157} before and during tics. In a previous Tourette syndrome DBS study, our group showed that following six months of DBS therapy, 3 out of 5 patients with DBS in the CM-PF thalamic region had reductions in low-frequency activity that were coupled with an overall reduction in tic severity \textsuperscript{158}. Still, statistical evidence supporting the existence of electrophysiological tic related activity within thalamocortical structures has yet to be shown. Understanding tic genesis and using this information to advance Tourette syndrome therapies, such as the development of closed-loop DBS, will require investigation into the chronic signatures underpinning tics. We sought to identify these electrophysiologic signatures using chronically implanted thalamic and cortical electrodes and to develop a tic detector that could initiate DBS when pathological activity is present.

**Materials and Methods**

**Subjects**

The first subject (TS01) is a 23-year-old female, who was diagnosed with TS at the age of 8. Her tics are dystonic in appearance and take on a number of forms including full arm extensions, shoulder jerks, neck twisting, grimacing, forceful upward eye movements, barking, and occasionally groans. A majority of this subject’s tics were lateralized to the right side of her body. She demonstrated the ability to suppress her
tics. The second subject (TS02) is a 25-year-old female who was also diagnosed with TS at the age of 8. Her tics included cursing, kissing sounds, yelling, blinking, snorting, shrugging, eye rolling, finger tapping, head bobbing, and hitting her own face. A majority of the tics were centralized to the face; tics involving the extremities were less frequent. This subject’s tics tended to reduce in intensity and frequency when she focused on a task (e.g., singing). Both subjects provided informed consent as approved by the University of Florida Institutional Review Board (IRB-01) and by the US Food and Drug Administration (FDA) through an investigational device exemption (IDE).

**Implantation and Localization of Electrodes**

High resolution T1+Gad and FGATIR MRI coupled with a deformable (patient-specific) brain atlas were used to plan the targets and trajectories of both the bilateral 4-contact CM-PF thalamic DBS leads (Medtronic 3387, Medtronic, LLC, Minneapolis, MN) and the bilateral 4-contact motor cortical subdural strip electrodes (Medtronic Resume II) through one frontal burr hole on each side of the skull. This MR-based plan was fused to a stereotactic CT acquired the morning of surgery after application of a CRW head frame. No sedation was used for head frame application or during the operative procedure. Burr holes and dural incisions were placed at the stereotactically identified sites after local anesthesia and the subcortical electrode arrays were placed over the hand motor cortex, since many motor tics involve involuntary movements of the hands and/or arm. The strips were positioned over the structural motor hand knob; and the hand sensorimotor cortex was localized intra-operatively using somatosensory evoked potentials (SSEP) and real-time functional mapping. After implantation of the subdural strips, a microelectrode was advanced using a micropositioner (FHC, Bowdoin, ME) along the planned thalamic trajectory to allow for physiological
monitoring. The advancing electrode was held steady at multiple depths through the trajectory in order to allow for consistent recordings of single neurons at specified depths along the DBS lead trajectory. DBS leads were implanted and intra-operative macrostimulation was performed to assure that thresholds for stimulation-induced side effects were acceptable. A single Medtronic Stimloc cap (countersunk flush with the skull and modified to allow the egress of two leads) was used on each side to secure both the DBS leads and the cortical leads in place and intra-operative fluoroscopy was used to ensure that the leads were not displaced during this process. We co-registered pre-op MRI + patient specific atlas images with (1-month) delayed post-op high-resolution CTs to precisely identify the anatomic locations of each of the 16 implanted electrodes.

**Experimental Design**

Subjects were instructed to rest (suppress their tics to the best of their ability), to tic freely, and then to perform volitional movements (while suppressing tics); see Figure 3-1. Intraoperative LFPs were collected in a unipolar configuration from all 16 implanted contacts by using an external amplifier (Neuroscan Synamps 2, Compumedics, Charlotte, NC), and these LFPs were referenced to a subdermal electrode placed in the scalp. Postoperative LFPs were recorded in a bipolar configuration with the Activa PC+S (Medtronic, Inc., Minneapolis, MN) at 800 Hz or 422 Hz. The Activa PC+S is a first generation DBS device that is capable of recording and transferring neural data through telemetry, as well as stimulation\(^\text{160}\). There was at least 30 minutes between when stimulation was turned off when the patient arrived at the clinic and when “baseline” data was recorded. One channel of data from CM-PF depth contacts and one channel of data from cortical motor cortex contacts were collected simultaneously in 8-
minute segments in bipolar configuration. Postoperative recordings were taken from the empirically determined best contacts from intraoperative data collection. The empirically derived contacts were determined by identifying the electrodes with the highest $r^2$ value between the tic and baseline conditions. Surface EMG recordings, without accelerometers, were collected with TS01 (Ag/AgCl electrodes, Neuroscan Synamps 2). Accelerometers and surface EMG were used with TS02 (Delsys wireless EMG/accelerometer system, Natick, MA, @ 1925.93 Hz and 148.15 Hz, respectively). EMG/accelerometers were placed bilaterally on the forearm, bicep, and neck. Stimulation from the Activa PC+S was observed on neck EMG, which was used to synchronize the LFP and EMG/acceleration signals. Synchronization of video and EMG was achieved with a signal-syncing device developed in house. Our initial behavioral paradigms had instructed subjects to voluntarily mimic their tics as the control condition. However, subjects indicated that this inadvertently led to real tic initiation, and may have biased a clear delineation between tic and voluntary movements. Therefore, subjects were instructed to perform naturalistic volitional movements that did not necessarily appear like their tics.

**Intraoperative $R^2$ Analysis**

Coefficient of determination ($r^2$) analysis was performed between movement free baseline data and the test conditions (voluntary left hand movement, right hand movement, or tics). The $r^2$ measure represents the proportion of the signal feature that is accounted for by the test condition. The larger this value, the larger the proportion of the signal feature that can be accounted for by the test condition $16^1$. Significance was calculated by determining the probability that a given $r^2$ value would be observed within an F-cumulative density function defined by the number of data points in the baseline
and task (e.g., ticcing, or volitional movement) condition. A p-value of .05 was used to
determine statistical significance of the calculated unsigned $r^2$ value between the
baseline and testing conditions. The null hypothesis is that the signal feature does not
account for differences between the baseline and the task condition for the given $r^2$
value.

**Support Vector Machine**

A support vector machine \(^{162}\) was trained on 30 seconds of tic-free baseline and
30 seconds of tic data collected at the beginning of each follow-up visit. LFPs were
band pass filtered into non-overlapping 10 Hz bins in the 1-100 Hz range, rectified,
down-sampled to 10 Hz, and smoothed with a 40 Hz low pass filter prior to training and
classification. The 40 Hz low pass filter improved detection rates without greatly
distorting the data under visual inspection. We used the top 3 discriminating features
from the original 20 (10 spectral bins each from CM-PF and motor cortex). The most
significant features were selected by identifying the top 3 bins from CM-PF and/or motor
cortical features that had the highest $r^2$ statistic comparing baseline and tic training data.
The input to the support vector machine was the power from the top 3 bands and the
output was a binary decision of “tic” or “not a tic”. Feature selection and the support
vector machine were retrained with each follow up visit. Detection was evaluated using
recall (i.e., sensitivity) and precision.

Recall is identical to sensitivity, but precision (also known as positive predictive
value) was chosen over specificity because the former does not depend upon true
negatives (i.e., when absence of tics did not lead to detection). Tics are paroxysmal
events, and thus the occurrence and absence of tics are unbalanced. A detector applied
to an unbalanced dataset evaluated with specificity could detect zero events, but still
achieve a high rating because the large number of true negatives would falsely inflate the scores. We calculated recall and precision for simple tics (single muscle group), complex tics (multiple muscle group), and long complex tics (multiple muscle group and lasting longer than 5 seconds). A true positive was defined as detection at the beginning of the tic, or occurring for at least 70% of the duration of the tic. A false positive was defined as a detection that was not concurrent with a tic, or within 2 seconds of the onset/end of a tic. A false negative was defined as a tic with no detections at its onset, or less than 70% detection of the tic duration.

Results

Intraoperative Recordings

We observed statistically significant low (1-10 Hz) and high (30-100 Hz) frequency CM-PF activity during tics, which were not present during volitional movements (p<.05). Statistically significant high frequency activity within premotor and motor contacts was observed during volitional movements, but no statistically significant activity was observed within CM-PF contacts (p<.05) (Figure 3-2B). We observed similar patterns of statistically significant CM-PF and motor cortex activity in TS02 (p<.05) (Figure 3-2D). Statistically significant cortical activity from the hand motor region during volitional movement and tics in both patients were more clearly observed in the most posterior contacts (p<.05).

Postoperative Recordings

Fig. 3 shows examples of tics and volitional movements as captured by EMG activity, along with neural recordings. Data was collected monthly for 6 months following implantation in a bipolar configuration. Stimulation was disabled during data collection. Low frequency (1-10 Hz) CM-PF activity was observed during tics in postoperative data.
from both subjects (Figure 3-3 and Figure 3-4). An increase in the low frequency CM-PF LFP was observed concurrent with or preceding the desynchronization of motor cortex beta activity at the onset of tics. Volitional movements involving the same body regions as tics did not evoke low frequency CM-PF activity. High-frequency (40-100 Hz) changes in CM-PF activity were not observed postoperatively during tics. This was most likely due to the higher noise floor of the implanted devices or high frequency attenuation that was potentially caused by the bipolar electrode configuration (see Supplementary Materials).

**Tic Detection**

We constructed a tic detector and examined the consistency and reproducibility of the clinical tic signatures over the course of a 6 month period. Detection results for both subjects are available in Table 1. The most effective signal for tic detection varied with time. This was likely a result of variable signal quality, changes in tic appearance, patient stress, stimulation efficacy, or physiological factors. The CM-PF signal was in general more robust with TS01. TS01 had more long complex tics than TS02 and this type of tic seemed to be the most detectable. Simpler tics may not be associated with as large of a signal in CM-PF and are easier to see as changes in M1 activity. Long complex tics were concurrent with a highly detectable thalamocortical signature with average recall 88.6%, average precision 96.3% in both patients. Complex tics were detected with an average recall of 63.9% and precision of 36.6% and simple tics were detected with an average recall of 39.3% and precision of 37.9% across both patients.

In total, long complex tics accounted for 54% of all tics, complex tics accounted for 31% of all tics, and simple tics accounted for 15% of all tics. 79% (139/176) of all positive detections were within a 100ms window of tic onset. 14% of all positive detections were
observed before tic onset (on average 800ms before tic onset) and 7% of positive detections were observed after tic onset (on average 500ms after tic onset).

Feature selection varied from month to month across both patients. CM-PF low-frequency bands (1-30 Hz) were the most discriminating features in months 2,3,5,6 for TS01 and months 1,5 for TS02. A combination of CM-PF activity in the low-frequencies (1-20 Hz) and motor cortex activity in multiple bands (1-10 Hz, 20-40 Hz), including beta, were the most discriminating features in month 4 for TS01 and in months 2,3,4, and 6 for TS02. The patients were under open-loop DBS for the entirety of the study. DBS was only disabled during data recordings to eliminate artifacts resulting from stimulation during the study. False positives were not observed during volitional movements. Most false positives did not coincide with any particular event or motion; others coincided with yawning, moments where patients described their reaction as surprised, or itching sensations. We also tested detection using the features obtained from the first month, which were 1-30 Hz CM-PF for both patients. The detection of long complex tics was preserved even when the detector was not retrained.

**Discussion**

**Signal or Motion Artifact?**

Data collected intraoperatively from both subjects exhibited properties that demonstrate that tic related signals are not movement artifacts. Intraoperative R² analysis revealed high amplitude activity within thalamic and cortical structures contralateral to tic, but less activity within structures ipsilateral to tics. These intraoperative recordings were taken prior to the tunneling of cables through the neck and while the patients’ heads were securely mounted with a head frame. The largest source of artifact, in this case, would be from movement generated at the tissue
electrode interface. Therefore, if the tic related signal was driven by movement artifact, there would have to be more force delivered to the hemisphere of the brain contralateral to movement than the ipsilateral hemisphere. The dampening of forces through tissue would suggest that it is unlikely for a force traveling a longer distance to be larger than a force travelling a shorter distance. Therefore the increase in activity within contralateral structures cannot be reduced to only movement artifact.

Postoperative data collection showed high specificity for tic related signals. Out of the various combinations of bipolar signal pairs, only a few channels showed a strong signal when tics were present in both patients. Multiple, if not all, electrode pairs should have exhibited changes in activity if the tic signal was actually a movement artifact or the result of cable twisting within the neck. Again, for TS01, whose tics were highly lateralized, tic signatures were present only in the contralateral hemisphere. The recordings in the hemisphere ipsilateral to the tic motions should have been contaminated with these features had they been motion artifacts.

**Tics and DBS**

It has been hypothesized that thalamocortical basal ganglia dysfunction is a key component of Tourette syndrome and tic genesis. DBS of CM-PF and globus pallidus are associated with favorable therapeutic outcomes in TS. Tic related electrophysiological activity of globus pallidus has been observed and reported and we now present evidence of tic related electrophysiological activity within the CM-PF. In our analysis, we observed that low frequency CM-PF activity increased and beta motor cortex activity decreased during tics. Changes in CM-PF activity were not observed during volitional movements, but decrease in beta amplitude in motor cortex activity were associated with both tics and volitional movements (see Figure 3-3 and Figure 3-
4). A large increase in M1 beta activity was sometimes observed prior to a tic, which helped in differentiating tics from volitional movements. These observations, as well as the observations from previous studies \(^{158}\) implies that increased low frequency CM-PF thalamus activity is associated with undesired motor patterns. In addition, this evidence suggests that tics may have a specific biomarker that could be tied to the pathophysiological mechanisms underpinning tics.

Using video obtained at each month’s visit, we detected long complex tics with an average recall of 88.6% and the average precision 96.3%. These results are promising, however a tic detector should also be able to run without retraining. We retested our detector using features obtained at the first month’s visit, which were 1-30 Hz CM-PF for both patients and found that the detection of long complex tics was preserved. This is important as long complex tics are considered to be the most disabling type of tic in Tourette syndrome patients and as we observed, could be the most appropriate for invasive therapies such as DBS or ablative interventions \(^{111}\). We found detection of simple tics to be difficult as a change in cortical or thalamic signals was only observed 39.3% of the time; likewise, Obeso et al. found that simple tics were generally not associated with cortical premotor potentials \(^{163}\).

The features selected in the tic detector to attain best performance were not stationary over subsequent months. Chronic DBS therapy could have modulated neural activity, and led to the changes in the features selected across the months. The waxing/waning nature of tics and their temporal evolution may also be responsible for changes in the feature selection process. Still, just like the clinical programming that
needs to be optimized over subsequent months, feature selection for the design of an optimal tic detector may have to be optimized across several months.

In the baseline condition, we asked the subjects to suppress their tics. It is possible that suppression of tics differs from a natural baseline condition when no tics are occurring. One might suggest that the urge to tic may still be present in these patients even though they are not ticing. We asked our patients to indicate when they had an urge to tic and we found no changes in activity during urges in comparison to baseline conditions. We therefore concluded that for this preliminary paper, using the tic free baseline as a control for tics was a fair comparison.

Careful measurement of the neural correlates of tics allowed for quantitative assessment of tic onset and frequency in this study. This information is the prerequisite to developing advanced treatment strategies such as closed-loop (“adaptive”) deep brain stimulation. In the future we plan to use the tic-associated neurophysiologic features that we identified to enable chronic closed-loop DBS in our TS patients.

**Future Directions**

Future work can focus on network communication between thalamic and cortical leads. Event related network connectivity can be assessed by investigating tic, no tic, volitional movement, therapeutic stimulation, and non-therapeutic stimulation individually. Evoked potentials are a direct measure of causality. Analysis of the evoked potentials generated from therapeutic and non-therapeutic stimulations can provide insight into underlying mechanisms of DBS and frequency specific network dynamics. Assessment of evoked potentials can provide information about thalamic to cortical causality, but we will not stimulate cortical regions to minimize the risk of seizure. This
means that we will not have access to cortical to thalamic evoked potentials. Other measures will be employed to further assess network dynamics. Wavelet coherence (WC) is a measure of phase synchrony between two individual signals. WC is particularly useful because it can be used on single trials of data. The exact reproducibility of tics is low, due to their involuntary nature. Therefore it is very difficult to get repeat trials of tics; single trial analysis is essential. Using wavelet coherence we will assess changes in synchrony between thalamic and cortical regions as a function of time on a single trial basis. To determine predictive causality we will use a method called Granger Causality. This method tests the ability of one data series to predict another. Predictive causality using Granger Causality is a widely used metric for showing network relationships in a number of physiological recording modalities, as well as economics. To assess forecasting in the thalamo-cortical network we will start with the Least Mean Squares algorithm. The least mean squares algorithm is an adaptive algorithm capable of learning information about features in a signal, or dependences in two different signals. Forecasting of cortical activity via thalamic activity, or vice versa, can be tested using this technique. Statistical analysis of forecasting from LMS can assess the relationship between the two brain regions and may also be useful in determining key frequencies of network communication.
Figure 3-1. A) Overview of the study and long-term data collection. Open-loop DBS was enabled 1 month after implantation surgery. Stimulation was turned off during data collection. Closed-loop DBS will be underway at months 18 and beyond. B) LFP from thalamic and CM-Pf and M1 electrodes were collected at each monthly visit during three conditions: baseline (resting), ticing, and volitional movements. An electrical synchronization pulse was delivered at the beginning of each recording to synchronize video, EMG and LFP data. DBS was turned off for a minimum of 30 minutes prior to data collection. C) Various volitional movements were interleaved with resting periods during the volitional movement condition.
Figure 3-2. Intraoperative r² analysis of tics and volitional movements. A-C) Placement of electrodes in TS01 and TS02 are shown in X-rays. B-D) Intraoperative data was recorded in a unipolar configuration from all 16 contacts simultaneously. Significant (p<.05) contralateral broadband gamma activity was observed for volitional movements and tics (localized primarily to right side of body in TS01) in premotor(TS01) and motor contacts(TS01 and TS02). Significant (p<.05) high frequency activity was observed in CM contacts only during the tic condition (TS01 and TS02).
Figure 3-3. CM is associated with tics and not volitional movements. Data from follow up visit month 2: neural activity from M1 and CM-PF (top two rows), EMG activity from various locations. Subject TS01 was instructed to tic freely. Tic onset denoted by red dotted line: A) A neck wrenching tic (simple), B) Rapid arm throwing tic (complex long), C) Arm wrenching tic (complex), D) Arm throwing and neck twisting tic (complex long). In a separate trial the subject was asked to perform a series of volitional movements. Movement onset denoted by red dotted line: E) Talking and opening/closing hands rapidly, F-G) Opening/closing hands, H-I) Rapidly shaking hands. No tics were observed during the volitional movement condition.
Figure 3-4. Differentiating tics and volitional movements. Shown is the time series and spectrogram for each condition. A-D) correspond to TS01, Images E-H) correspond to TS02. B,F) Increases in CM low frequency LFP are concurrent with A,E) motor cortex beta desynchronization LFP at the onset of tics. D,H) No increases in low frequency CM LFP are observed during volitional movements, such as grasping (shown), but C,G) motor cortex beta desynchronization is still observed. Data for TS01 was from month 3 and data from TS02 was from month 2.
CHAPTER 4
THE EFFECTS OF STIMULATION

Introduction

Emerging evidence suggests an important relationship exists between neural oscillations and the manifestations of neurological disorders\(^{164,165}\). Moreover, the coupling of oscillations, such as the synchronization of local high-frequency activity with the phase of low frequency rhythms, may play a role in disease states\(^{166,167}\), as well as in normal functioning\(^{168}\). Advanced signal processing techniques have been developed\(^{169}\) to characterize the coupling of oscillations and a common measure has been used, phase amplitude coupling (PAC), as a metric for network level activity within subcortical\(^{170}\) and cortical structures\(^{171,172}\). Previous research has shown that PAC plays a role in regulating attention\(^{168}\), movement\(^{173}\), and decision-making\(^{174}\). PAC has been studied in human patients with dystonia\(^{167}\), schizophrenia\(^{175}\), and epilepsy\(^{166}\), but its role in the pathophysiology of these disorders remains unclear. Current research is aimed at improving the understanding of pathophysiological neural signatures by studying neural recordings from patients implanted with chronic deep brain stimulation\(^{176–180}\).

Deep brain stimulation is an invasive neuromodulative therapy, and newly emerging devices, such as the Activa PC+S neurostimulator\(^{160}\), are capable of delivering stimulation and recording electrophysiological activity. Recordings collecting during the implantation of DBS or from post-operative visits allow researchers to investigate the dynamics of neural activity. One of the primary indications for DBS, and thus one of the most heavily studied neurological disorders, is Parkinson’s disease\(^{181–183}\). Parkinson’s disease (PD) is a complex hypokinetic movement disorder characterized by rigidity, bradykinesia, loss of movement control, and tremor\(^{184}\). In a
recent study, it was observed that patients with PD exhibited exaggerated PAC within M1. Modulation of subthalamic nucleus (STN) via high frequency deep brain stimulation (DBS) suppressed PAC within M1 in PD\textsuperscript{185}. Stimulation of STN, which decoupled cortical PAC, was associated with improvements in parkinsonian symptoms\textsuperscript{185}. These findings implicate PAC in dysfunctional neural network processing and suggest that PAC could be a possible marker of pathophysiology in PD. Investigating PAC in other basal ganglia disorders could improve our understanding of the role that PAC plays in other clinical phenotypes.

To supplement the understanding of PAC in movement disorders, we studied two patients with Tourette syndrome (TS), who were implanted with DBS electrodes in the centromedian-parafascicular nucleus of the thalamus (Cm-Pf) and also implanted with electrocorticographic (ECoG) strips over the primary motor cortex (M1). Chronic recordings from these sites were performed using the Activa PC+S novel subcutaneous bidirectional neural interfaces. TS is a hyperkinetic neurological disorder characterized by undesired motor and vocal tics\textsuperscript{24–26}. DBS of the Cm-Pf has been reported to reduce the severity of tics in individuals with TS\textsuperscript{188}, but the mechanisms underlying the efficacy of DBS remain poorly understood\textsuperscript{155}. To study these mechanisms, we investigated the presence of M1-PAC in these patients when they were at rest and studied how this coupling changes when the subjects are exposed to various frequencies of stimulation in CM-Pf. We hypothesized that stimulation of Cm-Pf would evoke changes in the spectral or coupling measures of M1. In our investigation, we observed PAC patterns that suggested differences in coupling of TS as compared to
PD, and these findings highlight a potential fundamental difference in the brain physiology of hyperkinetic versus hypokinetic disorders.

**Materials and Methods**

**Experimental Setup**

Following DBS implantation, the subjects returned for monthly follow-up visits the first 6 months post-surgery. A trained clinical programmer, under physician guidance, assessed various stimulation parameters and iteratively (at each follow-up visit) determined the “clinically defined best stimulation settings” for Cm-Pf with both neurostimulators. Stimulation was not delivered to cortical regions as cortex was utilized only in the recording mode.

After the identification of therapeutic settings, a second set of nontherapeutic stimulation parameters was determined. The nontherapeutic setting was a low frequency, charge balanced version of the predefined therapeutic settings. Each subject was slowly introduced to the nontherapeutic settings and adjustments were made, as necessary, to eliminate any discomfort or side effects that may have been elicited, see Table 1 in the supplementary materials. Therapeutic and nontherapeutic stimulations were delivered and recordings were performed unilaterally in this study. We identified the laterality of therapeutic stimulation that the patient and physician reported as “most beneficial” and then delivered unilateral therapeutic and sham stimulations to this side only.

At each follow up visit, a series of experiments were performed to investigate Cm-Pf and M1 neural activity at rest and any changes in this activity that might result from stimulation of Cm-Pf. Data was collected via Medtronic Activa PC+S implantable neurostimulators (Medtronic LLC, Minneapolis, MN), which are capable of chronic
neural recordings from the implanted electrodes. The experimental paradigm is illustrated in Figure 4-2. A 4-minute baseline recording with stimulation off was recorded at the beginning of each session at 800 Hz. Next, stimulation (therapeutic or nontherapeutic) was applied for 10 minutes and then it was turned off again. During the last two minutes of stimulation LFP recordings from Cm-Pf and from M1 were captured, along with two minutes of recordings after the stimulation was turned off. Therefore, a 4-minute recording was captured where the first 2 minutes contained stimulation and the last two minutes contained no stimulation. Stimulation was activated for 8 minutes prior to data collection to allow transient effects to dissipate. A 30-minute gap of no stimulation was placed in between recordings to minimize residual effects of previous experiments. Subjects were asked to remain at rest during all recordings and were also instructed to suppress their tics to the best of their ability. Electromyography (EMG) and inertia data were recorded using the Trigo Wireless EMG system (Delsys, Natick, MA), as well as video footage, concurrently with LFP data to verify that there was minimal subject movement. LFP, EMG, and Video data were aligned using a synchronization pulse based alignment system developed in house.

**Data Analysis**

One-minute segments of “stimulation on”, “stimulation off”, and “baseline” data were isolated from the raw data collected during four post-surgical monthly visits. Visual inspection of raw and spectral data ensured that any transient artifacts, i.e., time periods where the stimulator was immediately turned on or off, were not included in data segments. This resulted in 5 different conditions: baseline (no stimulation), therapeutic stimulation on, post-therapeutic stimulation, non-therapeutic stimulation on, and post non-therapeutic stimulation. Data was sampled at 800 Hz with a 0.1-100 Hz hardware
bandpass filter using Medtronic Activa PC+S. Data analysis was performed offline using Matlab software (MathWorks, Natick, MA).

The time series LFP data was spectrally analyzed. Spectral transforms of each condition were computed via a windowed fast Fourier transform. A window size of 1.2 seconds and an overlap of .05 seconds were used to calculate the spectrograms. Spectrograms were calculated with a 1 Hz frequency resolution.

The time series data was inspected for evidence of coupling. PAC was computed on the one-minute segments of data using the modulation index measure as described by Tort et al\textsuperscript{169}. PAC measures were calculated between CM-Pf phase and CM-Pf amplitude, CM-Pf phase and M1 amplitude, CM-Pf amplitude and M1 phase, and M1 phase and M1 amplitude. The phase information was analyzed in the 4-45 Hz range in 2 Hz bins. Amplitude information was analyzed in the 4-100 Hz range in 4 Hz bins. PAC amplitude was not considered beyond 100 Hz as the 100 Hz low pass filter of the Activa PC+S rejected this signal range.

**Statistical Analysis**

M1 recordings from both patients were consolidated for statistical analysis. 4 months of data from 6 two-day post-surgical monthly visits were available from each patient. Thus, there were a total of 8 datasets for each baseline, during nontherapeutic stimulation, post-nontherapeutic stimulation, during therapeutic stimulation, and post-therapeutic stimulation data set. We examined differences between power spectral densities (PSDs) and PAC across these conditions.

PSDs were statistically compared at low alpha-alpha (2-15 Hz) and gamma (30-80 Hz) frequency ranges for the baseline, post-nontherapeutic, and post therapeutic stimulation conditions using a Kruskal-Wallis statistical test\textsuperscript{189}. PSDs from data
collected during stimulation were subject to stimulation artifacts and the interpretation of these results was not clear. To mitigate concerns regarding stimulation artifacts, PSDs between only the baseline and post-stimulation conditions were considered. Test results with p-values less than 0.05 were considered to be significant.

PAC between baseline, nontherapeutic stimulation, post-nontherapeutic stimulation, therapeutic stimulation, and post-therapeutic stimulation data sets were compared. The modulation indices between the low alpha-alpha (2-15 Hz) phase and gamma (30-80 Hz) amplitude frequency ranges for each trial were averaged together, producing 8 alpha phase-gamma amplitude coupling measures for each condition. A Kruskal-Wallis test was performed between each condition for significance. Again, test results with p-values less than 0.05 were considered to be significant.

**Results**

Therapeutic stimulation effectively reduced tics as measured via the Modified Rush Tic Rating Scale\textsuperscript{190} for both patients (MRTRS). MRTRS scores during therapeutic stimulation delivery were improved on average by 58.3% across all months and ranged from at least 20% improvement up to 100% improvement when compared to the initial screening visit (no stimulation). Both patients' MRTRS scores were improved by over 60% at the 6\textsuperscript{th} month of the study.

Figure 4-3A shows one second segments of M1 raw activity with no stimulation (center), post-nontherapeutic low frequency stimulation (left), and post-therapeutic high frequency stimulation (right). A spectral analysis was performed to quantify modulation in M1 activity that could result from stimulation (see Figure 4-3B). The PSD of M1 was statistically compared between the rest (no stimulation), post-therapeutic stimulation, and post-nontherapeutic stimulation conditions. Power in the alpha and gamma
frequency bands alone could not delineate between the conditions (Figure 4-3C). Although the power of these frequencies could not discriminate between the conditions, visual inspection of raw data revealed that additional information might be present in the signal; high frequency activity was maximal at the peaks and minimal at the troughs of a lower frequency component in data recorded after the delivery of therapeutic stimulation (Figure 4-3A, right).

To quantify this apparent coupling, we calculated the PAC between various frequency bands. Synchronization in alpha-phase and gamma-amplitude coupling was observed within M1 contacts during and following therapeutic stimulation (see Figure 4-4). The same PAC pattern was also observed in the no DBS resting state, but the modulation index was significantly lower than during (p<0.05) and following (p<0.05) therapeutic stimulation as revealed by a Kruskal Wallis test. The administration of nontherapeutic stimulation did not significantly change cortical PAC synchronization during or following the stimulation when compared to the no DBS resting state.

PAC in thalamic electrodes was not interpretable due to a low amplitude cardiac cycle artifact within the thalamic time series data. The repetitive and phasic information of the cardiac cycle artifact was sufficiently large to mask any neural PAC (The cardiac cycle PAC was approximately 1000 times larger than neural PAC signatures). The cardiac cycle artifact may also have masked any cross-regional PAC between thalamic and cortical activity.

Data used in figure 4-5 was adapted from Hemptinne et al\textsuperscript{185}. More details on the results and experimental procedure can be found within their publication.
Discussion

Phase Amplitude Coupling in the Native State

The TS patients in this study manifested a low PAC M1 signature when no stimulation was delivered to Cm-Pf (Figure 4-4). Studies of motor execution in sensorimotor cortices have demonstrated that PAC is higher before movement onset and reduces in intensity with the execution the movement\textsuperscript{173}. Hence, M1 PAC likely plays a role in the execution or triggering of movement and can be marker of pathophysiology of movement disorders. PD studies of PAC revealed that exaggerated M1 coupling was correlated with rigidity and that DBS of the STN could suppress M1 PAC, while alleviating parkinsonian symptoms\textsuperscript{167,185}. The presence of exaggerated M1 PAC at baseline may therefore indicate an unfavorable state for the execution of smooth voluntary movement. This unfavorable baseline state may manifest clinically as an inability to initiate tasks or to produce rapid motions. Both of these abilities are impaired in PD.

In comparison to an exaggerated PAC in the hypokinetic disorder, PD, the lack of a healthy PAC state at baseline may be the cause of involuntary movement production in the hyperkinetic disorder, TS (see Figure 4-5). Although the data collected in this study was free of movement and tics, we did not observe significant M1 PAC at baseline. This cortical decoupling in the absence of voluntary motor initiation may lead to an unfavorable baseline state that is susceptible to the generation of undesired motor patterns and the clinical manifestation of tics that characterize TS.

Modulation of the Basal Ganglia-Thalamo-Cortical Network

The basal ganglia-thalamo-cortical network is a highly integrated and compartmentalized neural circuitry involved in the regulation or control of motion\textsuperscript{86} (see
Figure 4-6). Disruption of normal activity within nodes of this network can result in severe movement deficits. The observed deficits of neurological disorders are often reflective of malfunctioning of nuclei or connections within the network. DBS is an emerging surgical approach for the treatment of movement disorders, that surgically targets a node or region that is critically involved in the production of movement, however, the exact mechanisms that underpin its effectiveness are poorly understood. Combining the delivery of stimulation and the measurement of downstream targets can shed light on its potential mechanisms of action.

TS is a hyperkinetic disorder characterized most noticeably by excessive movement production. Previous studies observed stimulation of the Cm-Pf region to be associated with a reduction of tics. That is, therapeutic stimulation of Cm-Pf in TS was associated with the reduction of the likelihood of excessive movement production. In our study, we delivered therapeutic stimulation and due to the inclusion of cortical strip electrodes we could also measure downstream changes in M1 activity. An increase in M1 PAC was observed during and following the delivery of therapeutic stimulation into the Cm-Pf (Figure 4-5, top panel). Furthermore, the observation of increased coupling would suggest the possibility that M1 is shifting toward a state representative of overall movement inhibition at baseline that is less susceptible to the generation involuntary motor patterns. In other words, the delivery of therapeutic stimulation to the Cm-Pf downregulates excessive cortical movement execution.

In contrast, PD is a hypokinetic disorder characterized by rigidity and bradykinesia. The native state of exaggerated coupling, which was found in PD patients exhibiting hypokinetic behavior, was reduced via therapeutic STN DBS (Figure 4-5,
bottom panel; data described in de Hemptinne et al.\textsuperscript{185}). Moreover, the same stimulation settings clinically improved the motor symptoms in PD in these subjects.

Delivery of therapeutic stimulation to different targets within the same network can facilitate a better understanding of the biology and potentially mechanisms of action underpinning TS and PD. TS, a hyperkinetic disorder, presents electrophysiologically with decoupled cortical rhythms, and PD, a hypokinetic disorder, in contrast presents with excessively coupled cortical rhythms. Therapeutic DBS of the Cm-Pf region in TS results in an increase in cortical coupling and in contrast therapeutic DBS of STN in PD results in decreased cortical coupling. It will be important to explain the clinical benefits of DBS in the context of the basal ganglia-thalamo-cortical model (Figure 4-6). One hypothesis that fits with the model would be that cortical excitation or inhibition as a result of DBS actually modulates cortical PAC generators. In our study and in the recently published parallel study of PD, it was observed that DBS of the Cm-Pf and of the STN respectively couple and decouple cortical rhythms. We hypothesize that appropriate modulation of cortical movement execution potentials, as measured by PAC, could be an important underlying mechanism for the ultimate motor control resulting from therapeutic DBS. Thus DBS may recalibrate the baseline PAC in both hypokinetic and hyperkinetic disorders.

**Using M1 PAC to Identify Therapeutic Stimulation Settings for TS**

The current approach for therapeutic DBS parameter identification was an empiric pseudo-random process driven by interactions between the patient and clinician\textsuperscript{75,76,191}. In this study, we hypothesized and later demonstrated that therapeutic DBS settings induced changes in coupling within downstream cortical targets (see Figure 4-5). We also observed that stimulation with nontherapeutic settings did not
increase cortical coupling (see Figure 4-5). The association between coupling and stimulation frequency may possibly be related to voltage, pulse width, and to a much larger range of frequencies that we did not test. M1 PAC offers the first known neural correlate associated with the effectiveness of TS DBS, and more research will be required to validate its potential. These findings might also be observable in devices without recording capabilities, as coupling of alpha phase and low gamma amplitude can be captured through non-invasive approaches such as EEG\textsuperscript{192}. Studies investigating a larger range of stimulation parameters will be necessary to confirm the feasibility of this approach for device optimization.

**Conclusions**

This study revealed fundamental differences in cortical coupling in a hyperkinetic (TS) versus a hypokinetic disorder (PD). Moreover, it uncovered the therapeutic effects of DBS on these disorders by measuring the downstream neural changes induced by DBS. The treatment responses in these experiments were revealing in that following DBS, the hyperkinetic disorder (TS) was associated with increased cortical coupling, and the hypokinetic disorder (PD) was associated with decreased cortical decoupling. Identifying the physiological signatures associated with therapeutic outcomes may thus requires disease specific analysis, and cortical PAC could be one potentially important technique that can be applied for understanding brain function and predicting response to treatment. Observations across various stimulation settings may help refine the hypothesis that coupling or decoupling could be a marker of clinical effectiveness of DBS in hyperkinetic versus hypokinetic disorders.
Localization of Cortical and Subcortical Targets

Figure 4-1. Localization and validation of electrode placement. (TOP) A motorized stereotactic implantation trajectory was planned via analysis of fused MRI and CT scans. Single unit neuron activity was monitored during the implantation process for validation of placement. (BOTTOM) Electrocorticographic strips were placed over primary motor cortices and premotor cortices. Validation of placement was obtained via automated functional mapping using SIGFRIED. (RIGHT) Post-operative scout CT scans are shown and reveal the finalized setup with all 16 contacts in each patient.
Figure 4-2. Study Description. Stimulation settings were optimized at each visit by a trained clinician. Therapeutic stimulation was set at 160Hz. A charge matched nontherapeutic low frequency stimulation setting at 60Hz was calculated. Prior to any stimulation trials, a baseline recording was captured. Therapeutic stimulation was delivered for 10 minutes to allow for passage of transient effects prior to data collection. A 4-minute recording was then initiated and after 2 minutes the stimulation was turned off. Thirty minutes later, the same paradigm was repeated with the low frequency stimulation settings. All data was collected at 800 Hz.
A High Frequency DBS drives M1 Phase Amplitude Coupling (PAC), but spectral power is *unaltered*.

Figure 4-3. PAC is independent of spectral power. Data shown is from the implanted M1 ECOG strips. (TOP A) Visibly obvious gamma and alpha phase locking is observed within the raw data post high frequency stimulation delivery. Little to no phase locking is observed during the no stimulation and post low frequency stimulation conditions. (LEFT B) The average power spectral densities during no stimulation and post stimulation conditions are presented from both patients. (RIGHT C) Power within the alpha (blue) and gamma bands (red) do not change when comparing all three conditions.
Figure 4-4. High frequency DBS of CM drives M1 PAC. DBS was delivered to CM thalamic region contacts and the data was collected from M1 subdural strips. M1 activity was not significantly coupled at baseline. Administration of therapeutic high frequency stimulation resulted in coupling in M1 across alpha phase and gamma amplitude. Nontherapeutic low frequency stimulation, though matched for injected charge, did not increase synchronization when compared to baseline. The amplitude of the bar graphs represents the mean coupling in each condition across all trials and patients. The error bars represent the standard deviation of coupling across all trials and patients.
Figure 4-5. Synchronization and Desynchronization of Cortical PAC are markers of Therapeutic DBS. Administration of high frequency CM-Pf region DBS drives synchronization of the M1 PAC in TS patients. In contrast, the M1 PAC is synchronized at baseline and is reduced by high frequency STN region DBS in PD (PD images from de Hemptinne 2015).
Figure 4-6. The role of the basal ganglia-thalamo-cortical loop in movement disorders. Normal movement execution potential requires a balance of inhibitory and excitatory signals within basal ganglia structures. Aberrant striatal neurons acting upon basal ganglia structures results in impaired inhibition of cortical structures and excessive movement production in patients with Tourette Syndrome. Impaired dopaminergic input to striatal structures reduces movement execution potential via excessive cortical inhibition in patients with Parkinson’s Disease. (Adapted from Kendal 2006)
CHAPTER 5
CLOSED LOOP DEEP BRAIN STIMULATION

Introduction

Deep brain stimulation (DBS) is an invasive neuromodulatory therapy indicated for the treatment of movement and psychiatric disorders. The mechanisms of DBS are not clear and the most efficacious stimulation parameters and targets for stimulation are unknown. As of 2016, most DBS models deliver a continuous stream of alternating current, but responsive and scheduled stimulation paradigms are an emerging alternative. Responsive stimulation is the delivery of electrical stimulation “in response” to a detected pathophysiological signal and scheduled stimulation is the delivery of stimulation at regular intervals or periods of time throughout the day. Clinical research is underway to assess the effectiveness and feasibility of responsive stimulation paradigms in movement disorders, such as Tourette Syndrome.

Tourette Syndrome (TS) is a neuropsychiatric movement disorder characterized by involuntary motor and vocal tics. DBS is an emerging option for pharmacologically refractory cases of TS, but it has yet to receive FDA approval. In a previous study, we found that signatures of tics were present within thalamic and cortical leads in 2 patients with TS. We sought to further investigate these apparent signatures and assess the effectiveness of stimulation in response to detection. Herein we describe the case of a patient for whom we designed and implemented chronic closed loop deep brain stimulation and the notable observations that occurred during the process.

Approval for this study was obtained by the University of Florida Internal Review Board (IRB201300850). The patient (TS02 from prior study), aged 23, presented with primarily vocal tics such as cursing and shouting. Her motor tics included inappropriate
use of the middle finger, hitting her own face, blinking, eye rolling, and shoulder shrugging. The patient was implanted with bilateral DBS (Activa PC+S Medtronic, Minneapolis, MN) within the centromedian thalamus (CM thalamus) and with bilateral electrocorticographic (ECoG) strips over the hand region of the primary motor cortex(M1). Continuous stimulation was delivered bilaterally to the CM thalamus for 1 year following implantation. During this 1 year period, the patient attended monthly stimulation programming visits to optimize stimulation settings. By month 12 the patient had converged on a set of “clinically defined best stimulation settings”. Following each monthly programming session, data was collected from both CM thalamus and M1 to assess the potential for developing a responsive stimulation paradigm. Evidence of potential markers for tics within CM thalamus and M1 led our team to implement responsive stimulation in this patient. Low frequency activity (1-10 hz) in the CM thalamus and low-beta activity (20-30 Hz) in the primary motor cortex were the greatest predictors of tics in 6 month study of tic prediction using this patient’s electrophysiological data.

Prior to chronic implementation of closed loop DBS, we tested the system in the acute setting, see Figure 5-1. Our previous study demonstrated that low beta M1 was a feasible site for detecting tic related activity. We used this same configuration for chronic closed loop DBS, see next section for more details.

**Responsive Stimulation**

The Nexus-E System includes all the components of the Activa PC+S System. The major components of the Activa PC+S System include the Model 37604 Activa PC+S INS, Model 8840 Clinician Programmer, Model 8181 Sensing Programmer, and Model 37642 DBS Patient Programmer. All Activa PC+S System components remain
unchanged with the exception of the Activa PC+S firmware. A new component, the Nexus-E Activator is used in additional to the existing Activa PC+S System.

The Activa PC+S neurostimulator can sense and record local field potential (LFP) signals. The Activa PC+S neurostimulator has a linear discriminant detector that can be configured to generate a cluster detection signal event which can trigger a recording or trigger an event to be recorded in an event log, but this cluster detection signal cannot be used to make updates to the stimulation. As illustrated in Figure 5-2: System Overview, the purpose of the Nexus-E System is to “close-the-loop” by allowing the cluster detection signal to trigger a stimulation change.

A temporally responsive closed loop stimulation paradigm was proposed. This means that the stimulation is delivered in pulses based upon detection of a transient pathphysiological signal. The stimulation frequency, pulse width, and maximum voltage amplitude were defined by the patient’s “clinically defined best stimulation settings”. A clinical signature of tics was observed within the right CM thalamus and M1. A robust pathophysiological signal within CM thalamus suggested that it would be the ideal site for driving the responsive stimulation, but technical complications associated with the therapeutic electrode and recording conditions prohibited the use of CM thalamus for driving responsive stimulation. Stimulation and recording on the same electrode is possible with the Activa PC+S, but a bipolar recording and unipolar stimulation setup is required. The unipolar stimulation setting must be on a center contact and the bipolar recording contacts must be surrounding the unipolar stimulation contact. In the case of our patient, the therapeutic contact on her CM thalamus electrode was the deepest contact. Therefore we were unable to establish a bipolar recording setup that
surrounded the stimulating contact. As a result, we needed to use separate electrodes for stimulating and recording. Our previous research indicated that large increases in beta activity from M1 were also an attractive marker for tics. We chose to use M1 low-beta power (center frequency of 22.5 Hz and a bandwidth of 2.5 hz) as the driving feature behind our responsive stimulation. A simple M1 low beta threshold detection protocol was established similar to what is shown in Figure 5-1. The threshold value for detection was empirically determined by collecting data while the patient was ticcing and identifying a threshold that maximized detection of tics. Following detection of the pathophysiological signature, the stimulation was activated based upon the stimulation rise and fall protocol.

**Stimulation Rise and Fall Protocol**

Determining the settings for stimulation is a complex task that requires a balance of benefits and tradeoffs. The variables that need to be configured specifically for closed loop stimulation are: minimum voltage, maximum voltage, stimulation rise time, and stimulation fall time, see Figure 5-3. If the stimulation rise time is very short, then stimulation can be ramped up to its maximum value in a very short period of time; the minimum voltage can be very small or even 0 volts if the rise time is short enough. If the stimulation rise time is longer, then it will take longer for the maximum voltage to be achieved; the minimum voltage needs to be higher in this case if the maximum voltage is to be achieved in a relatively short period of time. If the amount of time necessary to reach to maximum voltage exceeds the duration of the pathophysiological signal or the symptom episode, then the responsive potential of the stimulation is not optimal. Therefore, identifying the optimal parameters is a balance of detection characteristics and patient response to the stimulation.
The ideal rise and fall times for stimulation, as well as the minimum voltage for stimulation were iteratively determined and tested with the patient. A lower minimum voltage and faster rise time was initially selected in an attempt to create the largest difference between maximum and minimum voltage and to deliver a more “responsive” stimulation profile. A minimum voltage of 0V, maximum voltage of 2.5V, rise rate of .6 V/s and fall rate of 1 V/s were initially set. Once responsive stimulation was initiated, the patient noted that “there was a bad taste” in her mouth when the stimulation would turn on. She noted that it was not intolerable and we decided to leave her on this closed loop stimulation paradigm for about an hour. The patient went to lunch during this hour.

Upon return the patient stated that the bad taste in her mouth made it very difficult to eat and she could not enjoy her food. The closed loop stimulation was providing the patient with a prolonged and undesirable gustatory alteration. The patient did not experience this side effect on open loop stimulation. We developed various strategies to try and minimize this side effect of bad taste. First we attempted to reduce the rise rate, but in doing so we found that the amount of time necessary to get to the maximum voltage was too long and the bad taste side effect still occurred when the stimulation was turned on. We hypothesized that the stimulation reaching 0 volts might be part of the bad taste side effect. A minimum voltage of 1.5V, maximum voltage of 2.5V, rise rate of .6 V/s, and a fall rate of 1 V/s were set. With these settings the patient reported a major reduction in the presence of the bad taste. After an additional hour of observation the patient noted that she was satisfied with the stimulation and she was sent home.
**Patient Reported Efficacy of Stimulation and Other Notables**

During the programming session, the patient indicated that the stimulation was modifying her sense of taste. Although no direct relationship can be established between the acutely observed gustatory modulation and this change after multiple months, it does suggest that there may be neuromodulatory potential for gustation in the CM thalamus. Further research into the relationship between gustation and stimulation could have implications for treatment of disorders such as obesity.

After the patient was sent home on her DBS settings she reported a tingling sensation in her left arm that was bothersome. The patient returned for a reprogramming session and a reduction in the stimulation voltage alleviated this sensation. During this final visit, the patient’s tic severity was evaluated. A total MRTRS severity score of 8 was obtained when the patient was on closed loop brain stimulation. This is a 60% reduction in tics when compared to her initial visit and a 30% reduction in tics when compared to open loop stimulation. The score obtained during this closed loop session equates to approximately 1 tic every two minutes, which is a notable improvement over her pre-stimulation score which equates to approximately 1 tic every 10-15 seconds.

**Compromises and Lessons from Closed Loop Implementation**

When considering patients that will eventually convert to closed loop DBS, it is important that the stimulation programmers be aware of the bipolar recording-unipolar stimulating compromise. Identifying optimal stimulation settings within the technical bounds of the closed loop system should be considered from the early programming sessions. This is less of an issue in patients with electrodes separately designated for recording and stimulating. Multiple patient visits should be allocated to identify the best
pathophysiological signals for that individual and acute testing of closed loop DBS is necessary to verify tolerability to stimulation.
Figure 5-1. Acute test of closed loop DBS. Increasing beta power from the primary motor cortex of this patient was used to drive detection and stimulation in this acute test. Tic onset was localized by a clinician and verified by acceleration and measurement of responsive stimulation to CM thalamus.
Figure 5-2. Nexus-E system enables closed loop. A firmware update allows for sensed activity to be used as a feature for activating and deactivating closed loop brain stimulation.
Figure 5-3. Stimulation ramp times. The transition times indicate the rates at which stimulation is incremented and decremented. Fine tuning of the transition times is necessary to ensure that the patient is tolerant to closed loop stimulation.
CHAPTER 5
CONCLUSIONS AND FUTURE DIRECTIONS

Our investigation of DBS in TS has shined light on the pathophysiological signatures of the disorder and uncovered various potential improvements to the therapy. Within the chronic recordings captured from the CM thalamus and M1, we observed tic related activity that was not present at rest. Large, low frequency, deflections within CM were strong predictors of tics in both of our patients. In addition to this, large increases in beta were observed at the onset of tics. We demonstrated, with machine learning, that these signals could be detected with a high precision and recall within both patients. The signals that we characterized suggested that it might be possible to deliver an intelligent therapy that delivered stimulation in response to tic detection. We tested out various stimulation protocols within the clinical environment and determined that we had sufficient evidence and the technical capabilities to deploy chronic closed loop brain stimulation to our patients. At the current stage, one patient has been converted to closed loop therapy and is reporting positive results; the second patient may consent to chronic closed loop stimulation at a future date. Our future studies will investigate the presence of similar signatures in new patients and identify the most clinically relevant closed loop settings for these patients. 8 patients will be implanted via the funding that has been received from the National Institutes of Health. Preliminary analysis of data collected from the first of these 8 patients has shown signatures of tics similar to the first two patients. Our current understanding of the research suggests that closed loop therapy may be a safer and more effective therapy in the long term.

We also sought out to understand how stimulation impacted the thalamocortical network. We followed the patients through 6 months of DBS programming and identified
a set of therapeutic stimulation settings and a set of nontherapeutic settings. We administered these stimulation settings to the patients at each follow up visit and investigated the response of the thalamocortical network. We could not clearly delineate any signatures of the CM thalamus during the stimulation, but M1 was very responsive to the CM thalamus stimulation. We found PAC signatures of therapeutic stimulation within M1 that were not present when no stimulation or nontherapeutic stimulation was delivered. The relationship between this signature in M1 and therapeutic settings suggested that it is possible to automatically determine therapeutic stimulation settings via recordings from M1. In addition to this: Our findings, as well as findings from our collaborative site, suggested that PAC in M1 is tied to the pathophysiology of TS and various other movement disorders. Our conclusion is that correction of movement disorders may involve proper regulation of M1 PAC. In our future studies we will study a wider range of stimulation settings to better understand the dynamics that most effectively modulate M1 PAC and replicate these results in additional patients. We will also use these signatures to try and automatically determine therapeutic stimulation settings.

Much has been found regarding the pathophysiology of TS during the course of this study, but replication in additional patients is necessary. The pathophysiological network underpinning TS is continuing to take shape and the tools necessary to treat this disorder are on the horizon. With enough time and study, Tourette Syndrome will one day be a thing of the past.
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BIOGRAPHICAL SKETCH

Jonathan Shute is a NIH T32 Fellow in the Department of Biomedical Engineering at the University of Florida. He received his master’s degree from the University of Florida and his bachelor’s degree from Florida Gulf Coast University. Jonathan holds numerous presentation awards and was voted best oral presentation for Biomedical Engineering at the 2016 University of Florida Pruitt Research Day. His research has been featured on CNN and is the content of an NIH R01 grant.