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Quantifying the Effects of Systematic STN-DBS Programming on Rest and Postural Tremor in Idiopathic Parkinson Disease Patients

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by

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Abstract

Parkinson's disease (PD) is a complex neurodegenerative disorder that encompasses both motor and non-motor symptoms. These symptoms and their severity are typically assessed by scale based measures in a clinical setting. Scale- based assessments of PD patients undergoing bilateral subthalamic nucleus deep brain stimulation surgery (STN-DBS) such as the Unified Parkinson Disease Rating Scale (UPDRS)are commonly used in a clinical setting to assess symptom severity and progression. However, the subjective nature of these and other clinical scales call into question both the sensitivity and accuracy of patient assessment over time. An objective quantification of rest and postural tremor of PD patients who have undergone STN-DBS has never been conducted. Furthermore, objective technologies that quantitatively assess the effects of STN-DBS programming on full body rest and postural tremor have not yet been fully explored. The study employed the use of a full body kinematic Inertial Motion Unit (IMU)based technology in order to study the short term and long term effects of Deep Brain Stimulation (DBS) on idiopathic PD patients. Not surprisingly both whole body rest and upper postural tremor reduced by six months following DBS surgery. An average best setting was identified for tremor reduction.

Keywords

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Chapter 1

1 Introduction to Parkinson's disease

Parkinson's disease (PD) is a complex and chronic neurodegenerative disorder of the central nervous system characterized by a set of unique motor and non-motor symptoms. PD has a prevalence of 1-2% above the age of 60 years and is 1.5 times more likely in the male population (Mehana and Lai, 2013). In the early stages of the disease the most obvious symptoms are movement-based and include tremor, rigidity, bradykinesia, postural instability and gait abnormalities (Bereczki, 2010; Jankovic, 2008). Typically, tremor begins asymmetrically and appears at rest and involves the hands, legs, jaw and lips (Jankovic, 2008; Gelb, Oliver, Gilman, 1999). As the disease progresses other non-motor symptoms may also arise and mild cognitive and behavioural deficits can be seen. Dementia commonly occurs in the more advanced stages of PD while depression is the most common neuropsychiatric co-morbidity for PD patients (Caballol and Tolosa, 2007; Lozano et al., 2002). Other neurobehavioral abnormalities that are notable in the more advanced stages of PD include: bradyphrenia (slowness of thought), apathy, enhanced fearfulness, anxiety disorders, speech impairment, emotional instability, sleep disturbances, visual and spatial impairment, psychosis as well as social anxiety and withdrawal (Mehana and Lai, 2013; Murray, Butner and Price, 2012; Lozano et al., 2002). Both the motor and non-motor symptoms of PD have a profound impact on patient quality of life. In particular the combination of motor and non-motor symptoms has been found to be detrimental to health related quality of life in the idiopathic PD population.

The purpose of the next section is to provide the reader with further knowledge on the

role that the basal ganglia plays in the execution of voluntary movement as well as the role of the neurotransmitter dopamine. It will provide a general background on the neural mechanisms at play in PD as well as some of the fundamental structures and circuits that are disrupted in this disease.

1.1 Basal Ganglia, Dopamine and the Control of Movement

Before one can fully understand the pathology of PD a background on neural networks, basic neuroanatomy and physiology is essential. Within the brain is a region called the basal ganglia and it is comprised of multiple subcortical nuclei situated at the base of the forebrain. Anatomically, the basal ganglia are found on both sides of the thalamus, outside and dorsal to the limbic system but below the cingulate gyrus and within the temporal lobes. The basal ganglia have vast interconnections with much of the cerebral cortex, brainstem and thalamus, and also have projections to other areas of the brain (Bergman et al., 2015; Fix, 2008). The basal ganglia play a critical role in the control and regulation of voluntary and purposeful movements (Bergman et al., 2015). It is also important in action selection, habits, procedural learning as well as in motor learning. The basal ganglia are the main site of neuropathology in PD.

The basal ganglia do not connect directly to spinal motor neurons and as a result they do not directly control the specific movements of muscles. Instead, the basal ganglia appear to function by aiding in the learning of coordinated movements and in facilitating the execution of learned motor patterns. The neurotransmitter dopamine plays an integral role within the basal ganglia circuit. In particular, dopamine plays a role in the operation of the basal ganglia's ability

to signalthe execution of desired movements, driving the motor learning process and identifying when desired movements are executed successfully and with ease.

The basal ganglia form a neural circuit or loop which receives inputs from the cerebral cortex. This information is processed and modulated through dopaminergic inputs from the substantia nigra. These inputs relay information back to the cortex through the thalamus which is a primary integration center(Bergman et al., 2015; Albin, Young and Penney, 1989). The basal ganglia consist of many components. The striatum is the largest component of the basal ganglia and plays a critical role in processing cortical inputs. Another component of the basal ganglia is the pallidum which is comprised of the globus pallidus (both external and internal divisions) and the ventral pallidum. The next component of the basal ganglia is the substantia nigra which is comprised of mesencephalic gray matter and the site of a vast number of dopaminergic neurons (Marín and Rubenstein, 2001). The substantia nigra is divided into the substantia nigra pars compacta and pars reticulata. The final component of the basal ganglia is the subthalamic nucleus which is diencephalic gray matter (Weyhenmyer and Gallman, 2007). This area is unique in that it is the only component of the basal ganglia that produces the excitatory neurotransmitter glutamate. The primary input nucleus of the basal ganglia is the striatum which is comprised of the caudate and putamen (Fix, 2008). The primary output nuclei of the basal ganglia are the globus pallidus pars interna (GPi) and substantia nigra pars reticulata. These areas are interconnected by the subthalamic nucleus and the globus pallidus pars externa (GPe)(Albin, Young and Penney, 1989). Refer to Figure 1 for a summary of these connections.

A significant amount of information processing that occurs by the basal ganglia is centered in the striatum (Bergman et al., 2015). There are several types of neurons within the

striatum, however the majority are of the medium spiny variety (named for their size and appearance). These neurons receive input from corticostriatal axons and they release an inhibitory neurotransmitter called GABA and send projections to two important downstream targets. These projections form what is called the direct pathway and the indirect pathway of the basal ganglia (Albin, Young and Penney, 1989). In addition to the medium spiny neurons described above, the striatum also contains several small collections of interneurons which release the neurotransmitter acetylcholine.

Striatal interneurons not only contain acetylcholine they also contain a host of other neurotransmitters including GABA, somatostatin and neuropeptide Y, and appear to synapse on striatal projection neurons. These neurons play an integral role in communication between both the direct and indirect pathways (Marín and Rubenstein, 2001).

A tightly regulated balance between both the direct and indirect basal ganglia pathways is essential for the regulation of voluntary movement (Albin, Young and Penney, 1989). When components of either circuit are impacted movement disorders may arise. The direct pathway includes many striatal neurons which express predominantly D1 type dopamine receptors. The direct pathway has projections directly to the output nucleus of the basal ganglia, the GPi. Neurons of the GPi tonically inhibit the thalamus, a primary somatic integration centre within the brain. The thalamus then sends widespread excitatory projections to the neocortex. These projections are key for the initiation of movement and the formation of learned motor patterns. Activation of the direct pathway therefore stimulates movement. The indirect pathway is formed by striatal neurons which primarily express D2 type dopamine receptors. These cells project to

the GPe and this in turn inhibits neurons within the subthalamic nucleus (STN) (DeLong, 1990). The excitatory glutamatergic neurons of the STN then project to the GPi. The activation of the indirect pathway disinhibits neurons of the STN which stimulates the GPi resulting in the inhibition of the thalamus. The activation of the indirect pathway therefore acts to inhibit movement (Bergman et al., 2015; Albin, Young and Penney, 1989).

There is differential dopamine receptor expression within the direct and indirect pathways of the basal ganglia (Nambu, 2015). This differential expression of D1 and D2 receptors leads to differential effects upon stimulation with dopamine. Heightened dopamine concentrations within the striatum tends to activate D1 receptors of the direct pathway yet tends to inhibit the D2 receptors of the indirect pathway. Therefore, heightened dopamine concentrations promote movement. In PD the quantity of dopamine producing cells within the substantia nigra and surrounding areas are reduced (Nambu, 2015). This leads the body to be in a state of dopamine deficiency when compared to healthy controls resulting in reduced activity within the direct pathway and an overactive indirect pathway. The resulting symptom is reduced and slowed movement, which is why PD is classified as a hypokinetic movement disorder.

It is important to note that this model of the functions and circuits of the basal ganglia is grossly simplified (Nambu, 2015; DeLong, 1990; Albin, Young and Penney, 1989). However, this model provides a basic understanding of neural circuitry at play in the normal and the diseased PD brain. It is now known that the basal ganglia system is far more complex than described above. However, this simplified model of basal ganglia function has been extremely useful in the fields of neurology and neuroscience at allowing one to develop a basic understanding of these brain regions and their effects on the human body which is why it has been included in this dissertation. Predictions made using this basic model of basal ganglia

circuitry have also allowed researchers and clinicians to discover viable treatments for PD patients (Nambu et al., 2015). An important prediction that can be made using this model is that in PD, the indirect pathway, specifically the STN should be overactive. This prediction has been shown to hold true when tested in a laboratory setting in particular in studies using *in vivo* electrical recordings in PD patients. In addition to this, neurosurgical interventions that target the STN, such as deep brain stimulation (DBS) are now commonly used to treat PD when pharmacological treatments are insufficient.

The next section in this dissertation will briefly discuss the neuropathology of Parkinson Disease and in particular the effects of cell loss and damage within the substantia nigra and other fundamental components of the basal ganglia circuit on motor symptoms and function over time.
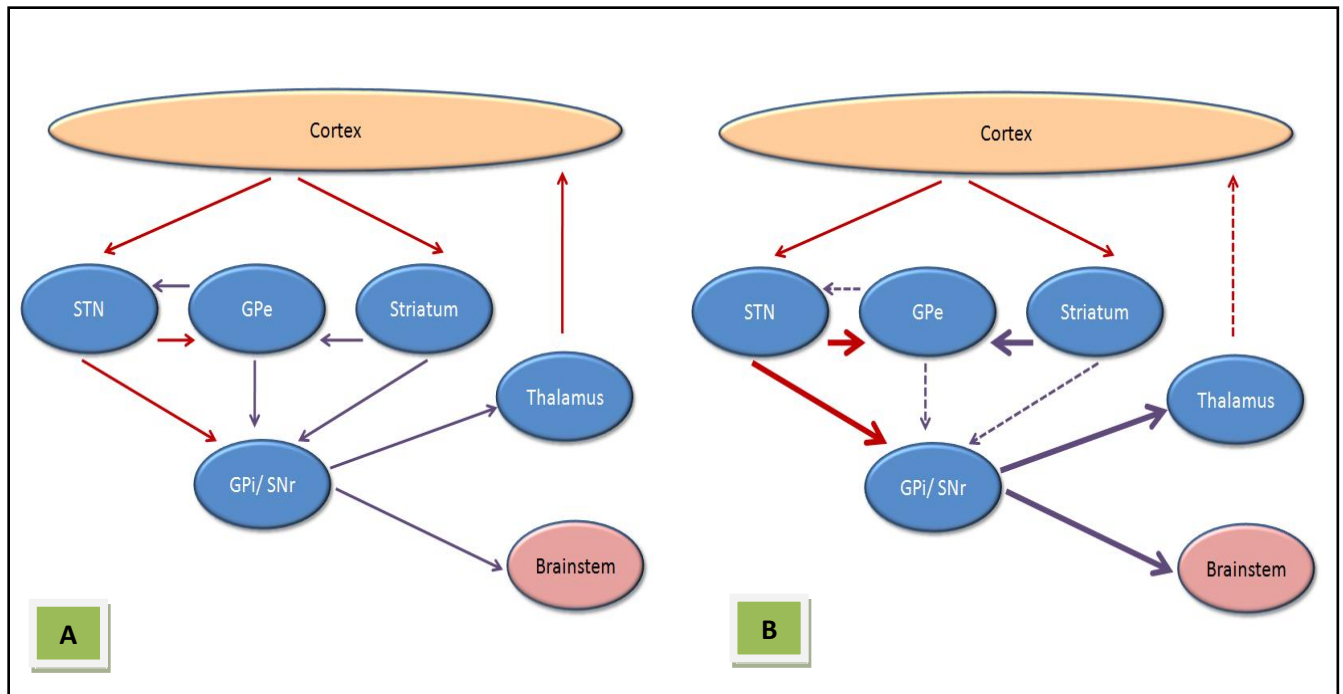
Figure 1: Simplified Diagram of the Motor Circuitry of the Basal Ganglia.

(A) Represents normal (healthy)brain circuitry (B) Represents the abnormal (disrupted)circuitry of the PD brain. The red arrows in this diagram represent glutaminergic projections (excitatory) while the purple arrows represent GABAergic projections (inhibitory). In diagram B which represents the affected PD brain the thickened arrows represent connections with increased activity while thin dashed lines are representative of decreased activity. It is important to note that the substantia nigra is home to dopaminergic neurons and these are depleted in PD.

1.2 Parkinson Disease Pathology

Pathologically, PD is characterized as a synucleinopathy and is associated with the abnormal accumulation of α-synuclein aggregates in neurons, nerve fibres or glial cells. The motor symptoms of PD are predominantly associated with the loss of neuromelanin-containing dopaminergic neurons in the substantianigra pars compacta (SNc). This eventually leads to striatal, more specifically putaminal degeneration (Brettschneider, Del Tredici, Lee and Trojanowski, 2015).The marked decrease in dopamine concentrations within the PD brain has a profound impact on mobility. Degeneration of other brainstem neurons has also been observed in PD and is thought to contribute to both motor and non-motor impairments. Some patients also have autonomic complications resulting in constipation, bladder and sphincter dysfunction as well as orthostatic hypotension. Sensory issues including pain andwhole body paresthesiacan also be experienced. Dermatological problems and vestibular dysfunction have also been well noted in this population (Jankovic, 2008). The next section will discuss one cardinal Parkinson's symptom, tremor, in more detail and the effects various treatments have on this symptom.

1.3 Tremor: A cardinal symptom of interest

Tremor is defined as an unintentional, rhythmic form of oscillatory muscle movements that involves one or multiple parts of the body. It can affect the hands, arms, head, face, voice, trunk and legs. Tremor is one of the most common motor symptoms of PD and as a consequence tremor detection plays a critical role in patient treatment and management. The first presenting symptom in most idiopathic PD patients is a slow tremor that worsens at rest that is commonly

unilateral. However, various types of tremor can present in PD including types of action tremor such as postural tremor, emergent tremor and isometric tremor. Tremor can be categorized by various time and frequency domain characteristics. Tremor type and tremor severity are typically differentiated by specific kinematic features including tremor amplitude, dominant frequency, peak power and duration of tremor. Higher amplitude tremors are of greater severity and may produce functional disability in PD patients irrespective of optimal pharmaceutical therapy.

Rest Tremor occurs when the muscles are relaxed such as when the hands are laying on the lap, resting on a chair, or arms are hanging next to the trunk while standing. Rest Tremor (RT) is evident in the distal components of the limbs including the hand and fingers and it gradually involves the entire limb thereafter. RT has a number of unique characteristics that differentiate it from other types and causes of tremor. In particular, RT is slow with a frequency typically ranging from 3.5 to 7.5 Hz. Another form of tremor that is commonly seen in the PD population is Postural tremor. Postural tremor occurs in body segments during the maintenance of a posture. Postural tremor frequency ranges typically from 4 to 12 Hz. Although tremor can vary in its type and in its severity it can be quite debilitating to patients who experience it. As a result, it is extremely important for clinicians to be able to track tremor severity and identify useful treatment options thereafter. Although, DBS has been found to be an effective treatment for refractory tremor in PD patients an objective, randomized and controlled assessment of different DBS settings has not been explored for full body rest and postural tremor. Employing an objective full body motion capture suit would enable the longitudinal tracking of tremor severity over time.

The next section will discuss the current pharmacological treatment options available to individuals diagnosed with idiopathic PD that are most commonly prescribed by clinicians for

the treatment of refractory motor symptoms. This section will also discuss the mechanism by which these drugs work within the brain and periphery and how they have an impact on Parkinsonian symptoms over time.

1.4 Pharmacological Treatments for Parkinson Disease

Levodopa has been used worldwide for over 40 years in the treatment of PD (The National Collaborating Centre for Chronic Conditions, 2006). Levodopa is a dopamine precursor which is converted in the body to dopamine by a naturally occurring enzyme called DOPA decarboxylase. The conversion of levodopa to dopamine occurs within both the central nervous system and the peripheral circulation. When used as a treatment in PD, levodopa is able to restore the dopamine concentrations that have been diminished as a result of nigrastriatal cell degeneration (Fahn et al., 2004). Levodopa is effective as a treatment because unlike dopamine, it is able to cross the blood brain barrier. This results in the activation of dopamine receptors inthe central nervous system and improvement of the motor symptoms of PD (Pahwa and Lyons, 2009). However, activation of peripheral dopamine receptors causes several unpleasant side effects including nausea, abdominal discomfort and vomiting. As a result, levodopa is often taken in combination with other drugs. Typically, a peripheral DOPA decarboxylase inhibitor such as carbidopa is prescribed. Carbidopa which is a highly polarcompoundis incapable of crossing the blood brain barrier unlike levodopa. However, it is able to effectively prevent the peripheral conversion of levodopa to dopamine resulting in a reduction of unwanted peripheral levodopa induced side effects.

Carbidopa is also often combined with levodopa in order in order to inhibit dopa decarboxylase in the periphery, increasing the amount of levodopa in the bloodstream thus

making it more accessible to the brain. In North America, this levodopa/carbidopa combination is often sold under the commercial name Sinemet however there are also other commercially sold versions of this drug combination. In the majority of patients the levodopa/carbidopa combination significantly improves mobility and normal daily functioning during the first 5-10 years of the disease (Morgan et al., 2014).

Other drugs that inhibit catechol-O-methyltransferase (COMT) such as tolcapone and entacapone are also prescribed to individuals with PD. These drugs are taken in conjunction with levodopa in order to reduce the amount of dopamine breakdown within the body. However, these treatments are less commonly prescribed in comparison to the levodopa/carbidopa combination.

Levodopa is best started with a minimum effective dose which is typically in the range of 50-100 mg/day taken in combination with a decarboxylase inhibitor on average 3-5 times daily (Chadhuri and Ondo, 2009). However, PD is a progressive and chronic neurodegenerative disorder as such symptoms tend to worsen over time. Due to this fact, medication doses need to be steadily increased in order to tackle motor symptoms as they continue to worsen and progress (Chadhury and Ondo, 2009). Levodopa effectively treats the symptoms of PD but does not slow the progression of the disease; it is not a cure (Jankovic, 2008). Worldwide, levodopa/carbidopa is recognized as the most efficacious pharmacological treatment for PD motor symptoms; viewed as the "clinical gold standard"(Jankovic, 2008). However, like many pharmacological agents on the market levodopa/carbidopa is not without its long term drawbacks or side effects.

The next section will discuss some of the current drawbacks of prolonged levodopa use on idiopathic PD patients as well as the impact of drug induced dyskinesias on daily functioning and the need for alternative therapies and treatments.

1.5 Levodopa induced motor fluctuations and current pharmacological treatment limitations

While current treatments using levodopa/carbidopa and dopamine agonists are effective at alleviating many of the motor symptoms of PD, these pharmacological agents are only effective for a limited period of time (Rascol et al. 2009). Approximately five years after the initiation of therapy a majority of patients develop medication related motor complications including levodopa induced dyskinesias (LID) and severe motor fluctuations (Groiss et al. 2009; Olanow et al. 2001). LID are choreic, stereotypic and dystonic movements that have a significant impact on quality of life and daily functioning(Koch, 2010). Over time patients may also become insensitive to the heightened drug doses thus diminishing the therapeutic benefits (Ahlskog and Muenter, 2001).

Given these current treatment limitations new treatment options and therapies must be examined in conjunction with the commonplace pharmaceutical therapies. DBS is an adjunctive therapy that seeks to reduce the symptoms of advanced, L-dopa responsive PD patients who are not sufficiently controlled by medication and who have experienced medication related motor complications (Odekerken et al., 2014). DBS is a relatively new technique and as such its full potential remains elusive. The next section will provide a brief history and introduction to the development of the DBS surgical technique and its' effects on PD motor symptoms.

1.6 Introduction to Deep Brain Stimulation (DBS)

DBS is a technique that involves the surgical implantation of electrodes into targeted regions within the brain for the treatment of various refractory symptoms (Volkmann et al.,

2014; Okun et al. 2009) To date, DBS of small neural targets within the brain by the use of a neural pacemaker device is the most effective neurosurgical procedure available to idiopathic PD patients(Lozano et al., 2002). This technique has been found to restore gross motor function. The pioneering of the modern era of deep brain stimulation began with the work of Benabid and colleagues at the University of Grenoble in France during the mid-1980s (Groiss et al., 2009;Benabid et al., 1987). It was during this time that the effects of high-frequency stimulation were elucidated and were found to result in several clinical benefits. These clinical benefits were found to be analogous to those achieved by lesioning procedures used in the treatment of movement disorders previously (Benabid et al. 1987).

DBS of the ventral intermedius nucleus (VIM) and the motor thalamus were first performed for the treatment of refractory Parkinsonian tremor (Benabid et al., 1987). Due to the reversible nature of DBS, thalamic DBS is now the preferred intervention for the treatment of intractable tremor when compared to prior neural lesioning procedures (Benabid et al., 2002). Over the last decade, various nuclei within the basal ganglia have been targeted in the treatment of several movement disorders (Groiss et al. 2009).

In the treatment of PD, the GPi and the STN have been two of the most extensively studied targets (Moro and Sidiropoulos., 2014). DBS of the STN has been found to improve several cardinal symptoms of PD including bradykinesia, rigidity, tremor, and postural instability. DBS of the GPi has been found to significantly reduce dyskinesias however it appears to be less effective at treating tremor and rigidity. Unlike, surgical lesioning procedures DBS allows the clinician to vary stimulation settings to personalize and cater treatment to each individual patient over time.Lesioning of the STN in particular, has a significant disadvantage in that it can lead to the production of hemiballism, and other choreiform abnormal movements.

Unlike lesioning procedures, it has been found that the use of standard stimulation parameters on the DBS device (3 Volts, 90 Microseconds, 130 Hertz) leads to minimal tissue damage (Moro andSidiropoulos.2014;Groiss et al., 2009). This makes the DBS procedure and its effects relatively reversible when compared to surgical ablation and lesioning procedures previously conducted to treat PD and intractable tremors (Pilitsis et al., 2008).Functional mobility is defined as the ability to move freely and easily and engage in activities of daily living. DBS has also been found to increase functional mobility as well as patient reported health related quality of life and has less reported adverse side effects than other surgical interventions (Kumar, 2002). As a result, DBS is now favoured by the majority of the clinical population for the treatment of most idiopathic PD cases that are no longer effectively managed with pharmaceutical therapy alone. However, strict eligibility screening before surgical intervention helps increase the likelihood of positive patient outcomes. The next section will outline the patient selection criteria for the DBS surgery as well as contraindications for the procedure.

1.6.1 DBS Patient Selection

Patient eligibility screening is imperative before DBS surgery ensues. DBS requires a surgical procedure and as such is not without risk. However, clinical screening is aimed at ameliorating many of the possible risks and limiting the likelihood of complications. Thus, an assessment of the relative costs and benefits for each patient must be conducted before an appropriate decision can be made (Beric et al., 2000).

It has been well established that STN-DBS is only beneficial and effective for individuals diagnosed with idiopathic PD (Moro et al. 2008). Age is also a primary predictor of health outcome in PD patients who undergo DBS surgery. It has been found that there is a relationship between age at the time of surgery and motor function improvement. As age

increases the possibility of risk also increases and the likelihood of clinical benefit decreases. Similarly, age is positively associated with increased complications following DBS surgery. With regards to DBS of the STN, responsiveness to dopamine replacement therapy before surgery is the greatest predictor of positive outcome for motor symptom management. Individuals who do not respond well to dopaminergic drugs or do not see improvement while on these therapies tend not to improve on or respond well to STN-DBS (Groiss et al., 2009). Finally, before the implantation of DBS electrodes for chronic stimulation takes place cognition and neuropsychiatric functioning must be considered. Severe cognitive deficits, neuropsychiatric diagnoses, dementias, psychoses or personality disorders, as well as a history of medical noncompliance are contraindications for DBS (Beric et al., 2000). A summary of the inclusion criteria for the DBS procedure can be found in Table 1. In order to limit the risks associated with a neurosurgical procedure it is important to uncover the mechanism of action and associated long term neural effects. The next section will discuss some of the current hypotheses on how and why DBS works within the PD brain.

DBS Surgery Patient Selection	
Inclusion Criteria	**Exclusion Criteria**
- Diagnosis of Idiopathic PD - Cognitive Stability - Significant improvement on dopamine replacement therapies for several years - Significant reduction in drug therapy benefit after 5-10 years of use - Refractory motor symptoms including tremor and LIDs	- Cognitive dysfunction (Alzheimer's disease, other dementias) - Diagnosis of severe psychiatric disorder (Depression, Psychoses, Personality Disorders) - Immunological diseases and complications - Malignant co morbidity that reduces life expectancy - Other neurologic condition - Brain atrophy

Table 1: DBS Surgery Inclusion and Exclusion Criteria

This table outlines the criteria that are used to assess whether a patient is a good or poor candidate for DBS surgery. If the individual meets the inclusion criteria and is void of any of exclusion criteria, DBS may be considered a viable treatment option.

1.6.2 DBS Mechanism of Action

As aforementioned many individuals are disabled by the disease despite treatment with dopamine replacement therapies. For patients who are no longer sufficiently controlled by drug treatment, neurosurgery is a viable option. To date, DBS is the most efficacious neurosurgery available to patients with the ability to help restore motor function. The question that remains is how this technique functions within the brain. Once the electrodes are implanted into the patient's brain and sufficient recovery time has been given the clinician uses the DBS programming device to alter the amount of electrical stimulation administered to the brain to best benefit the patient. DBS is catered to each individual in order to ameliorate and control their unique symptoms. Some patients require higher voltage stimulation while others are more sensitive to stimulation and are set at lower voltages. Although the positive benefits of this neurosurgical intervention is unparalleled in the field the precise mechanism of action still remains elusive (Kringelbach, Jenkinson, Owen, and Aziz, 2007). DBS is thought to work by masking the abnormal firing patterns and neuron oscillations that exist in the pathological STN (Lozano et al., 2007). Many potential explanations have been postulated on the mechanism of action for DBS although there is still no generalized consensus.

One group has posited that the stimulus variables utilized in DBS patients are likely to activate large axons (Lozano and Eltahawy, 2004). The activation of large axons via high frequency stimulation within the brain could inhibit the STN due to the release of inhibitory neurotransmitters. This may also result in network dysfunction by disrupting the pattern of neuronal firing in the targeted region (Lozano and Eltahawy, 2004).

Studies conducted by other research groups have identified several neural outcomes of DBS and potential mechanisms of action. It has been suggested thatDBS may work by any of the

following: depolarizing cells, halting neural activity within the specific targeted regions, channel blocking, energy depletion, activation of inhibitory neurotransmitters, activation of excitatory neurotransmitters, effecting non-neural cells and effecting local ion concentrations (Okun, 2009). Electrical stimulation of the STN in particular, has been shown to lead to many outcomes, including: cell inhibition, fiber excitation, calcium release, increased neuromodulator release, heightened cerebral blood flow and increased neurogenesis (Okun, 2012). However, DBS may not function in the same way at every neural target (Lozano et al., 2002).

The long term effects of DBS on neurophysiology have not been examined in any controlled animal or clinical studies (Benabid, Benazzous, and Pollak, 2002). However, it is likely that long term chronic stimulation could result in plastic changes to neural networks. The many neural mechanisms both local and remote in nature are influenced directly by the application of electrical current. All of the effects mentioned above must be taken into consideration when aiming to understand DBS as a clinical intervention and its therapeutic benefit. Lozano et al. (2002) have suggested that what we are observing in patients as a clinical effect could be due to the sum of many components. Continued research in DBS is necessary to further uncover the mechanism at play. The next section of this dissertation will review two DBS targets traditionally utilized in the treatment of idiopathic PD and some of the benefits and drawbacks of each.

1.6.3 DBS Neural Stimulation Targets

Two of the most commonly studied neural targets for DBS are the STN and GPi (Burchiel, Anderson, Favre, and Hammerstad, 1999). Globally, the STN is the gold standard DBS-target in the treatment of idiopathic PD. Cardinal levodopa-responsive motor symptoms

including tremor, bradykinesia, rigidity and postural instability can be successfully treated and managed through STN-DBS. Typically, STN-DBS is performed bilaterally in order to effectively treat both sides of body. Another popular target for the treatment of PD motor symptoms is the GPi as aforementioned. In particular, GPi-DBS has been immensely successful at alleviating LIDs in PD patients (Groiss et al., 2009). The marked reduction of LIDs allows for the clinician to further increase dopaminergic medications to further improve motor functioning. Several studies have compared motor outcomes of individuals who have undergone STN and GPi-DBS and no notable differences have been found (Okun et al., 2009). However, one of the main reasons the STN is a preferred DBS target in the treatment of PD is that patients can be effectively weaned off their dopamine replacement therapies (Weaver et al., 2006; Volkman et al., 2004). Some long term studies examining the efficacy of GPi-DBS have also found that positive motor effects tend to weaken over prolonged use (Odekerken et al., 2013). Another drawback to GPi-DBS is that higher stimulator voltage settings are also required which reduces the battery life of the device (Volkmann et al. 2004). Once a target is selected and the surgery is performed the next step after a post-operative healing period is programming the DBS device to best fit the patient's symptoms and needs. The next section will discuss the post-operative programming procedures that are normally applied following the STN-DBS procedure.
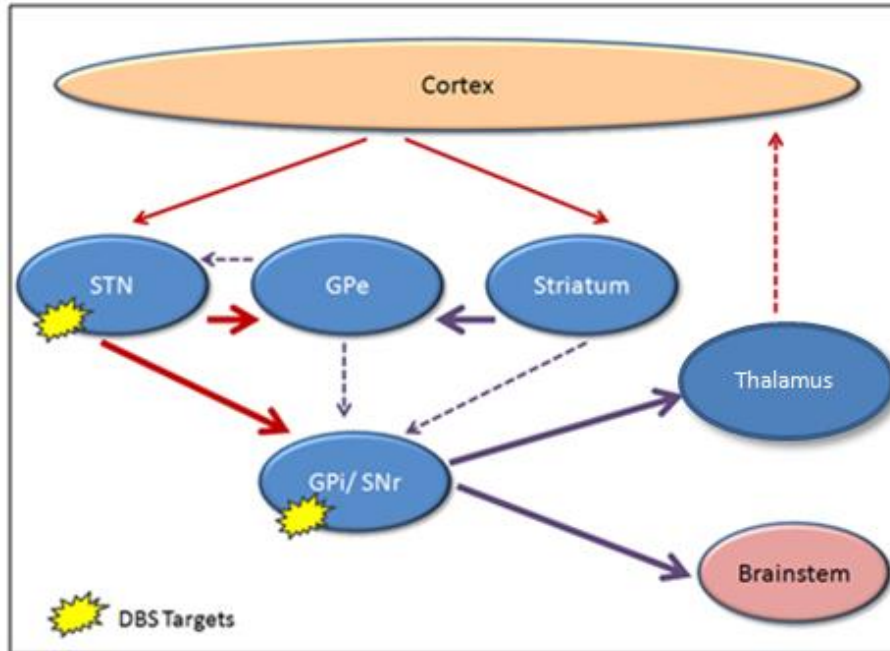
Figure 2: Common Targets for DBS in the treatment of PD

The above diagram represents the abnormal (disrupted)circuitry of the PD brain. The red arrows in this diagram represent glutamatergic projections (excitatory) while the purple arrows represent GABAergic projections (inhibitory). The thickened arrows represent connections with increased activity while thin dashed lines are representative of decreased activity. This diagram provides a simplified outline of the basal ganglia circuitry in the affected PD brain. Two of the main DBS targets used in the treatment of PD motor symptoms 1) STN and 2) GPi are shown above.

1.6.4 The Subthalamic Nucleus

The STN has been identified as an important target in DBS to ameliorate many of the complex motor symptoms associated with PD (Hamani et al., 2004). The STN is an important basal ganglia output modulator as it projects to the globus pallidus as well as to the substantia nigra, brainstem and striatum. The STN also receives afferents from various brain areas including the cerebral cortex, globus pallidus externus, brainstem and thalamus. It has been illustrated that in models of PD, this nucleus might be dysfunctional (Okun et al., 2009). Neurons of the STN have been found to fire in oscillatory patterns that are highly related to tremor onset (Lozano et al., 2002). Lesions of the STN and DBS of this area have been able to ameliorate many of the major motor symptoms in PD and reverse some of these electrophysiological effects (Levy et al., 2002). In the STN it is believed that DBS is acting to disrupt the abnormal oscillatory firing of the nucleus therefore positively impacting motor symptoms in the PD patients (Hamani et al., 2002). Therefore it has suggested that high frequency stimulation of the STN results in inhibition of STN output. However, other studies have challenged this view suggesting that stimulation of the STN increases output. The mechanism through which DBS stimulation of the STN ameliorates the motor symptoms of PD is still unknown and quite controversial.

1.6.5 DBS Post-operative Stimulator Settings and Programming Procedures

After the patient is given an appropriate amount of time to heal following STN-DBS surgery postoperative stimulator settings must be adjusted. This process remains an extremely time consuming process and requires a clinical examination. Both medication dose and stimulator settings must be adapted in unison in order to limit the patient's experience of profound dyskinesias or other adverse side effects and to optimize clinical benefit. There are a great number of healthcare costs associated with the DBS procedure and subsequent postoperative programming procedure. Although the costs associated with surgery are commonly fixed, a great deal of time and money is required to perform all of the necessary outpatient programming sessions (Mera et al., 2011).

It has been well documented now that many individuals who have undergone DBS surgery tend to experience an improvement in symptoms immediately following the procedure without out yet having the device turned on or programmed. This phenomenon has been called the microlesion effect (MLE) and has been extensively studied in the idiopathic PD population (Singh, Kammermeier, Mehrkens and Botzel, 2012). One such research group assessed the presence of MLE in 74 individuals who underwent DBS of the STN in order to determine the relationship between MLE presence and clinical outcome (Tykocki et al. 2008). The results proved the presence of MLE in the early postoperative period before activation of the DBS device in the majority of patients. Interestingly, the presence of a MLE effect following STN-DBS surgery acted as a positive predictor of health outcome for the patient group. It was found that a positive correlation existed between MLE and improvement degree following DBS device

activation. Several other research groups found similar results when assessing MLE following both STN-DBS and GPi-DBS (Tykocki, Nauman, Koziara and Mandat, 2013). The presence of MLE in a particular patient is now thought to act as a predictor of positive clinical outcome following the DBS procedure.

MLE is transient and is thought to be the result of penetrating the neural tissue surrounding the electrode lead, although the precise mechanism of action currently remains unknown. Over time this effect fades and many of the motor symptoms tend to return. In some cases this effect can last several months but in the majority of cases it dissipates within the first week following surgery(Tykocki et al. 2008).

As aforementioned, once the patient has been given sufficient time to heal (which can vary from 1-2 weeks in the majority of cases) and the MLE has faded a trained clinician or nurse practitioner must carefully test all four electrode contacts of each lead on each side of the brain. Once this assessment is completed the contact which has the most positive effects coupled with the highest threshold for side effects is selected for chronic neural stimulation. The patient would then undergo successive clinical assessments over the following weeks and months which would allow their clinician to effectively reduce their dopamine replacement medication doses and gradually increase stimulation voltage. This is done gradually and successivelyby the patient's clinician or movement disorder neurologist until satisfactory mobility is achieved without significantmotor side effects or dyskinesias being present (Volkmann et al., 2006,2000, 2002). The activation of one contact within an electrode is termed monopolar stimulation, while activation of two contacts is termed bipolar stimulation.The most commonly employed mode of chronic stimulation used worldwide ismonopolar stimulation. However, bipolar stimulation is sometimes used and is currently growing in favour. The most common stimulation parameters

used include a voltage of 2.5-3.5 V, 60-90µs and a frequency of 130-180 Hz (Volkmann et al., 2006). Depending on the patients' longer term outcome on the programmed DBS settings, necessary adjustments may need to be made (Groisse et al., 2009). Some individuals may experience side effects over time which would result in the need to activate a different contact or change the mode of stimulation (from monopolar to biopolar for example). Stimulation induced dyskinesias and other DBS motor complications that have been noted in the literature tend to appear after a delay in time (Hunka et al., 2005; Okun et al., 2003).

It has also been well noted that STN-DBS can cause transient alterations in cognition, perception, memory, mood and subjective well-being (Funkiewitz et al., 2003). Changes in affectmay occur over chronic stimulation iterations or as a result of a rapid changes in DBS settings (Wojtecki et al., 2007; Funkiewitz et al., 2003). Rapid alterations to DBS settings can result in excessive laughter and crying in some patients (Krack et al., 2001). This has been termed pseudobulbar affect and is the result of the current penetrating surrounding neuronal areas that are outside of DBS target (Okun et al., 2009). It has been noted that reducing dopamine replacement medications and stimulator voltages must be done extremely gradually in order to minimize the likelihood that a patient may develop severe affective and psychiatric disturbances (Okun et al. 2003).

It is clear that DBS programming is an extremely costly, time consuming and complex process (Mera et al., 2008; Fraix et al., 2006). It is estimated that each DBS adjustment in clinic can cost outwards of 1000 USD per appointment (Pereira et al., 2008). In order to ensure that patients experience the most profound clinical improvement following DBS programming it is best if settings are altered in a systematic way and in a controlled environment (Fraix et al., 2006). Access to a greater amount of postoperative care following DBS surgery at a specialized

movement disorder center from a trained movement disorders neurologist has been found to improve mobility outcomes and patient perceived health related quality of life following the procedure (Moro et al. 2006). Geographic location and disparities in socioeconomic status have a direct impact access to clinical care. Many of the costs associated with in clinic DBS adjustment could be ameliorated if an automated and objective full body assessment tool was designed and implemented. The next section will discuss some of the current DBS programming limitations faced by DBS programmers and clinicians and some of the new innovative ways we can improve this process.

1.6.6 DBS Programming Limitations

One of the primary goals of DBS is to stimulate the targeted brain area in a way that increases therapy benefit whilst minimizing negative or adverse side effects. This can be achieved by minimizing current spread to regions outside of the target nuclei by testing the effects of variable stimulation settings. Successful DBS therapy therefore relies heavily on proficient electrode programming among other complex variables. DBS leads to a modification of the firing rate and firing patterns of neurons within the basal ganglia, supporting the amelioration of common PD motor symptoms yet this is only possible through effective programming.

As mentioned previously, DBS has been shown to be beneficial in reducing common PD motor fluctuations in countless studies over the past decade (Wagle-Shukla and Okun, 2013). In particular, DBS is very good at alleviating medically intractable tremor (Krack et al., 1997). However, the combinations of stimulation parameters including contact location, electrode polarity, voltage, pulse width and the frequency of stimulation that can be modified to achieve

this result are vast and all possible combinations have not been fully explored (Benabid, Benazzous and Pollak, 2002; Moro et al., 2002). The voltage, measured in volts (V), is the intensity of the stimulation. The frequency, measured in pulses per second or Hertz (Hz) is the rate at which stimulation is repeated over a particular period of time. The pulse width which is measured in microseconds (μs), is the duration of the stimulation pulse. As it stands current DBS programming is highly reliant on subjective, trial and error clinical assessments (Ramasubbu, Anderson, Haffenden, Chavda, and Kiss, 2013).

DBS programming for optimal therapy benefit in patients remains a difficult task for clinicians due to the number of complex permutations available on the DBS device and the subjective trial and error nature of the programming process (Miocinovic, Somayajula, Chitnis, and Vitek, 2013). Each unique patient has their own set of symptoms, their own disease duration and medication history. What is ideal for one patient may not be ideal for the next. It requires a personalized setting on the stimulator to best suit patient needs. This level of complexitymakes it difficult to tackle programming within the confines of short clinic visits. The clinician is forcedto rely on clinical experience as a guide resulting in a subjective and potentially sub optimal device set point. The commonplace assessment tool employed in a clinical setting before and after DBS surgery is the Unified Parkinson Disease Rating Scale (UPDRS). However, this clinical assessment is subjective in nature and may not be sensitive enough to detect subtle differences in symptom severity in patientsover time and between patients(Hobart et al., 2007). The DBS programming procedure not only takes a significant amount of time but does not always produce optimal patient results because of the subjective nature of assessment. Clinical expertise provides programmers with a good starting point; however the complexity of the programming itself can

result in the underutilization of many settings (Miocinovic, Somayajula, Chitnis, and Vitek, 2013).

Overall, this has a direct impact on patient progress and clinical health outcomes because programming is limited to modifying simple settings that relate to short term visually observable clinical symptoms and signs. In order to overcome this weakness the utilization of an objective technology that can track moment by moment motor fluctuations should be employed to assess the efficacy of a number of stimulation settings.

The next portion of this dissertation will discuss several different motion capture technologies that have been used to record human motion in real time as well as some of potential clinical applications and drawbacks.

1.7 Motion capture technology used for motor symptom assessment

Over the last decade a variety of motion capture technologies have been developed which are able to accurately detect and wirelessly record movement in real time. A variety of these kinematic assessment technologies have been developed in order to objectively assess gross motor function and task performance. Some of these include: accelerometry, gyroscope-based technologies, touch screen technologies, smart-phone technologies,video-based motion capture technologies, electromyography and Inertial Measurement Unit (IMU) systems (Dai et al., 2013; Rigas et al., 2012; Salarian et al., 2007; Askari et al., 2010; LeMoyne et al., 2010). Of the variety of objective motion capture technologies available accelerometry is by far the most commonly

implemented mobility assessment tool (Mostile et al., 2010). In particular accelerometryhas been commonly employed to assess tremor in PD patients (Ang, Khosla and Riviere, 2003; Thielgen et al., 2003). Thielgen et al.(2003) were able to show that accelerometers can be used to automatically and accurately quantify tremor severity during 24 hour ambulatory home monitoring in PD patients. Others like Mostile et al. (2010) utilized a combination of accelerometers and gyroscopes to track the severity of essential tremor. However, accelerometry has a significant drawback in that sensor placement vastly influences outcomes (Salarian et al., 2007).

IMU based systems incorporate accelerometers, gyroscopes and magnetometers to calculate motion.IMU sensors are highly accurate and effective at quantifying tremor but current published studieshave relied on the data from a single or dual IMU attached to a finger or the wrist (Dai et al., 2013). Mera et al. (2004) utilized an IMU attached to the wrist in order to test and optimize STN-DBS programming in 2 PD patients. This study however was limited as it only utilized 1 sensor which was attached to the wrist and only included 2 case studies.Some other researchers have attempted to optimize DBS programming using single or dual motion sensors in order to quantitatively track the efficacy of certain stimulation parameters(Rigas et al., 2012).

It is clear that the scientific community can see the value of using an objective technology to track the symptoms of individuals with movement disorders. However, none of the studies mentioned above have employed an IMU system capable of recording the whole body. This has limitedour understanding of tremor as it presents in the head, upper extremities and lower extremities. The complexity of PD symptomatology requires us to monitor and assess multiple parts of the body to better understand gross mobility and motor symptom progression

over time. As we study bilateral DBS it is important to monitor tremor on both sides of the body and from multiple body segments. Many of the existing kinematic technologies cited above have not been used to monitor STN-DBS patients at multiple time points or to monitor whole body effects of DBS programming. Of the studies that have assessed the efficacy of STN-DBS many have utilized the UPDRS alone as a measure of improvement. This is subjective and does not provide the sensitivity or accuracy an objective kinematic system does. Studies which have included STN-DBS patients and focused on long-term effects often only assessed patients once pre-operatively and once post-operatively.

Full body kinematic assessments have never been conducted in an idiopathic PD population in order to track both the chronic and acute effects of both clinical programming (by a clinician using standard assessment procedures) and randomized predefined stimulation parameters after STN-DBS surgery. With many of the challenges and limitations of the current methods in mind a novel study protocol was designed. The next section will describe how this pilot study protocol aimed to overcome previous study limitations.

1.8 Overcoming previous study limitations with objective measures

Several fundamental limitations exist in bilateral STN-DBS programming and clinical efficacy:

Limitation 1: The lack of objective measures used to quantify symptom severity before and after DBS surgery.

Limitation 2: The lack of systematic examination of multiple DBS settings (different combinations and variations in voltage, frequency and pulse width) and their effects on symptoms.

Limitation 3: No existing longitudinal assessments of rest and postural tremor of the whole body following bilateral STN-DBS using objective measures.

In order to overcome the limitations of other studies currently in the literature we implemented a full body motion capture suit in this study in order to track the effect of clinical programming over time and the effects of 18 predetermined DBS settings on whole body tremor severity. The full body motion capture suit, IGS-180 (which will be described in more detail in the methods section)enabled us to assess multiple programming settings and their effects on patients over time.

Patients were asked to perform a series of motor tasks while wearing the suit. The tasks were designed to test the severity of their motor symptoms, in particular rest and postural tremor. This device allowed for the moment to moment tracking of patient motor symptoms and provided kinematic information for mobility analysis.

1.8.1 Aims of the current study

In this study, we monitored PD patients once pre-operatively and in eight post-operative visits and identified several aims.

Aim 1: The first aim is to objectively track tremor throughout the clinical programming process and to test the efficacy of clinical programming on rest and postural tremor.

Aim 2: The second aim is to compare the efficacy of 18 predetermined DBS settings at reducing rest and postural tremor.

Aim 3: The third aim is to compare the UPDRS to an objective IMU based motion capture system at detecting motor symptom fluctuations over time.

Aim 4: The fourth aim is to examine the impact of the DBS procedure and this DBS programming system on the quality of life and mood of the patients involved.

1.8.2 Hypotheses

We have developed several hypotheses based on previous findings.

Hypothesis 1: We hypothesize that both rest and postural tremor will improve for patients following bilateral STN-DBS surgery and Clinical Programming by a trained Movement Disorders Neurologist.

Hypothesis 2: We also hypothesize that out of all of the 18 predetermined settings tested in the lab there will be a unique "optimal setting" for each patient which results in the most dramatic reduction in both whole body rest tremor and another optimal setting which results in the most dramatic reduction in upper limb postural tremor.

Hypothesis 3: We also hypothesize that there will be an average best setting which results in the most dramatic tremor reduction in the PD group overall.

Hypothesis 4: We hypothesize that quality of life will improve following DBS surgery and subsequent programming and that depression will decrease over time.

Chapter 2

Methods

2.1 Participants

An objective quantification of rest and postural tremor was conducted in 7 PD patients who had undergone bilateral STN-DBS neurosurgery and subsequent clinical programming over a period of24 weeks. Patients were recruited to the study based on the criteria outlined below:

Study inclusion criteria were:

1. Diagnosis of idiopathic Parkinson's disease
2. Debilitating motor symptoms (tremor, stiffness) as a result of reduced pharmaceutical therapy effectiveness
3. Severe motor fluctuations including functionally disabling off periods and LIDs during on periods
4. Met eligibility and screening requirements for the DBS procedure as determined by the medical best practice standards at London Health Sciences Centre
5. Able to give informed consent
6. Able to attend all clinic adjustment visits and lab visits
7. Cognitive Stability including no dementias or psychiatric abnormalities

Study exclusion criteria were:

1. Previous brain atrophy resulting in brain surgery or implantation of cardiac pacemaker
2. Moderately severe Parkinsonism in the context of unstable pharmacological treatment

3. Unresponsiveness to dopamine replacement therapy

4. Diagnosis of dementias, Alzheimer's or severe cognitive impairment

5. Severe psychiatric symptoms and disorders (including, depression, anxiety or hallucinations)

6. Poor general health (including comorbid diagnoses)

7. History of poor medical compliance

All patients met these inclusion criteria before participating in the study. All patients were enrolled prior to their scheduled DBS surgery and conducted a pre-operative baseline assessment. Seven healthy aged matched controls were also assessed once in the laboratory to acquire comparison data. All study participants were recruited from the Movement Disorder Clinic at Western University Hospital in London, Ontario, Canada. After study enrolment and the preoperative assessments were completedall of the PD patients received bilateral implantations of quadripolar electrodes (Medtronic Inc., Minneapolis, MN, USA) into the subthalamic nuclei of both the left and right cerebral hemispheres during stereotactic DBS neurosurgery. All of the STN-DBS neurosurgeries took place at Western University Hospital in London, Ontario, Canada. Three neurosurgeons performed the surgery on our patient group. This study was approved by Western University Ethics (Human Subjects Research Ethics Board (HSREB) # 103928). All participants provided written informed consent before study participation. A copy of the Consent form can be found in Appendix A.

All patients completed clinical scales and kinematic assessments throughout a total of 9 visits (1 preoperative, 8 postoperative) at the South Street Annex Research Facility in London, Ontario, Canada (A division of the London Health Sciences Centre). Control patients completed the same kinematic assessments during 1 visit, however no clinical scale data was collected. As

mentioned above, all patients were enrolled before their surgery date was scheduled and completed a pre-operative lab visit approximately 1 week before their scheduled surgery. Post-operatively, patients were assessed as outlined in Table 3. Programming sessions on each patient's DBS device began 4 weeks post-operatively.

2.2 UPDRS and Self-Report Clinical Scales

A set of clinical scales and questionnaires that assess motor and non-motor symptoms as well as patient perceived quality of life were administered to the patients and completed at the beginning of each lab visit. These included The Parkinson Disease Questionnaire- 8 (PDQ-8) and the Geriatric Depression Scale (GDS). The UPDRS was administered by a trained research associate at every visit. A copy of the scales used in this study can be found in Appendix A.

The Unified Parkinson Disease Rating Scale (UPDRS)

The UPDRS was administered and ranked by a trained research associate at every visit. All assessments were also videotaped. The UPDRS is the standard clinical evaluation for PD, commonly used to assess patient symptom severity and DBS programming efficacy (Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease, 2003). The UPDRS evaluates PD symptom severity on a 0-4 scale. The UPDRS assesses rest and action tremor based on a series of motor tasks.

The Parkinson's Disease Questionnaire- 8 (PDQ-8)

The PDQ-8is a shorter version derived from the full length original questionnaire, the Parkinson Disease Questionnaire-39. The PDQ-8 is a questionnaire that examines several domains of self-perceived quality of life in individuals diagnosed with PD(Jenkinson,

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Fitzpatrick, Peto, Greenhall and Hyman, 1997). The PDQ-8 was derived by taking one question from each of the 8 domains outlined on the original PDQ-39. These domains include: mobility, ADLs, emotional well-being, stigma, social support, cognition, communication and overall bodily discomfort. The questions used on the PDQ-8 were selected based on the strength of their correlation with the total domain score (Martínez-Martín et al., 2004). Each of these questions is assessed on a 0-4 scale. The summed score is then divided by total possible score and given as a percentage score out of 100. The PDQ-8 was explained and administered to each participant by the same research associate at every visit.

The Geriatric Depression Scale (GDS)

The GDS is a 30-item self-report questionnaire which is used to assess the severity of depression in the elderly (Yesavage et al., 1983). This scale was first developed in the early 1980s by J.A. Yesavage and colleagues. Instead of a traditional 4 or 5 category Likert scale, the GDS requires the individual to answer questions with a "yes" or "no" response. The simplicity of the test allows it to be used with ease with an elderly population who may be experiencing mild cognitive impairments (Parmelee and Katz, 1990). This questionnaire is commonly used in conjunction with other clinical scales as part of a routine geriatric health assessment. Every answer provided can be given either a 0 or 1 score. The scale is rated on a grid which identifies a score of 0-9 as normal, 10-19 as mildly depressed and 20-30 as severely depressed (Yesavage et al., 1983). The GDS has well established reliability and validity when compared to other clinical rating scales that assess depression (Yesavage et al., 2000). At every lab visit each patient completed this assessment on their own following instruction from a trained research associate.

2.3 Full Body Kinematic Assessments using the Motion Capture Suit (IGS-180)

Rest and postural tremor were measured using the Animazoo IGS-180 full body motion capture suit capable of measuring body kinematics (Synertial, Brighton, East Sussex). Kinematics are the motion of bodies without reference to the mass or force. This motion capture device is a light weight, multi-sensor and fully portable data collection system of full body motion, consisting of 17 inertial measurement units (IMUs). The IMUs provide a great deal of accurate raw data including 3D orientation, acceleration and rate of turn (gyro rate) which allows for the extraction of a number of features for the evaluation of PD motor symptoms; namely rest and postural tremor severity. This type of full body motion capture technology has never been used to assess the efficacy of clinical programming and predefined randomized settings on PD patients who have undergone bilateral STN-DBS.

2.4 Laboratory Protocol

In order to quantify the efficacy of clinical DBS programming for therapy benefit in our PD population each PD patient was objectively assessed using the IGS-180 motion capture suit and the UPDRS. The first visit was a preoperative lab visit that represented our patients' "baseline" or their symptom severity before therapeutic intervention (STN-DBS). Three different surgeons performed the DBS surgeries on our patient group. The patients were then assessed in lab one week after surgery; at this point however, their DBS device was not yet turned on. Two weeks following surgery the device was turned on by a movement disorder neurologist and contact monitoring and selection was completed in clinic. A copy of the contact monitoring

tracking sheet can be found in Appendix A. The best contact point was then selected for each side of the brain through a standard clinical assessment. The movement disorders neurologist then programmed the patient's stimulator to a standard initial setting of 1.5 Volts, 130 Hertz and 90 microseconds using the contacts selected. The device was then left at this setting and patients were then assessed in the lab later that same day.

Adjustments to the voltage were made by the same movement disorder neurologist over designated clinic visits as determined clinically necessary. All clinic visits were aligned with lab visits. One month post-operatively patients were assessed and adjusted by a movement disorders neurologist at their clinic visit and later programmed and assessed by the trained research team in the lab where the effects of 3 out of the 18 predefined settings were tested. There were three ranges (low, medium and high) for each parameter that could be altered on the device; voltages, pulsewidths and frequencies. The patients were assessed and tested in this way once every month for a total of 6 months post operatively using the IGS-180 motion capture suit and multiple UPDRS assessments. Each laboratory visit consisted of:

1) Testing the patient on their clinical setting (the setting they walked into lab with as programmed by their neurologist)

 2) Testing the effects of 3 out of the total 18 predefined settings.

It is important to note that the order that the settings were tested in was randomized for each patient to reduce the impact of ordering effects. A summary of the 18 predefined settings is outlined in Table 2.

Setting Number	Voltage (V)	Frequency (Hz)	Pulse Width (μsec)
1	3	60	60
2	3	60	150
3	3	120	60
4	3	120	150
5	3	60	210
6	3	180	60
7	3	120	210
8	3	180	150
9	4.5	60	60
10	4.5	60	150
11	4.5	120	60
12	4.5	120	150
13	4.5	60	210
14	4.5	180	60
15	4.5	120	210
16	4.5	180	150
17	2	120	150
18	2	180	210

Table 2: The predefined stimulation parameters.

This table outlines the 18 predefined stimulation settings that were used in this study. All patients were tested on each of the settings. The test-order was randomized for each patient.

During each lab visit kinematic assessments were completed in order to test the effects of DBS programming. The kinematic assessment consisted of 2 motor tasks. While wearing the IGS-180 suit, the participants performed two standard motor tasks that were developed to evaluate 1) Rest Tremor and 2) Postural Tremor. Each task was performed twice and recorded for a total of 20 seconds each time. The angular displacements of the upper extremities, lower extremities and head were wirelessly recorded and transferred to a personal computeras the patient performed the task and this data was used for subsequent analysis. Each lab visit was also video recorded. A detailed description of the motor tasks is provided below in Figure 3. A detailed summary of the lab protocol is also found in Table 4.

Task	Description
Relaxed position	 The participants were asked to rest their arms in a neutral position; back hunched forward, both forearms resting on arm rests, and hands hanging loosely off the edge of the arm rests. They were asked not to fight any tremor or involuntary movements. The participants held this position for 20 seconds.
Posture	 While sitting, participants fully extended their arms forward with hands in pronation at shoulder height level. They were asked not to voluntarily fight or resist any tremor or involuntary movements. The participants held this position for 20 seconds.

Figure 3: Motor Tasks

This diagram provides a description of both motor tasks used in this study. The first was

designed to examine rest tremor in all the extremities and the second was designed to test

postural tremor emergence in the upper extremities.

Visit Number	Summary of Visit
V0 (Preoperative Visit)	• The patient was asked to come to our research facility, The South Street Annex at London Health Sciences in London Ontario Canada one week pre-operatively where we ran the kinematic assessments to capture baseline data. • During this pre-op session patients completed the 2 predefined motor tasks (kinematic assessment) while wearing the IGS-180 motion capture suit. • They were also assessed by a trained research associate using the UPDRS. • All other clinical questionnaires were completed independently by the patient (PDQ-8, GDS).
V1 (1 week postoperative with device off)	• During this visit the DBS device is not yet turned on. • Patients completed the kinematic assessment while wearing the IGS-180 motion capture suit. • They were then assessed by a trained research associate using the UPDRS. • All other clinical questionnaires were completed independently by the patient (PDQ-8, GDS).
V2 (2 weeks postoperative with device on)	• At V2: The device is turned on and contact monitoring is completed by the movement disorders neurologist. • Patients completed the kinematic assessment while wearing the IGS-180 motion capture suit. • They were then assessed by a trained research associate using the UPDRS. • All other clinical questionnaires were completed independently by the patient (PDQ-8, GDS).
V3-V8 (Post-operative programming visits with device on)	• Session 0: We obtained baseline recordings before the randomized programming sessions began. This was done to test the efficacy of clinical programming by the Movement disorder neurologist. The UPDRS was completed thereafter. • At each lab visit 3 programming sessions where the patients DBS device settings were changed according to our previously determined programming guide were completed. We tested 3 of the 18 predefined settings at each visit. The sessions are outlined below: • Session 1: After adjusting the device to the first experimental setting we allowed the patient to rest for 1 hour before conducting the kinematic assessments. This time allowed the patient to adjust to the new setting and to allow for any motor changes to occur. The UPDRS was completed thereafter. • Session 2: The patient was then adjusted to the second experimental setting and the same protocol as listed above for Session 1 was followed. • Session 3: The patient was then adjusted to the third and final

| | experimental setting and the same protocol was repeated again. |
| | • After the third setting was tested the patients were adjusted back to their clinical setting (the setting they walked into lab with). All other clinical questionnaires were completed independently by patients during each visit. |

Table 3: Summary of Patient Lab Visits

This table provides a detailed summary of the laboratory protocol used in this study.

2.5 MATLAB Full Body Tremor Code: Data Extraction and Raw Data Analysis

All kinematic assessments were recorded using the IGS-180 suit and software. All recordings were saved as an animation file (.AN File) for subsequent playback and analysis. Each recorded motion capture animation file was re-watched using the Animademo Playback Software in order to identify the start frame and end frame for each task completed by each participant. All lab visits were also video recorded from start to finish in order to validate the accuracy of the animation files. This ensured that the motion capture recording was accurate and aligned with the real time video recording and allowed us to verify that all the IMU sensors were working appropriately at the time of recording.

After the start and end frame times for every task were collected they were saved in an Excel Sheet. As mentioned above all body suit recordings were automatically saved in the .AN format. In order to be analyzed further each .AN file was then converted first to .BVH format and then modified and saved as a .Text file for use in MATLAB. The start and end frame times discussed earlier were later inputted into the MATLAB code and utilized for further analysis. This parsed-out raw data was then inputted into and analyzed using a MATLAB Tremor Detection code developed by Dr. Mehdi Delrobaei, Post-doctoral Researcher and Engineer. This code was manually validated by a trained research associate in the lab to check for the accuracy of the calculated feature values.

One hundred and five features were extracted from the data collected during each seated motor task. Features came from a total of 35 body joints (8 joints in each arm, 8 joints in each

leg, and 3 joints for the head). These features were then collapsed to calculate the total tremor amplitudes in each of the arms, legs, and the head. Calculated tremor amplitudes for each participant and task were later inputted into an encrypted database for subsequent statistical analysis. The root mean squared of the signal was used to calculate the amplitude of the movement in the head, left arm, right arm, left leg and right leg. Based on the summed scores used in the UPDRS to assess motor improvements we identified 2 indices of tremor severity which summed the amplitudes of the individual body segments. A description of the rest and postural tremor indices are outlined in the next sections.
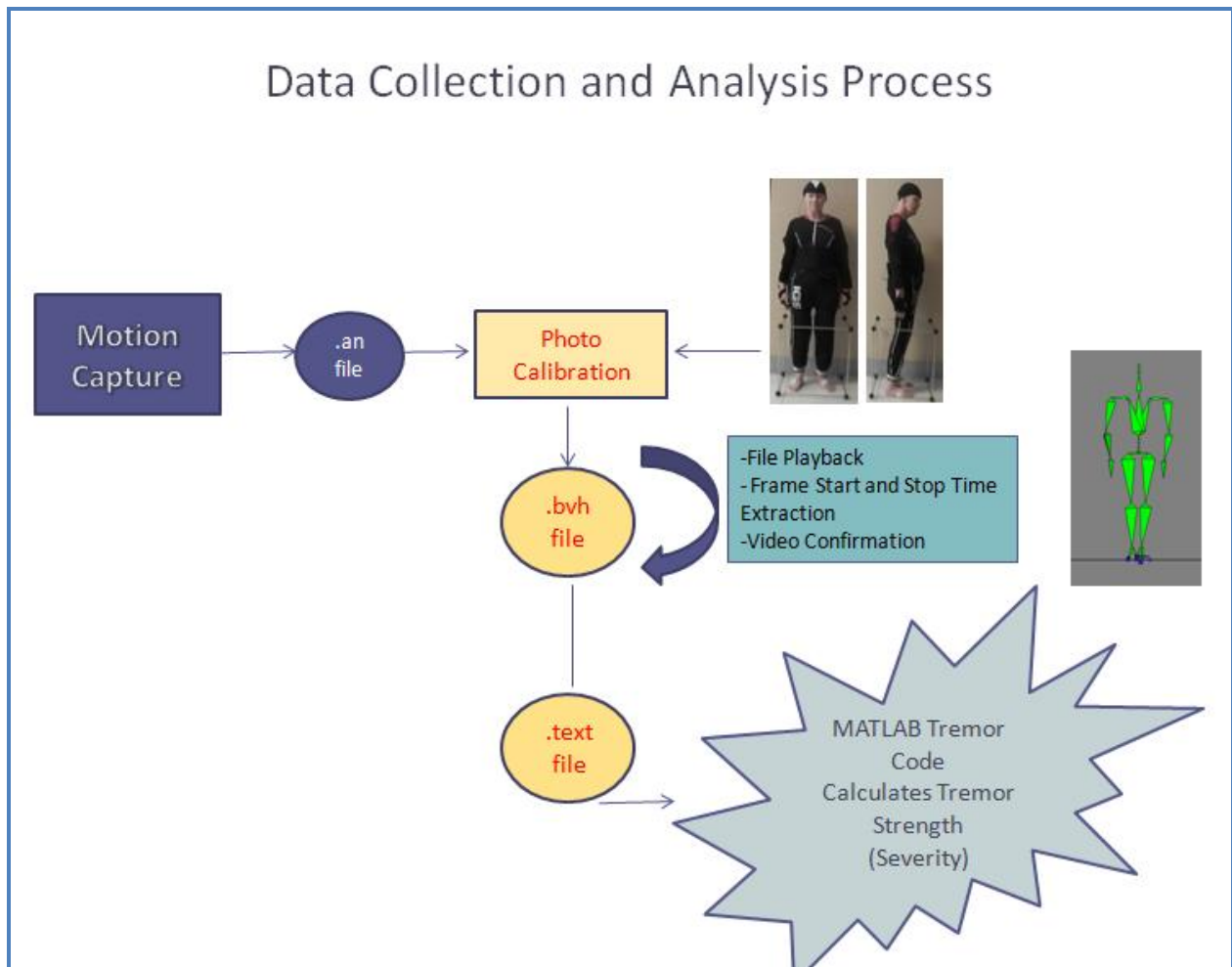
Figure4: Data Collection and Analysis Process

The diagram above presents a basic schematic of the data extraction process. Steps include: taking the motion capture recording while participant is wearing the IGS 180 suit and performing the motor tasks, wirelessly transferring the raw data to a CPU and saving it in the .an format, subsequent photo calibration, video confirmation and file conversion and data input into the MATLAB tremor code which then subsequently calculates tremor amplitudes.

2.6 Total Body Rest Tremor Index (TBRTI)

Total rest tremor amplitudes were calculated by the Tremor Code for 5body segments (both arms, both legs and the head) and these 5 individual amplitudes were then added together to generate an Index of Rest Tremor Severity which we have called the *Total Body Rest Tremor Index* or TBRTI. A higher TBRTI is indicative of more severe rest tremor while a lower TBRTI is indicative of mild tremor.

2.7 Upper Limb Postural Tremor Index (ULPTI)

Total postural tremor amplitudes were calculated by the Tremor Code for the left and right arms while the participant was maintaining a posture. These tremor amplitudes were then added together to generate an index of postural tremor severity, which we have called the *Upper Limb Postural Tremor Index* or *ULPTI*. Similar to the TBRTI score, a higher ULPTI is indicative of more severe postural tremor while a lower score is representative of mild tremor.

2.8 Results

All statistical analyses were conducted in IBM SPSS Version 20. Due to the small sample size and great deal of variability in our dataset, non-parametric statistical analyses were conducted. The Friedman ANOVA is a nonparametric test that is used to detect differences in treatments across multiple test attempts was used to analyze the data set. This statistical test is similar to the parametric repeated measures ANOVA. Subsequent Post Hoc analysis was conducted using the Friedman test for pair wise comparisons. This was done to detect significant differences between visits in the PD group. The nonparametric equivalent of the independent

samples T-test is the Man Whitney U Test and it was used to compare the control group to the patient group.

2.8.1 Effect of Clinical Programming on Whole Body Rest Tremor

Rest tremor statistical analysis was performed for 7 PD patients who completed all 9 laboratory visits(4 males, 3 females mean age=64.5 years ± 2.82 and mean PD duration=11.7 years ± 3.45) as well as for 7 healthy controls(3 males, 4 females;mean age=65.6 years ± 4.92805). By 6 months postoperatively the average DBS voltage patients were set to be 3.06 Volts ± 0.7138 while all patients were set to a pulse width of 90 microseconds and 130 hertz. A Pearson correlation between the TBTRI scores and UPDRS scores across visits was conducted. A positive correlation was found between the two variables(TBRTI score and Total Motor UPDRS score), r = 0.895, p=0.052. A summary of the demographic information for the PD cohort and their final DBS settings are provided in Table 4.

Patient ID	Sex	Age/ PD Duration (years)	Final stimulation parameters[*]			
			Left/Right Contacts	Voltage (V)	Frequency (Hz)	Pulse-Width (μSec)
01	F	68 / 17	C^+3^- / 8^+11^-	2.9	130	90
02	M	60 / 10	1^-2^+ / 9^-10^+	3	130	90
03	F	68 / 11	0^-1^+ / 10^-11^+	4.5	130	90
04	F	64 / 9	1^-3^+ / 10^-11^+	2.5	130	90
05	M	65 / 14	C^+2^- / 8^+11^-	3.4	130	90
06	M	67/7	1-3+/8-11+	2.5	130	90
07	M	66/14	C+2-/C+10-	2.6	130	90

Table 4: PD Patient Demographics.

Demographic information of the PD group including patient ID number, sex, PD duration, age and the final stimulation parameters each patient was set to 6 months postoperatively.

*All patients had the same voltage/frequency/pulse-width for both left and right STN.

A Mann-Whitney test indicated that the TBRTI of the healthy control group (M= 0.1795, SD= 0.17715) was significantly lower than that of the PD group preoperatively (M=1.7043, SD=2.7543,U=23, p=0.001). A non-parametric Friedman ANOVA of differences among repeated measures was conducted and rendered a Chi-square value of 25.66 which was significant (p=0.001). This indicates that the null hypothesis which states that there was no effect of treatment on the patient group over time can be effectively rejected. Subsequent post-hoc analysis was conducted using multiple Friedman tests. Several pair wise comparisons were made.

One week postoperatively, with the DBS device yet to be turned on, the PD group experienced a reduction in TBRTI (M=1.0765, SD=1.31498) in comparison to the preoperative score. A Friedman test was conducted and rendered a Chi-square value of 0.000 which was not significant (p=1.00).

Two weeks post operatively during which the DBS device was turned on the PD group experienced a further reduction in their TBRTI (M=0.9338, SD=1.18901) in comparison to the preoperative score. A Friedman test was conducted and rendered a Chi-square value of 1.143 which was not significant (p=0.285).

At one month postoperatively, the PD group experienced an increase in TBRTI (M=1.7325, SD=2.46591) when compared to the two week postoperative score. A Friedman test was conducted for this comparison and yielded a Chi-square value of 1.143 which was not significant (p=0.285). The PD group experienced a reduction in TBRTI at two months postoperative when compared to the preoperative score (p=0.593). The PD group experienced a further reduction at three months postoperative (M=0.8735, SD=0.83885) when compared to the

preoperative score (p=0.109). The PD group experienced an increase in TBRTI at four months postoperative (M=1.0931, SD=1.228) when compared to the 3 month postoperative score (p=0.593).   A further decrease in PD TBRTI was detected at five months post operatively (M=.3518, SD=0.45307). A Friedman test was conducted and rendered a Chi-square value of 7.143 which was statistically significant (p=0.008). Six months post operatively, the TBRTI for PD patients decreased (M=.5973, SD= 0.89090) when compared to the preoperative score. A Friedman test was conducted and rendered a Chi-square value of 10.286 which was statistically significant (p=0.001).

A Mann-Whitney test indicated that the TBRTI of the healthy control group was not significantly different than that of the PD group 6 months following surgery (U=61, p=0.089).
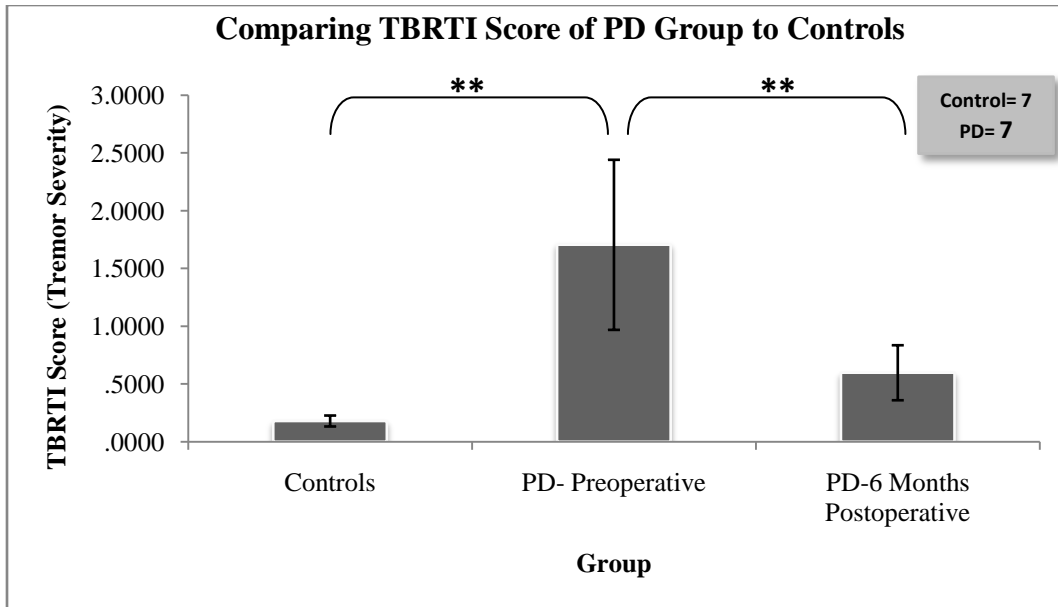
Figure 5:Comparison of TBRTI score of controls and PD patients before and after STN-DBS

Graph shows the TBRTI score of controls compared to the PD group before surgery and the PD-group 6 months after surgery. A non-parametric between groups comparison was done and showed that the control group and PD group before surgery were statistically different, controls having a lower TBRTI than the PD group (U=23, p=0.001). A Friedman test indicated that there was a significant reduction in TBRTI in the PD group 6 months following surgery

* p$\leq$ 0.05

** p$\leq$ 0.005

Error bars shown ± 1 standard error.
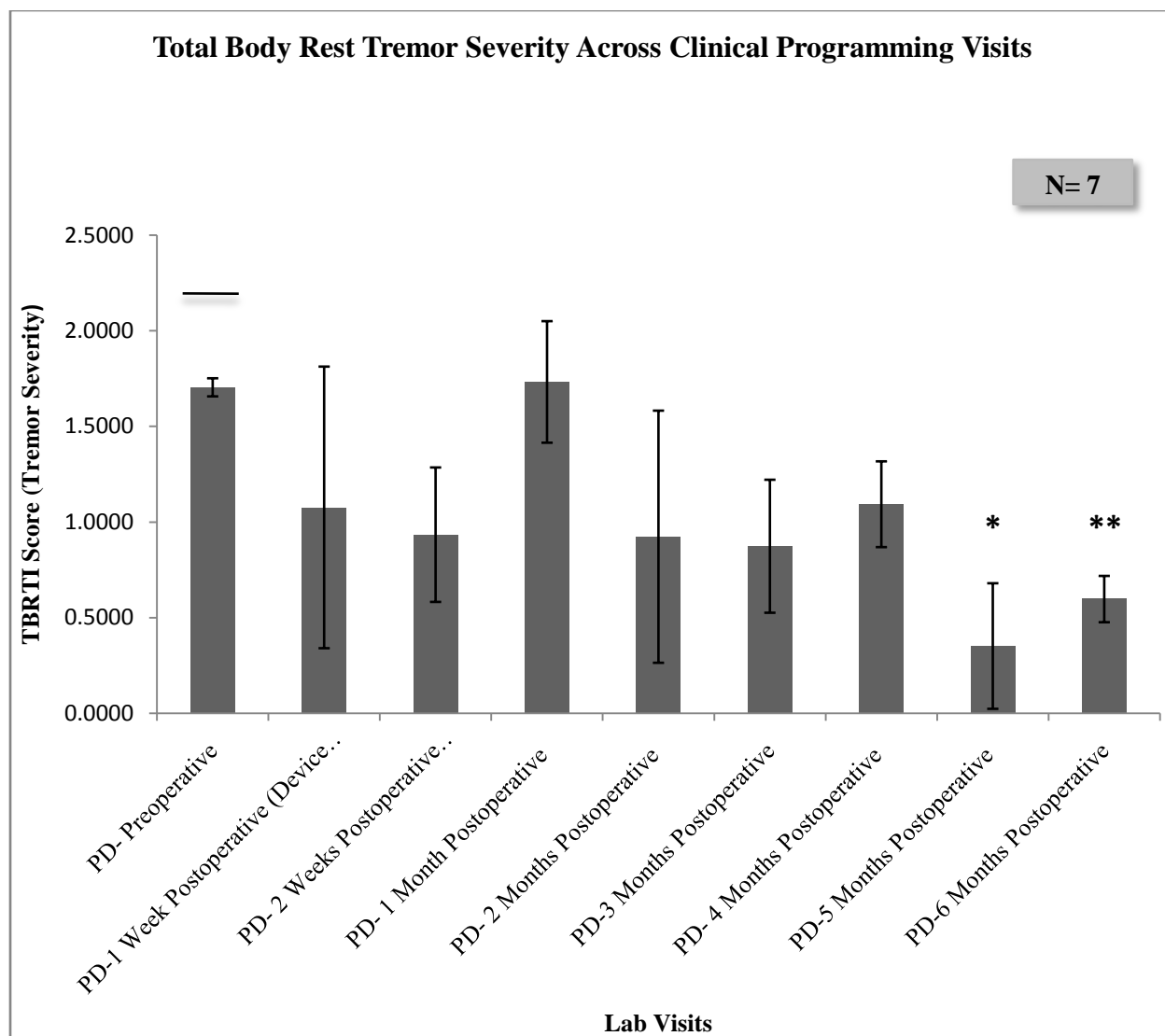
Figure 6: Comparison of TBRTI score of PD group before surgery to TBRTI at multiple time points after surgery.

Graph outlines the average TBRTI of the PD group before surgery and at multiple time points after surgery. All comparisons were made between the pre-operative conditions. The PD group experienced a statistically significant reduction in TBRTI at both 5 months (Chi square = 7.143, p =0.008) and 6 months (Chi square =10.286, p= 0.001) following DBS when compared to before surgery.

* p$\leq$ 0.05

** p$\leq$ 0.005

Standard error is represented by the error bars on the graph above.

2.8.2 Effect of Clinical Programming on Postural Tremor

Upper limb postural tremor statistical analysis was performed for 7 PD patients who completed all 9 laboratory visits as well as for 7 healthy controls. A Mann-Whitney test indicated that the ULPTRI of the healthy control group (M=0.1572, SD=0.16466) was significantly lower than that of the PD group preoperatively (M= 0.7029, SD=0.1782; U=31.5, p=0.002).

A non-parametric Friedman ANOVA of differences among repeated measures was conducted and rendered a Chi-square value of 25.48 which was significant (p=0.001). This indicates that the null hypothesis which states that there is no effect of treatment on the patient group over time can be effectively rejected. Subsequent post-hoc analysis was conducted using multiple Friedman tests. Several pair wise comparisons were made and are outlined below.

One week postoperatively, with the DBS device still turned off, the PD group experienced a reduction in ULPTI (M=0.4279, SD=0.12039) compared to the preoperative score. A Friedman test was conducted and rendered a Chi-square value of 4.57 which was statistically significant (p=0.033).

At two weeks postoperative during which the DBS device had been turned on the PD grouped experienced an increase in ULPTI (M=0.6343, SD=0.31257) when compared to the one week post-operative score. A Friedman test was conducted and rendered a Chi-square value of 1.14 which was not significant (p=0.285).

At one month postoperatively the PD group experienced a decrease in ULPTI (M=0.3507, SD=0.1157) when compared to the preoperative score. A Friedman test was conducted and rendered a Chi-square value 7.143 of which was significant (p=0.008).

At five months following DBS surgery the PD group experienced an increase in ULPTI (M= 0.4250, SD=0.1620) when compared to three months post operatively. A Friedman test was conducted and rendered a Chi-square value of 2.6 which was not significant (p=0.109). However, the ULPTI of the PD group five months post operatively was still significantly lower when compared to the preoperative baseline score. A Chi square value of 4.6 was rendered which was significant (p=0.033).

Six months post operatively the ULPTI of the PD group was reduced (M=0.3421, SD= 0.14595) when compared to the preoperative score (Chi Square value = 10.29, p=0.001). A Mann-Whitney test indicated that the ULPTI of the healthy control group was not significantly different than that of the PD group ULPTI score at 6 months postoperatively (U=90, p=0.713).
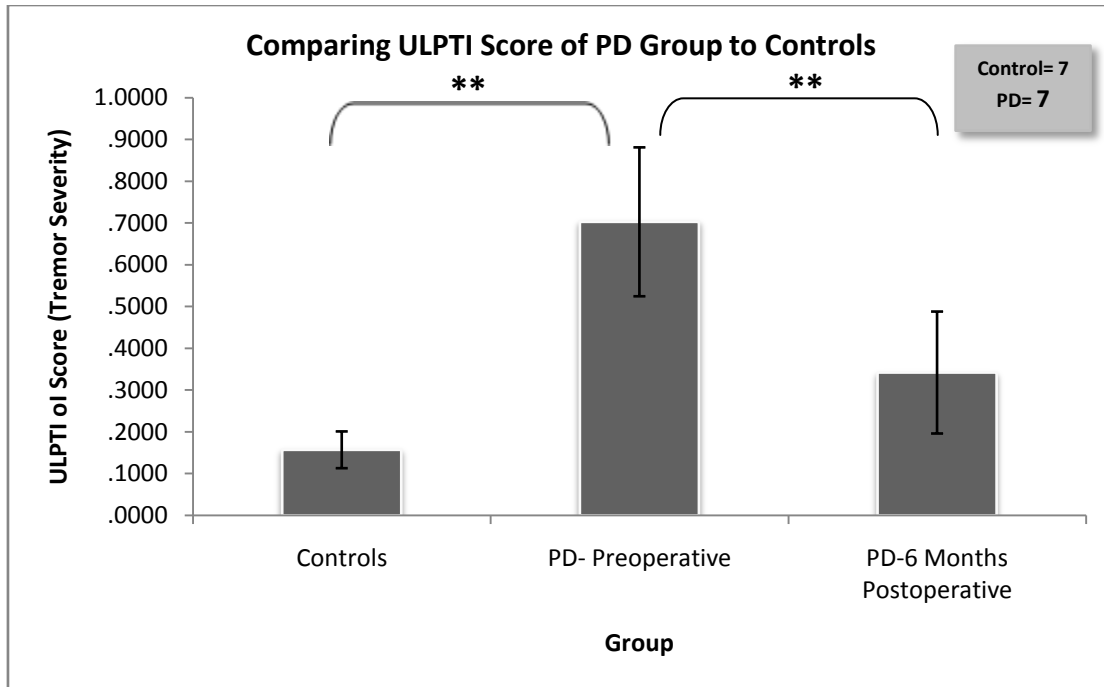
Figure 7: Comparison of ULPTI score of controls and PD patients before and after STN-DBS

Graph shows the ULPTI of the control group the PD group before surgery and the PD group 6 months following surgery. A non-parametric comparison of the control group and PD group before surgery indicated that the groups were statistically different, the controls having a lower ULPTI than the PD group (U=31.5, p=0.002). A Friedman test indicated that the PD group ULPTI was significantly reduced 6 months following surgery(Chi Square value = 10.29, p=0.001).

* $p \leq 0.05$
** $p \leq 0.005$
Standard error is represented by the error bars on the graph above.
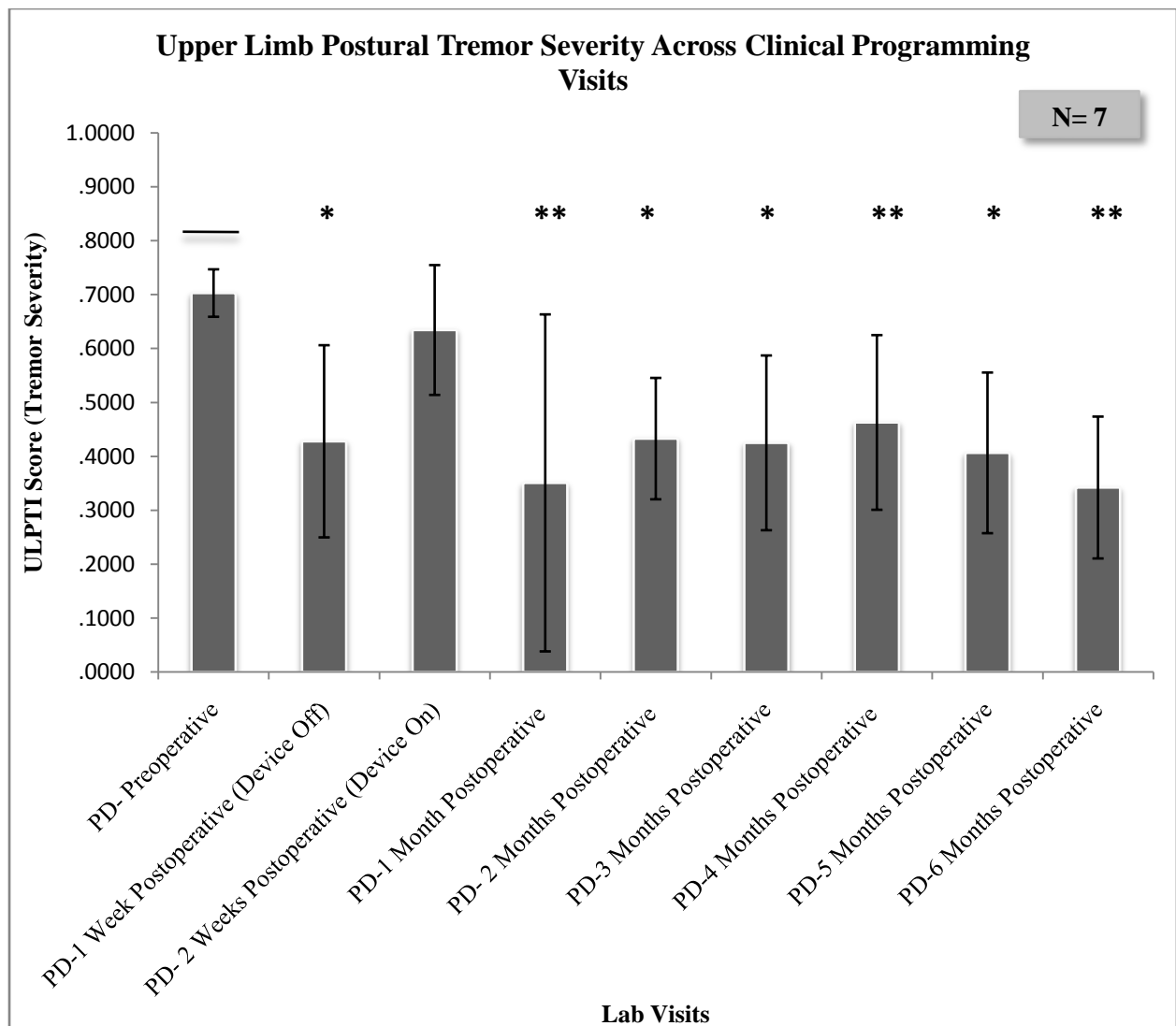
Figure8:Comparison of TBRTI score of PD group before surgery to TBRTI at multiple time points after surgery

Graph outlines the average ULPTI of the PD group before surgery and at multiple time points after surgery. All comparisons were made between the pre-operative conditions. The PD group experienced a statistically significant reduction in ULPTI at one week following surgery with the device still off as well as at one months, two months, three months, four months, five months and six months following DBS when compared to before surgery.

* p< 0.05

** p≤ 0.005

Standard error is represented by the error bars on the graph above.

2.8.3 Short-Term Effects of Predefined DBS Parameter Settings on TBRTI on Average

When compared to the preoperative score (M=1.7043, SD=2.7543) all of the predetermined settings with the exception of setting 14 resulted in an averagereduction in the TBRTI scores of the PD group. When compared tothe clinical programming setting at 6 months following surgery (M=0.5973, SD= .89090) only 3 settings resulted in greater tremor reduction. These settings were setting 10(4.5 V, 60 Hz and 150μsec;M=0.495, SD=0.14393), setting 17(2V, 120 Hz and 150 μsec; M=0.5356, SD=0.14679) and setting 7 (3V, 120 Hz and 210 μsec; M=0.5770, SD=0.10034).A non-parametric Friedman ANOVA of differences among repeated measures was conducted and rendered a Chi-square value of 20.3 which was not significant (p=0.373).Setting 10 resulted in the greatest reduction in tremor when compared to the preoperative TBRTI score (Chi Square = 2.57, p=0.109) and the postoperative TBRTI score at 6 months (Chi Square =1.143, p=0.285). The effects of setting 10 on TBRTI in the PD group was compared to the TBRTI of healthy controls using a Mann Whitney test. The TBRTI of healthy controls was significantly lower than the TBRTI of patients programmed to setting 10 (U=42, p=0.010). There were no statistically different settings compared to the preoperative score.
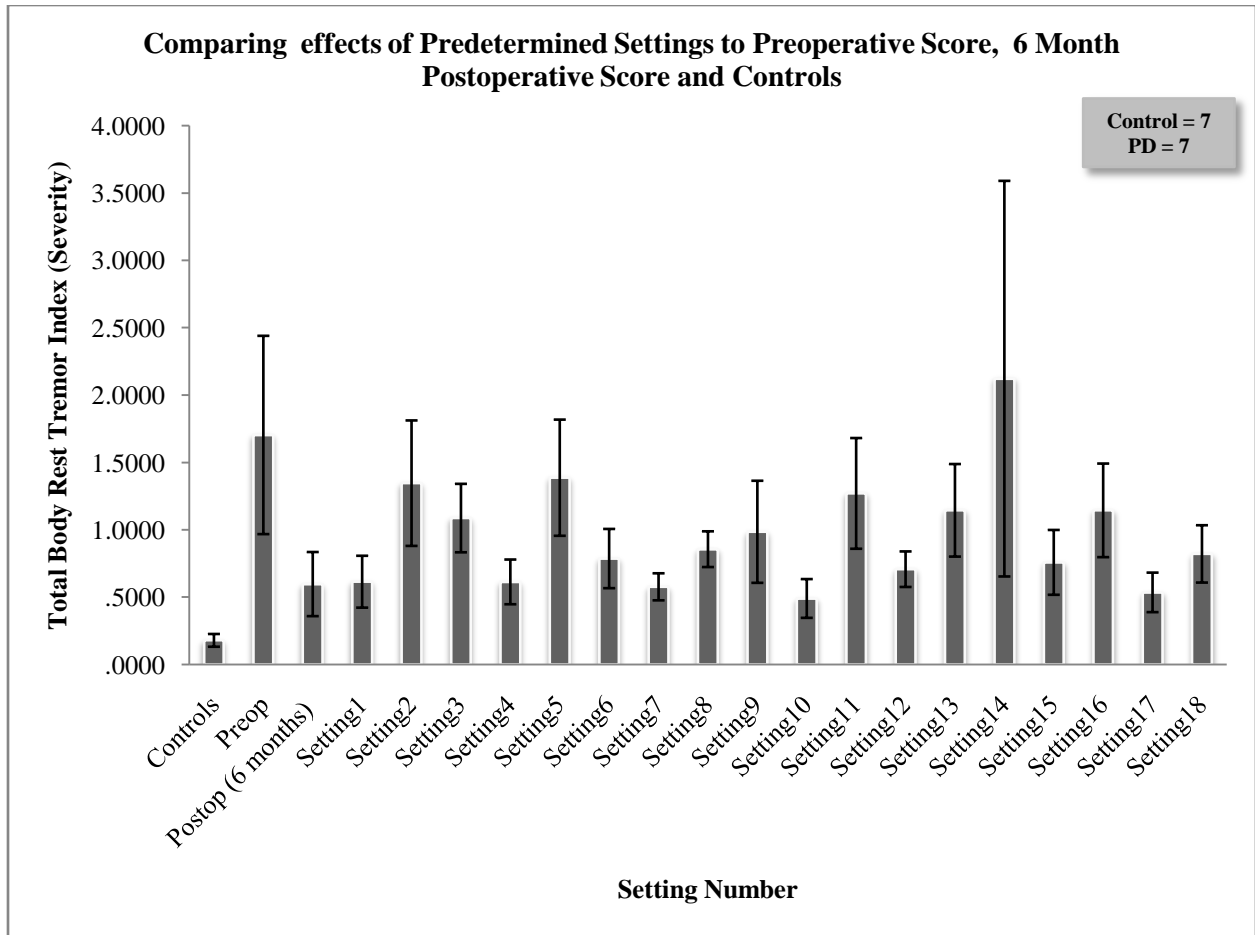
Figure 9: Comparison of 18 predefined settings and their effect on reducing TBRTI

The graph above shows the average TBRTI scores of the control group, the PD group before surgery, the PD group following 6 months of clinical DBS programming and the 18 predefined settings tested in the laboratory setting. This provides a comparison of the TBRTI scores of all these groups. One setting exacerbated tremor severity while several others decreased them.

*Standard error is represented by the error bars on the graph above.

Increasing Frequency. Settings 2, 4 and 8 were compared, all of which have a voltage of 3V and a pulse-width of 150μsec. No significant differences were found between these settings upon statistical analysis using a Friedman test of differences across treatments (Chi Square= 19.2, p= 0.223). A Mann-Whitney test indicated that the TBRTI score of the healthy control group was significantly lower than that of the TBRTI score of the PD group while programmed to setting 4 (U=35, p=0.004) and setting 2 (U=28, p =0.001) and setting 8 (U=16, p=0.000).Setting 4 resulted in the greatest tremor reduction in this grouping however this reduction was not statistically significant.

Setting Number	Voltage (V)	Frequency (Hz)	Pulse Width (µsec)
2	3	60	150
4	3	120	150
8	3	180	150
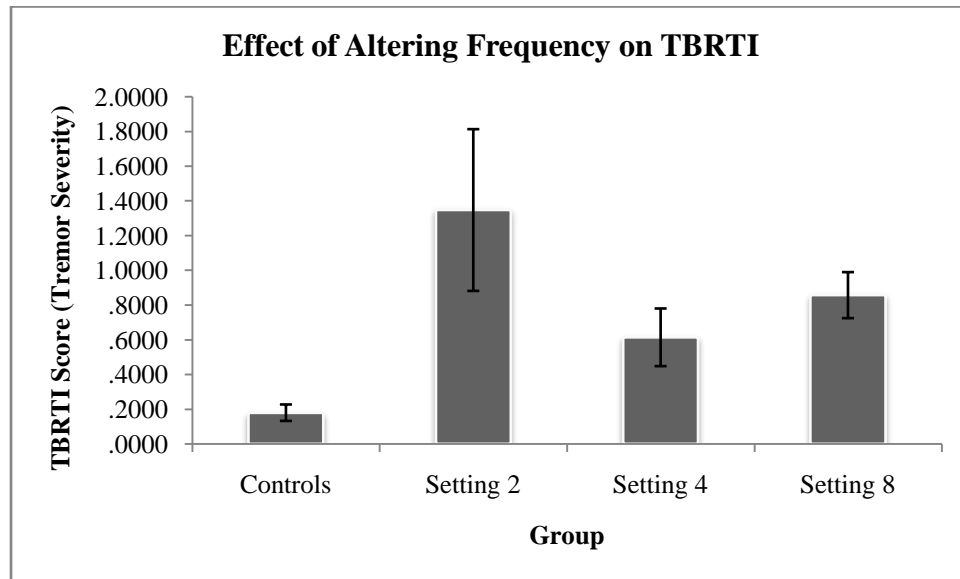
Figure 10: Quantifying the effect of altering frequency on TBRTI score

This figure compares 3 settings where both voltage and pulse width were kept constant and frequency was altered. Setting 4 which had a medium frequency resulted in the most marked reduction in TBRTI score, however this reduction was not statically significant when compared to the preoperative TBRTI score. None of the 3 settings resulted in a statistically significant change in TBRTI score when compared to the preoperative score.

*Standard error is represented by the error bars on the graph above.

Increasing Voltage. Settings4,12 and 17 were compared. These settings all have a frequency of 120Hz and a pulse-width of 150μsec. No significant differences were found between these settings upon statistical analysis using a Friedman test of differences across treatments (Chi Square = 1.857, p=0.395). A Mann-Whitney test indicated that the TBRTI of the healthy control group was significantly lower than that of the TBRTI of the PD group while programmed to setting 12 (U=31, p=0.002) and setting 17 (U=49, p =0.024).Setting 17 resulted in the greatest tremor reduction in this grouping however this reduction was not statistically significant when compared to the preoperative score.

Setting Number	Voltage (V)	Frequency (Hz)	Pulse Width (μsec)
4	3	120	150
12	4.5	120	150
17	2	120	150
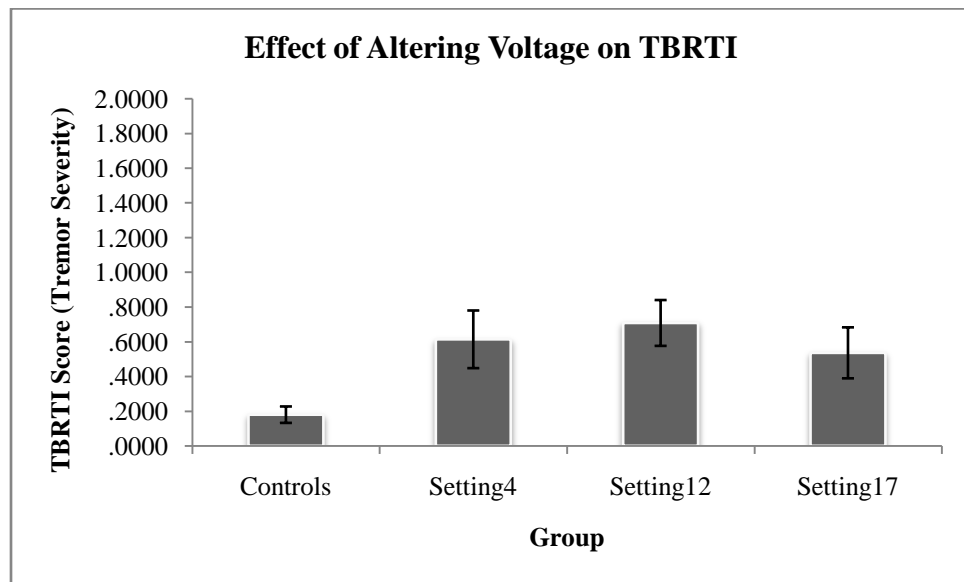
Figure 11: Quantifying the effect of altering voltage on TBRTI score

This figure compares 3 settings where both frequency and pulse width were kept constant and voltage was altered (low, medium or high). Setting 17 which had a low voltage resulted in the most marked reduction in TBRTI score, however this reduction was not statically significant when compared to the preoperative TBRTI score. None of the 3 settings resulted in a statistically significant change in TBRTI score when compared to the preoperative score.

*Standard error is represented by the error bars on the graph above.

Increasing Pulse-width. Settings 3, 4 and 7 were compared, all of which have a frequency of 120 Hz and a voltage of 3V.No significant differences were found between these settings upon statistical analysis using a Friedman test of differences across treatments (Chi square =3, p= 0.223). A Mann-Whitney test indicated that the TBRTI of the healthy control group was significantly lower than that of the TBRTI of the PD group while programmed to setting 3 (U=14, p=0.00) and setting 7 (U=15, p= 0.00). Setting 7 resulted in the greatest tremor reduction in this grouping.

Setting Number	Voltage (V)	Frequency (Hz)	Pulse Width (µsec)
3	3	120	60
4	3	120	150
7	3	120	210
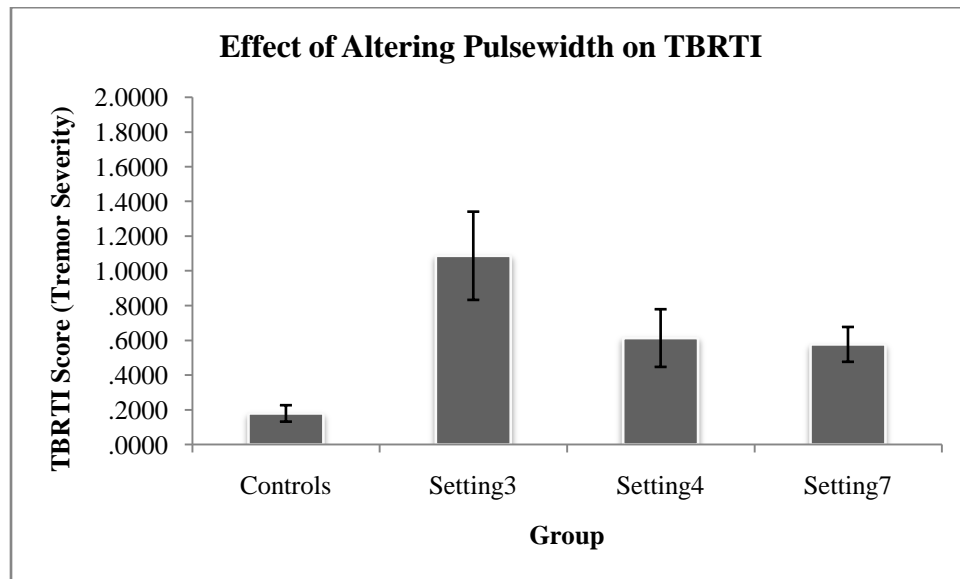
Figure 12: Quantifying the effect of altering pulse width on TBRTI score

This figure compares 3 settings where both voltage and frequency were kept constant and pulse width was altered (low, medium, high). Setting 4 which had a medium pulse width resulted in the most marked reduction in TBRTI score, however this reduction was not statically significant when compared to the preoperative TBRTI score. None of the 3 settings resulted in a statistically significant change in TBRTI score when compared to the preoperative score.

*Standard error is represented by the error bars on the graph above.

2.8.4 Case Studies: UPDRS and TBRTI Scores for Individual Patients

DBS-01

DBS-01 presented with a total UPDRS score of 13.5 and a TBRTI score of 2.4, one week before DBS surgery. Following 6 months of clinical DBS programming this patient's UPDRS score was reduced to 11 and their TBRTI score was reduced to 0.18. The predefined setting that resulted in the greatest reduction in their TBRTI score was setting 17, which reduced their score to 0.08. For this patient, most settings resulted in a reduction in TBRTI score, some much more so than others.
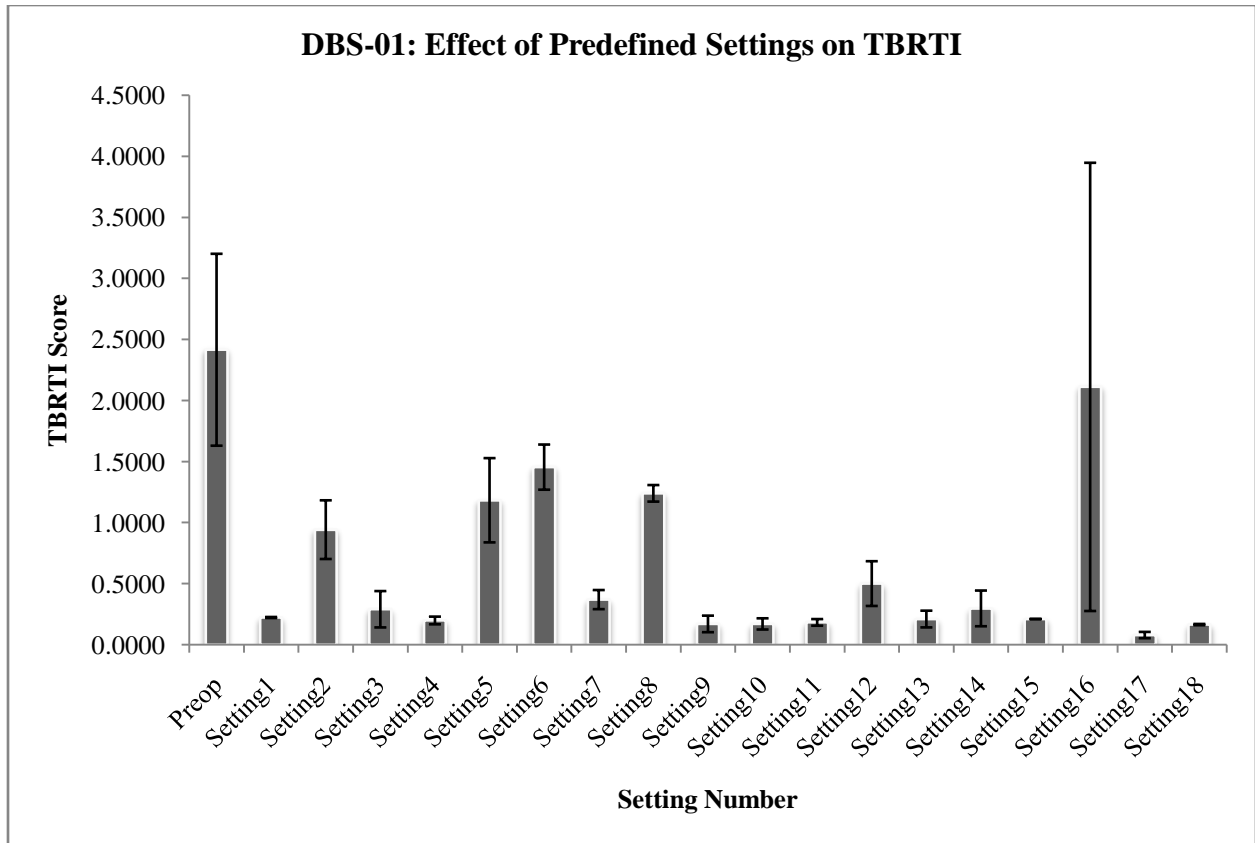
Figure 13: The effect of predefined settings on DBS-01's tremor severity

This graph shows the effect of the 18 predefined settings on one of the patients in this study in comparison to their preoperative score.

DBS-02

DBS-02 presented with a total UPDRS Score of 45 and a TBRTI score of 0.68 one week before DBS surgery. Following 6 months of clinical DBS programming this patients UPDRS score was reduced to 12.5 and their TBRTI score was reduced to 0.25. The predefined setting that resulted in the greatest reduction in their TBRTI score was setting 10, which reduced their score to 0.15. For this patient, many settings had little effect, but a few produced marked reductions in TBRTI score.

Figure14:The effect of predefined settings on DBS-02's tremor severity

This graph shows the effect of the 18 predefined settings on one of the patients in this study in comparison to their preoperative score.

DBS-03

       DBS-03 presented with a total UPDRS Score of 30 and a TBRTI score of 1.74 one week before DBS surgery. Following 6 months of clinical DBS programming this patients UPDRS score was reduced to 12.5 and their TBRTI score was reduced to 1.02. The predefined setting that resulted in the greatest reduction in their TBRTI score was setting 10, which reduced their score to 0.16. This patient has a very low pre-operative TBRTI score and most settings did not reduce it further. One setting produced a marked increase in score.
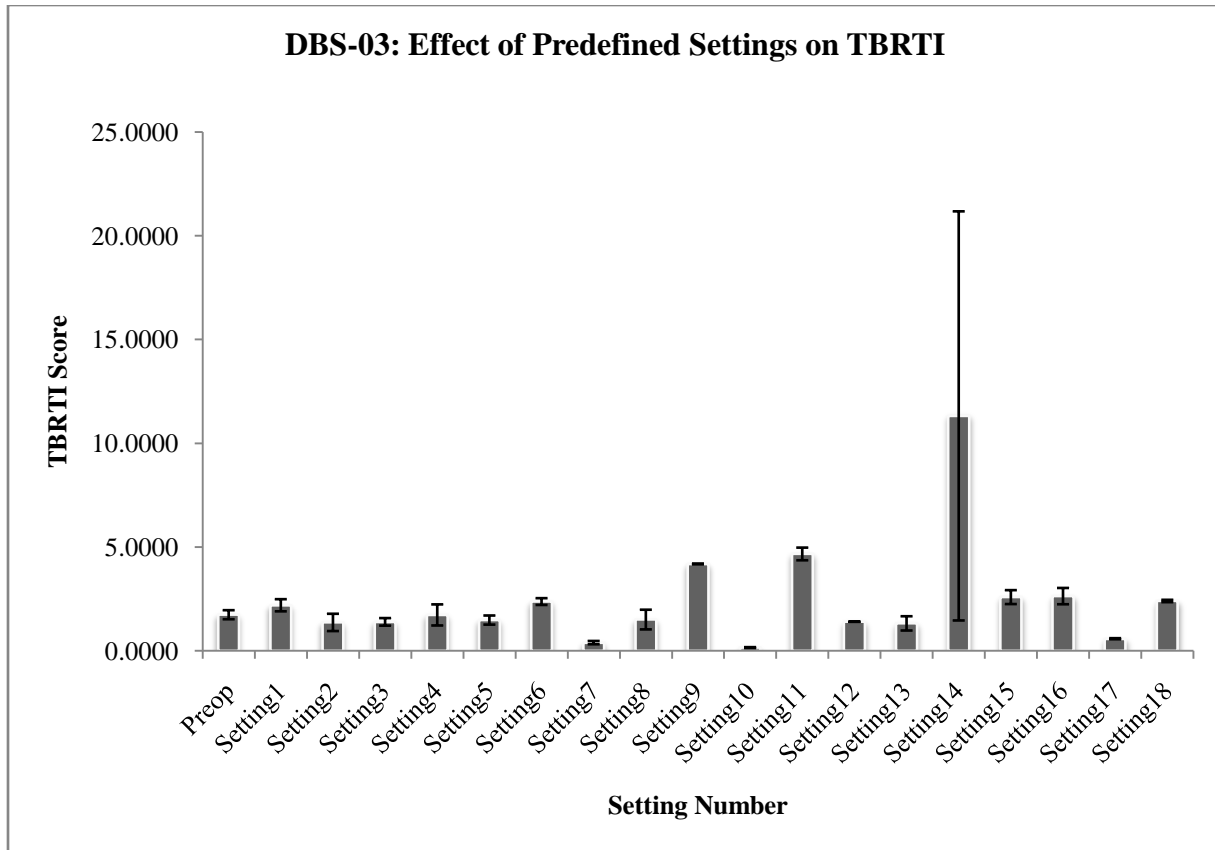
Figure 15: The effect of predefined settings on DBS-03's tremor severity

This graph shows the effect of the 18 predefined settings on one of the patients in this study in comparison to their preoperative score.

DBS-04

DBS-04 presented with a total UPDRS Score of 20.5 and a TBRTI score of 5.76 one week before DBS surgery. Following 6 months of clinical DBS programming this patients UPDRS score was reduced to 17.5 and their TBRTI score was reduced to 2.45. The predefined setting that resulted in the greatest reduction in their TBRTI score was setting 16, which reduced their score to 0.13. All of the predefined settings resulted in a reduction in tremor for this particular patient, none exacerbated tremor above the preoperative score.
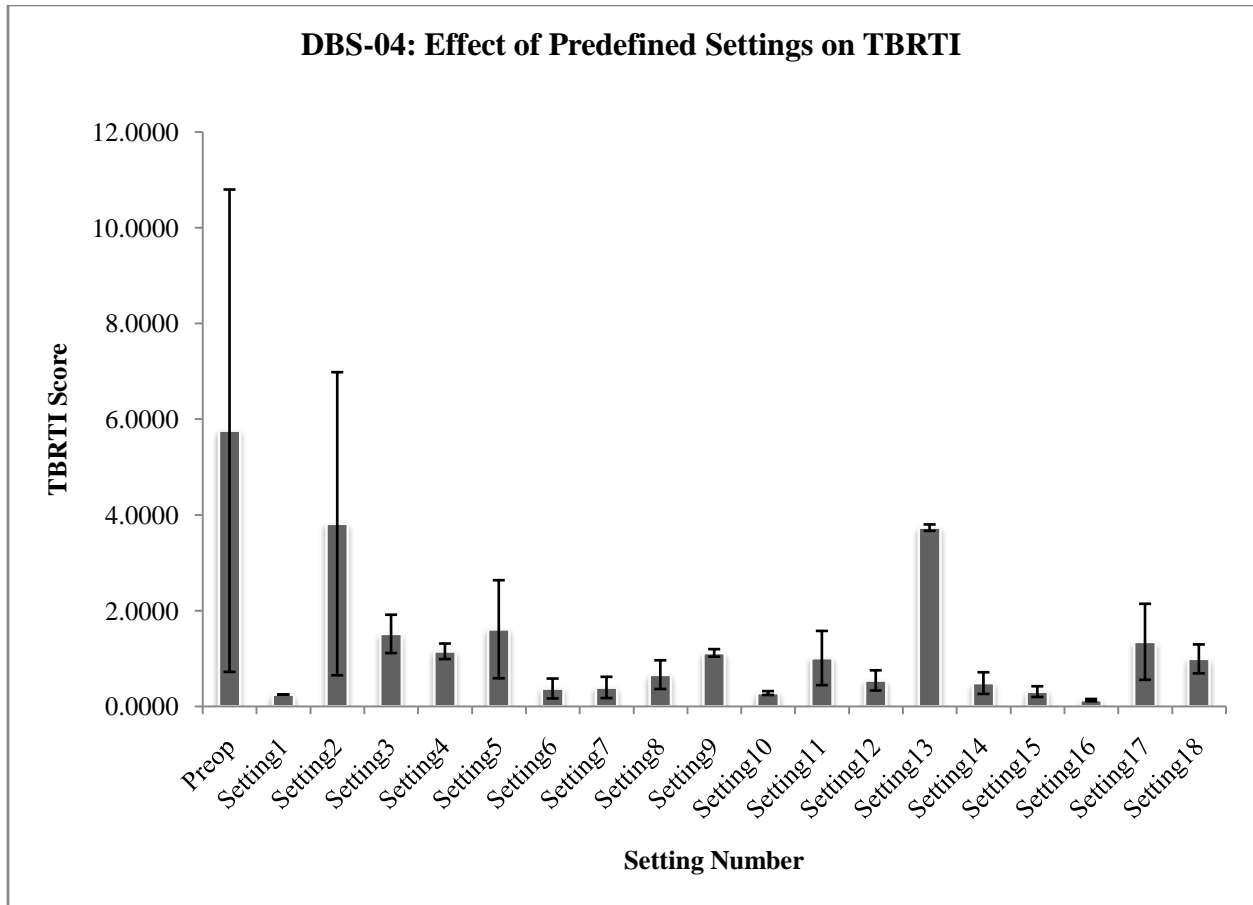
Figure 16: The effect of predefined settings on DBS-04's tremor severity

This graph shows the effect of the 18 predefined settings on one of the patients in this study in comparison to their preoperative score.

DBS-05

DBS-05 presented with a total UPDRS score of 13 and a TBRTI score of 0.20 one week before DBS surgery. Following 6 months of clinical DBS programming this patient's UPDRS score was reduced to 9.5 and their TBRTI score was reduced to 0.13. The predefined setting that resulted in the greatest reduction in their TBRTI score was setting 9, which reduced their score to 0.07. This patient started with a low TBRTI score, with many of the settings markedly increasing their score.
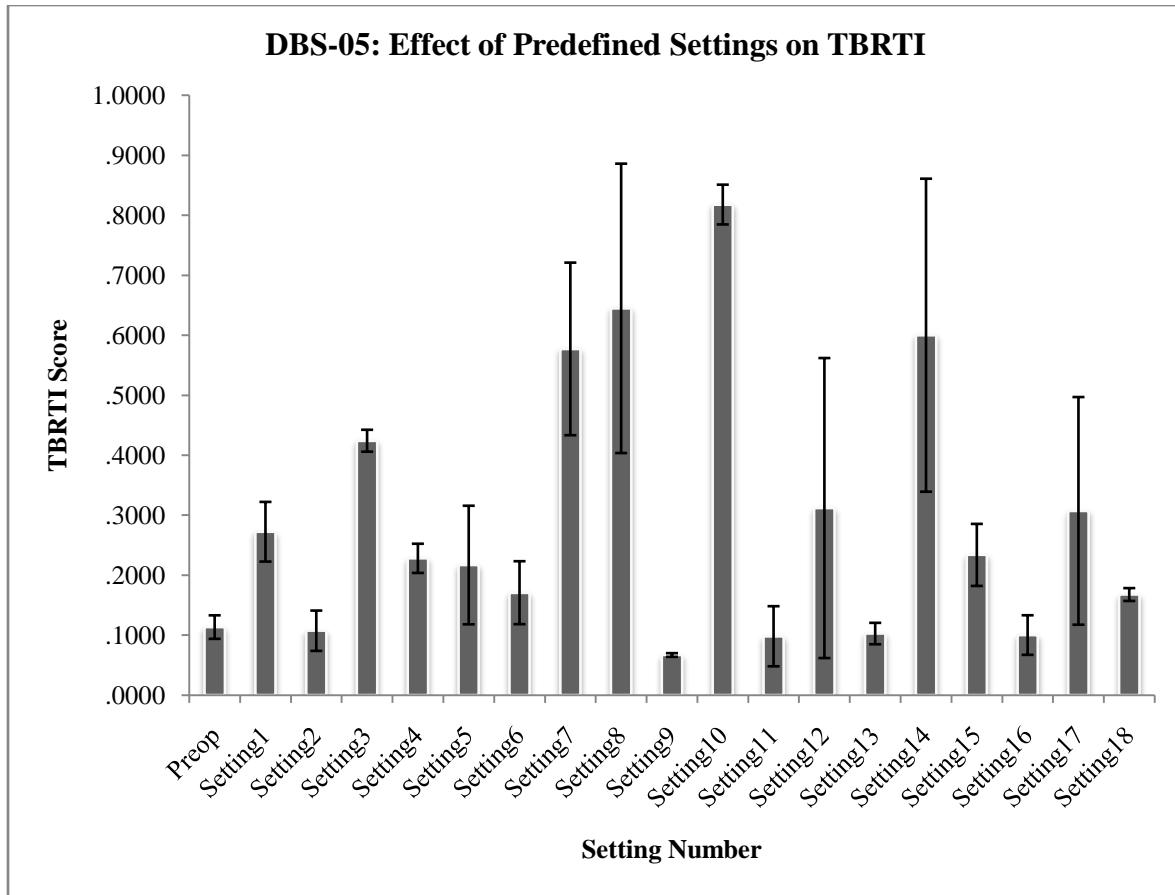
Figure 17: The effect of predefined settings on DBS-05's tremor severity

This graph shows the effect of the 18 predefined settings on one of the patients in this study in comparison to their preoperative score.

DBS-06

DBS-06 presented with a total UPDRS score of 43.5 and a TBRTI score of 0.11 one week before DBS surgery. Following 6 months of clinical DBS programming this patient's UPDRS score was reduced to 18.5 and their TBRTI score was reduced to 0.15. The predefined setting that resulted in the greatest reduction in their TBRTI score was setting 6 which reduced their score to 0.12. This patient started with a low TBRTI score with five of the predefined settings caused marked increases in the TBRTI all others lead to a reduction in TBRTI score.
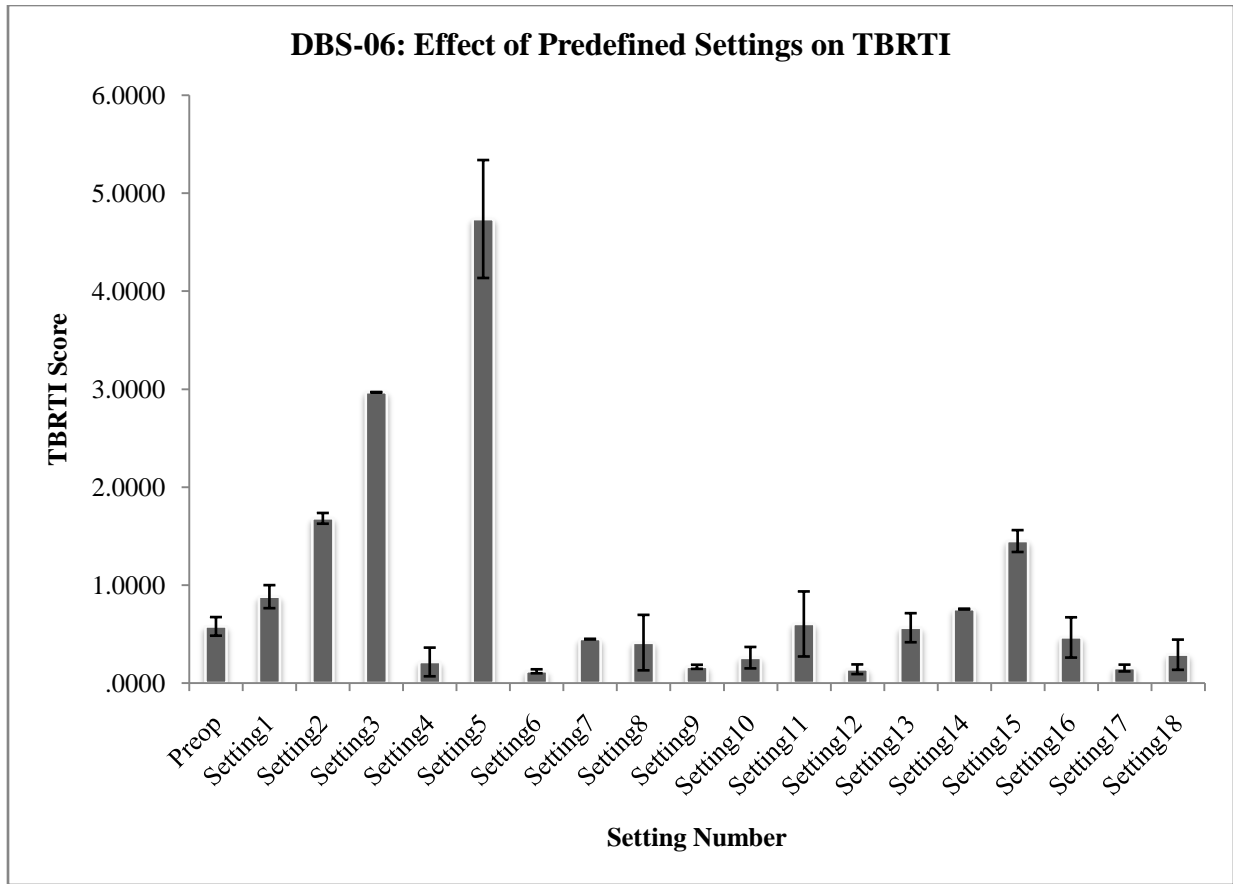
Figure 18: The effect of predefined settings on DBS-06's tremor severity

This graph shows the effect of the 18 predefined settings on one of the patients in this study in comparison to their preoperative score.

DBS-07

DBS-07 presented with a total UPDRS score of 28.5 and a TBRTI score of 0.58 one week before DBS surgery. Following 6 months of clinical DBS programming this patient's UPDRS score was reduced to 4.54. The predefined setting that resulted in the greatest reduction in their TBRTI score was setting 5 which reduced their score to 0.17. Many of the predefined settings resulted in increasing the TBRTI of this patient.
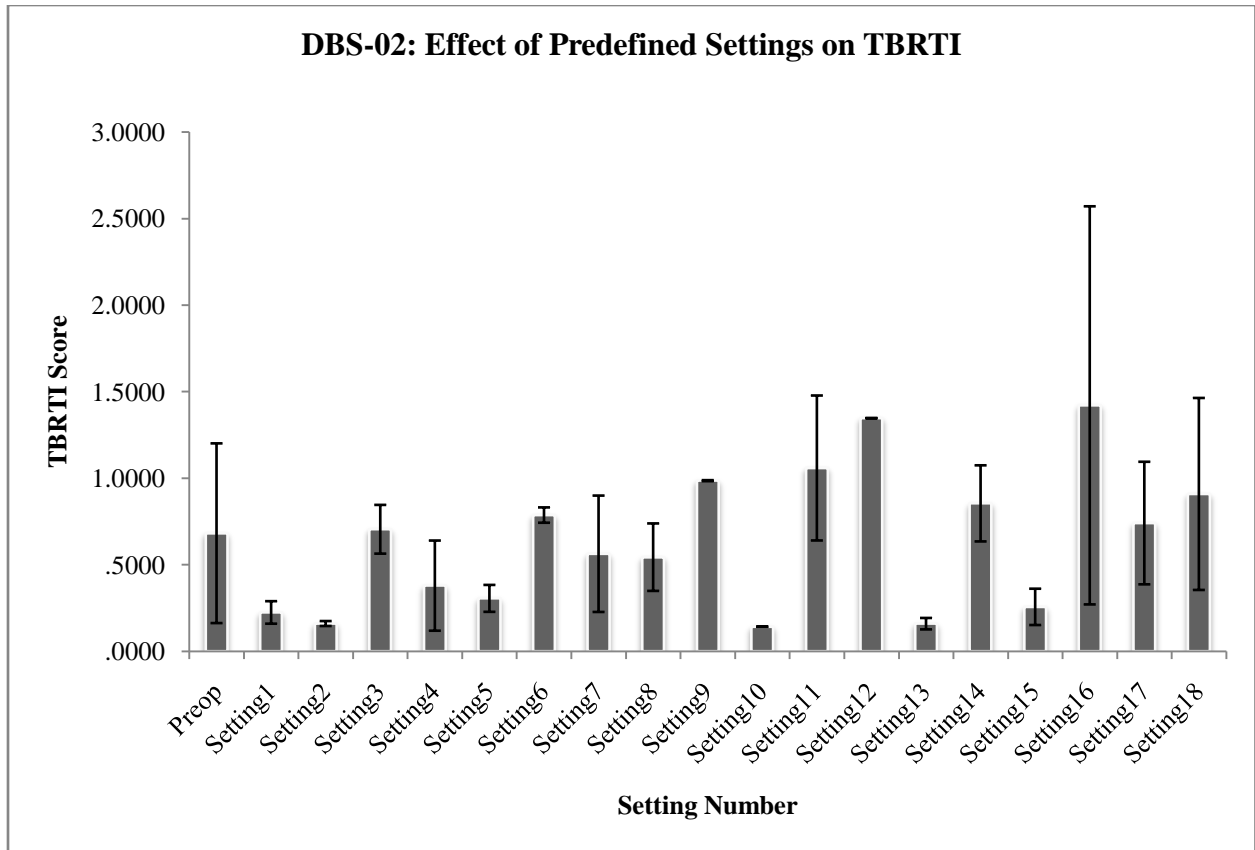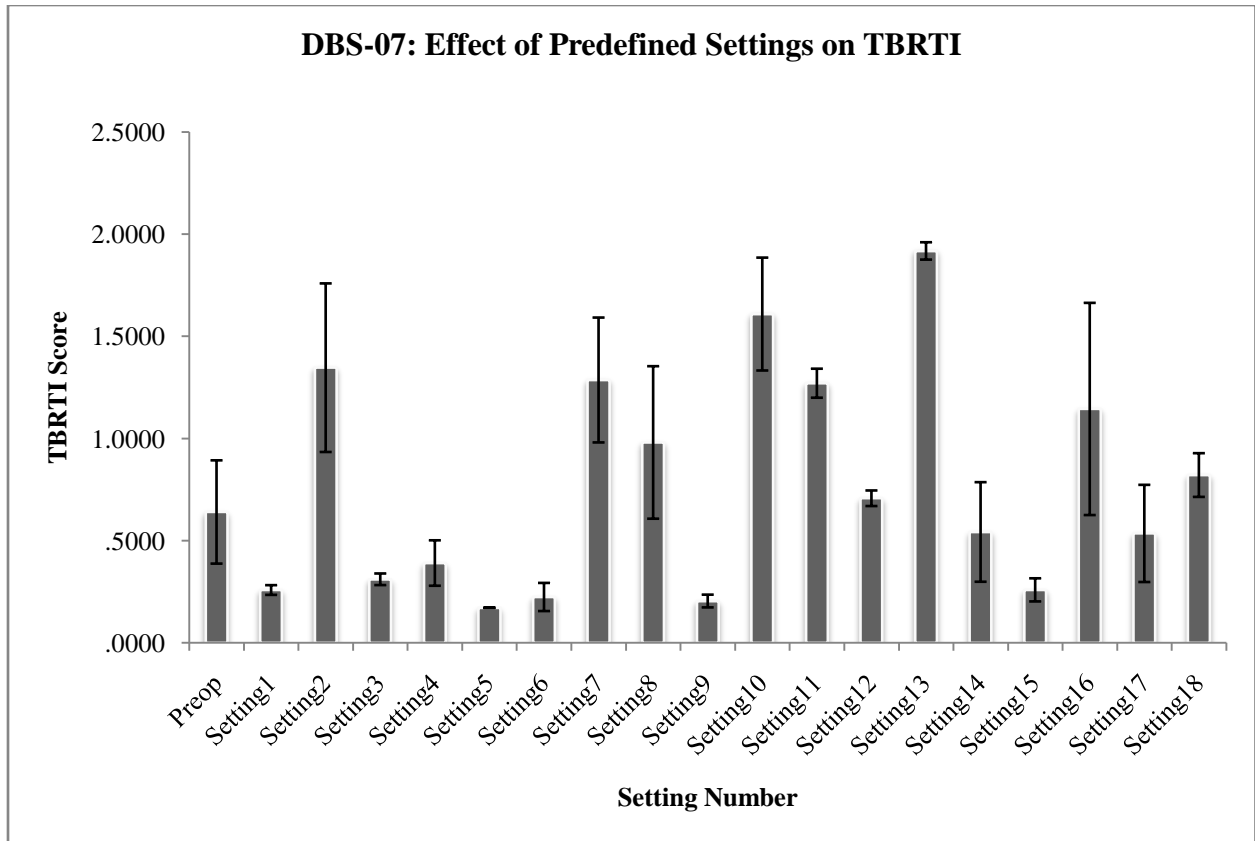
Figure 19: The effect of predefined settings on DBS-07's tremor severity

This graph shows the effect of the 18 predefined settings on one of the patients in this study in comparison to their preoperative score.

2.8.5 UPDRS-III Motor Scores

Patients showed a Total Motor UPDRS score of 30.08 ± 12.56 before the surgical intervention. 6-months post-operatively, patients showed a Total Motor UPDRS score of 12.5 ± 5.17. This result showed an average percent change of 58 ± 0.41 % from before surgery to 6 months following DBS surgery, which was significantly different (Chi square $=7$; p $=0.008$). Overall, these results suggest a motor symptom improvement following the DBS procedure and subsequent clinical programming iterations including improvements in both rest and postural tremor.
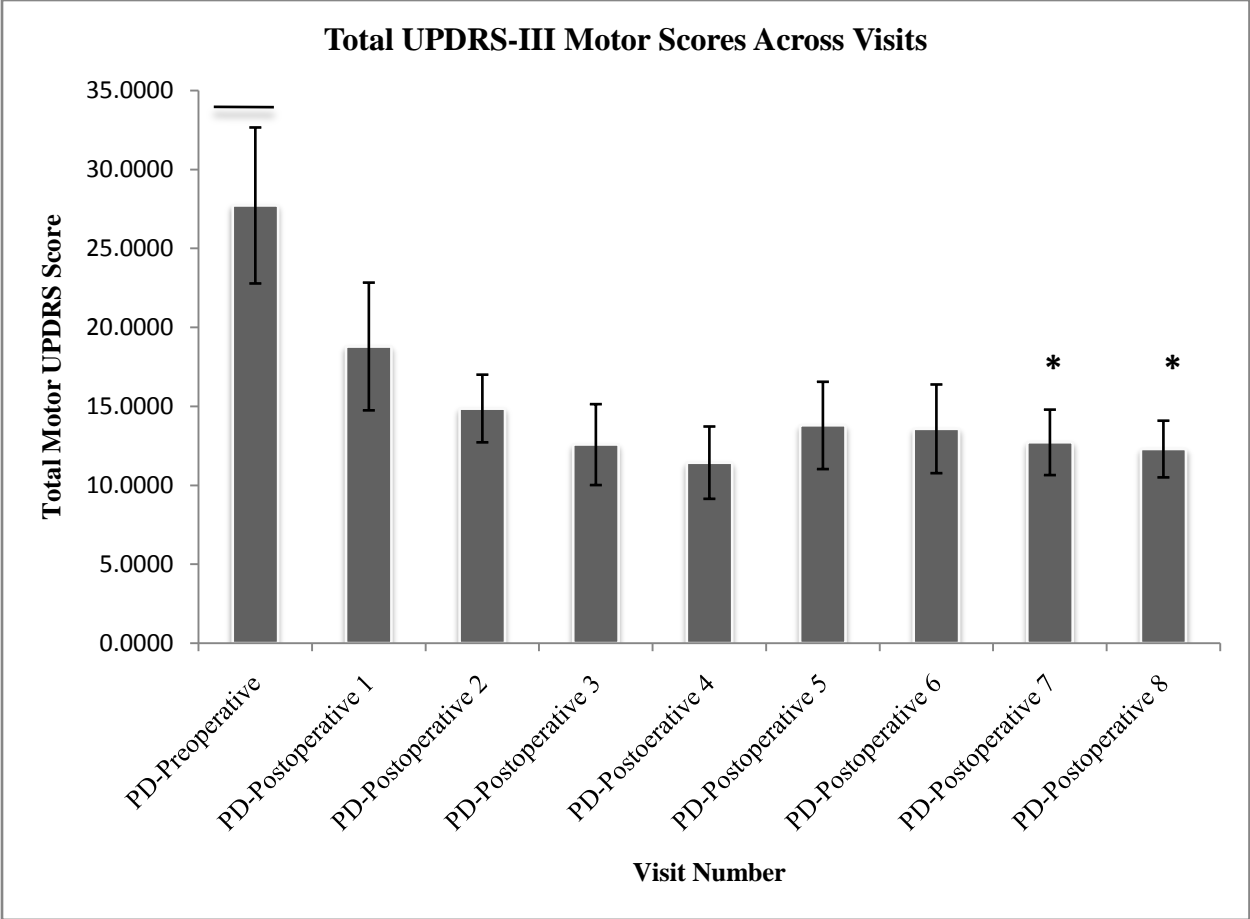
Figure 20: Total Motor UPDRS Score across programming visits

Average UPDRS scores of all 7 PD patients across laboratory visits in comparison to their UPDRS scores before DBS surgery. At 5 months and 6 months following surgery there is a statistically significant reduction in UPDRS score.

Total UPDRS Scores

	V0	V1	V2	V3	V4	V5	V6	V7	V8
DBS-01	13.5	9	12	10	14	18	3	7	11
DBS-02	45	27	12	10	10	15	19	17	12.5
DBS-03	30	15	18	15	8	9	9.5	15.5	12.5
DBS-04	20.5	11	9	11	19.5	18	17	17	17.5
DBS-05	13	18	26	26	8	7.5	17.5	8.5	9.5
DBS-06	43.5	39	15	4	18	25	23	18.5	18.5
DBS-07	28.5	12.5	12	12	2.5	4	6	5.5	4.54

Table 5:Individual PD patient UPDRS scores across laboratory visits

Chart outlines the individual UPDRS scores of all 7 PD patients before surgery and at 8 postoperative laboratory visits following clinical DBS programming.

2.8.6 Quality of Life Over time

All patients completed a self-report questionnaire called the PDQ-8 at the end of every laboratory visit. They were asked to give us answers based on how they have been feeling on average since their last visit to the clinic and laboratory. The PDQ-8 provides a generalized score of overall quality of life at any given time point for individuals who complete it. The PDQ-8 provides a score indicating the overall health related quality of life profile of the individual in question. Total PDQ-8 scores for each patient are provided in the table below. A Friedman ANOVA was conducted on the patients' PDQ-8 scores over time and yielded a Chi-square value of 16.7 and a p-value of 0.034 indicating a significant relationship within the dataset. Post-hoc analysis was done using multiple Friedman tests. There was a significant difference between the average PD-Q scores of the PD group at the preoperative visit when compared to 1 month following surgery (Chi square =7; p =0.008) and 2 months following surgery (Chi square=3.57; p =0.05). The average PDQ-8 scores at 1 month and 2 months following surgery were significantly lower than the preoperative baseline score, indicating an improvement in patient health related quality of life during this period of time. However from 3 months onward PDQ-8 scores increase markedly bringing health related quality of life back to baseline levels.
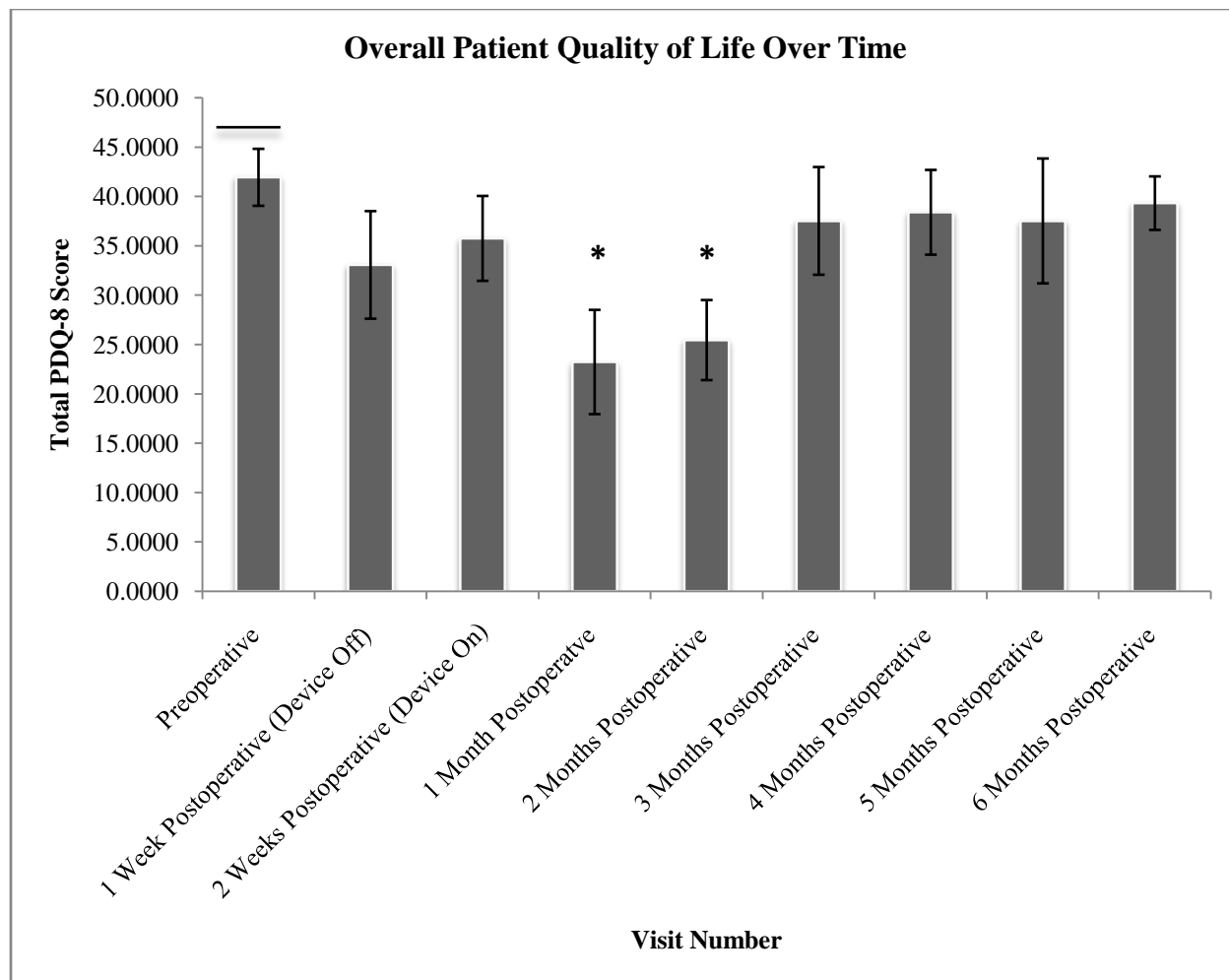
Figure 21: Average PDQ-8 Scores across laboratory visits

This figure provides the PDQ-8 scores across laboratory visits of the PD group. There was a significant reduction in the PDQ-8 score at 1 month following surgery (Chi square =7; p =0.008) and 2 months following surgery (Chi square=3.57; p =0.05) when compared to preoperative score, indicating an improvement in patient health related quality of life during this period of time. However, from 3 months onward PDQ-8 scores increase markedly bringing health related quality of life back to baseline levels.

Total PDQ-8Scores

	V0	V1	V2	V3	V4	V5	V6	V7	V8
DBS-01	43.6	31.3	28.1	6.25	15.6	21.9	31.3	9.38	40.6
DBS-02	37.4	28.1	34.4	25	40.6	40.6	53.1	53.1	43.8
DBS-03	43.8	43.8	53.1	25	18.8	56.3	37.5	56.3	43.8
DBS-04	50	18.8	34.4	43.8	37.5	25	28.1	31.3	31.3
DBS-05	28.1	12.5	18.8	9.4	12.5	21.9	25	34.4	34.4
DBS-06	50	50	34.5	15.6	25	46.9	53.1	28.1	31.3
DBS-07	40.6	46.9	46.9	37.5	28.1	50	40.6	50	50

Table 6: Total PDQ-8 scores of individual patients across visits

This table outlines the raw PDQ-8 scores of individual patients enrolled in the study at multiple time points.

2.8.7 Depression over time

Due to the fact that the neuropsychiatric disorder with the highest prevalence in the PD population is depression it was important that we track our PD group's mood across multiple programming visits. The GDS which is a self-report questionnaire which identifies depression severity was completed by all patients at the end of each laboratory visit. They were asked to give us answers based on how they have been feeling on average since their last visit to the clinic and laboratory. Total GDS scores for each patient are provided in the table below. A Friedman ANOVA was conducted on the patients GDS scores over time and yielded a Chi-square value of 12.1 and a p-value of 0.148 indicating that there was not a significant relationship within the dataset. It appears that depression was neither alleviated nor exacerbated in any way over the course of the study.
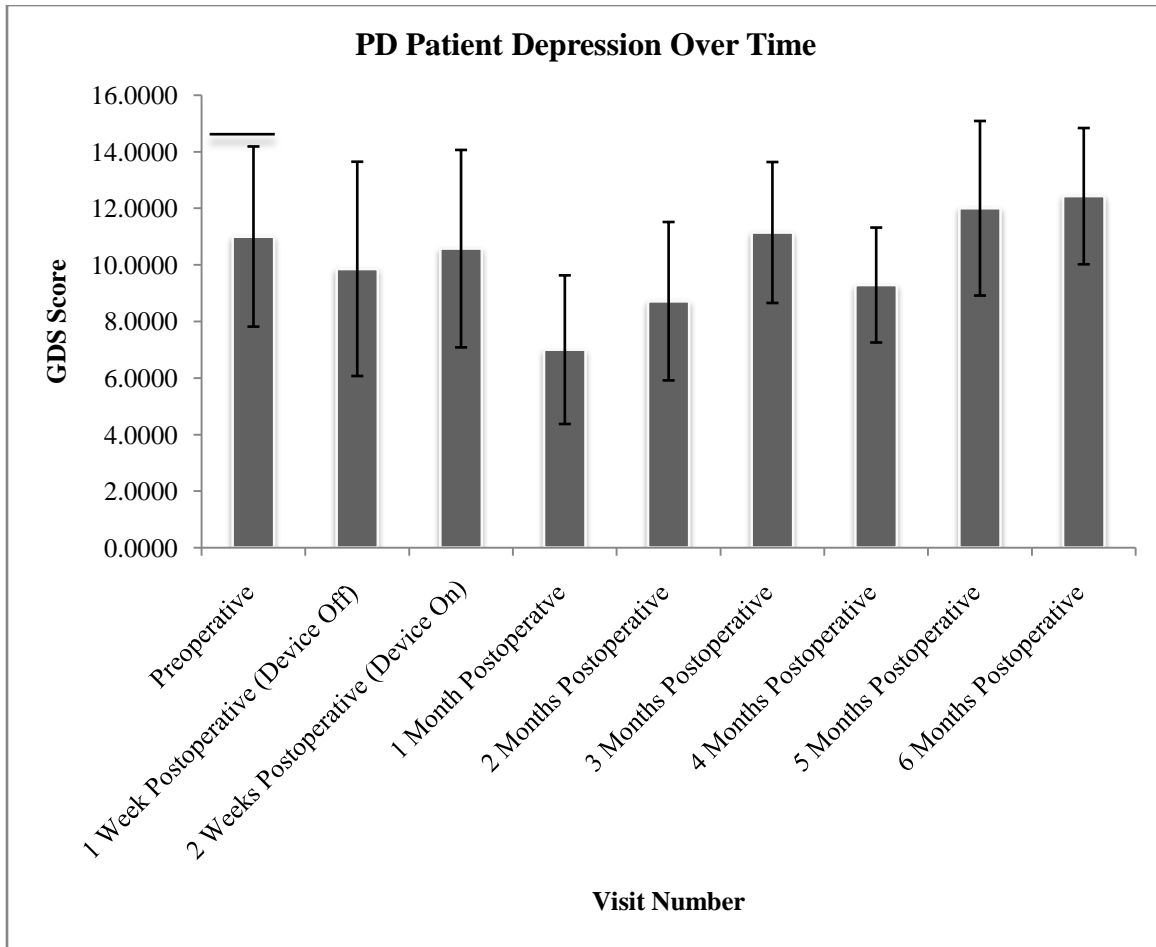
Figure 22: GDS scores of PD patients over time

The graph displays the GDS scores of patients before surgery and following DBS surgery and subsequent programming. There was no significant change in depression across laboratory visits in the PD group.

Total GDS Scores

	V0	V1	V2	V3	V4	V5	V6	V7	V8
DBS-01	2	1	3	1	1	2	5	0	2
DBS-02	4	5	4	5	8	12	8	8	12
DBS-03	21	18	16	6	7	16	6	17	12
DBS-04	10	7	12	9	9	10	9	9	12
DBS-05	6	0	2	0	3	4	9	21	18
DBS-06	10	10	9	7	9	13	7	7	9
DBS-07	24	28	28	21	24	21	21	22	22

Table 7: Total GDS scores of individual patients across visits

This chart outlines the individual GDS scores of patients across laboratory visits. Some patients had moderate depression before surgery while others had not experienced any symptoms of depression. Depression was not significantly impacted throughout the duration of the study.

Chapter 3

3 Discussion and Conclusions

The Animazoo IGS-180 system was able to successfully quantify the severity of 2 cardinal motor symptoms in our idiopathic PD group. Both rest and postural tremor were effortlessly tracked and recorded accurately using the IMU-based system. The accuracy of the system was validated by correlation with the motor UPDRS. The UPDRS has been extensively validated as an accurate measure of PD symptom improvement over time (Groiss et al., 2009) The IMU system was found to be comfortable and non-invasive by all patients enrolled in the study and easy to use by all of the researchers. This was determined by asking all participants involved if they found the suit and device comfortable and easy to move in and all laboratory team members if they found the software easy to use. 100 percent of the participants found the suit to not impede them in any, found it comfortable, easy to wear (n=7) and 100 percent of the laboratory team members found the sensors and software easy to use (n=5).

Previous studies have shown that STN-DBS improves tremor in PD (Lageman, Cash and Mickens, 2014;Groiss et al., 2009; Okun et al., 2009; Lozano et al., 2007). Several of our findings are consistent with the literature. Patients who underwent STN-DBS in our study experienced marked symptom improvements by five and six months of programming and this was verified to be statistically significant using two measurements 1) the UPDRS score and 2) the calculated TBRTI scores, which were a measure of tremor severity.

It is evident based on the data presented in this thesis that six months of clinical programming resulted in a marked reduction in total body rest and upper limb postural tremor.

However, in the case of upper limb postural tremor it is interesting to note that we see a similar degree of benefit immediately post-operatively (with the DBS device still off) compared to six months post-operatively. This might suggest that the MLE is driving the response to DBS. It is difficult to determine the impact DBS has on symptoms alone (without the influence of confounding factors like the MLE) without a control condition where the DBS is left off for 6 months and patient symptoms are similarly tracked and monitored. A limitation of the current study protocol is the absence of a control like this.

Before surgery, PD patients had significantly more severe tremor when compared to the healthy controls. This result was expected as rest tremor is a common motor symptom seen in PD but is uncommon in the healthy population (Groiss et al., 2009; Okun, 2009). As a result of clinical programming, rest tremor was largely reduced such that PD patients were no different than controls at 6 months following surgery. Rest tremor was more pronounced than postural tremor in the PD group which is representative of the PD population as a whole and has been noted in previous literature (Okun, 2009; Jankovic, 2008). The average clinical setting patients were set to by their movement disorder neurologist at six months following programming was 3 volts, 90 microseconds and 130 Hertz. This setting resulted in statistically significant alleviation of tremor by six months. This setting also resulted in a statistically significant reduction in upper limb postural tremor by six months. It is important to note that rest tremor was reduced in all body segments including the head, upper limbs and lower limbs by 6 months of programming.

The DBS devices that were implanted into all PD patients' brains were not constant current systems. Impedance was therefore not taken into consideration or accounted for when analyzing this dataset. Using this DBS device, clinicians are able to adjust DBS settings using a voltage mode, where the delivered voltage remains constant. A new constant-current mode has

since become available to clinicians and this would allow for the programmer to set the current to a certain range and allow the stimulator to automatically adjust the voltage as impedance changes. Therefore, in our study protocol even if all patients were set to the same predefined setting the current may not be the same in all patients since the impedance may vary. This has a profound effect on the generalizability of the findings. In future the study protocol should be refined to take impendence into consideration and identify if there is an ideal amount of current that drives the programming process.

Looking at each patient individually, we identified that they achieved greatest tremor reduction on one of the predefined settings, and this was different for each patient with the exception of 2 patients that achieved greatest therapeutic benefit on Setting 10. One concern in a study of this kind is variability between patients and the generalizability of the findings. There is a great deal of variability from patient to patient in terms of anatomical composition, symptom severity, age of PD symptom onset and medication regimen, all of which could have an impact on DBS programming and influence outcomes. No one setting was identified to guide the optimization process.

An average best setting was identified for tremor reduction upon analysis (Setting 10) which resulted in tremor reduction in six out of seven patients however it exacerbated tremor in one patient when compared to the preoperative score. Narrowing down a series of average best settings for tremor reduction provides clinicians with a better starting point; a pool of best settings which they may test on their patients that could potentially provide significant clinical benefit. Yet, it is evident based on these results that although identifying a pool of best settings for each PD symptom may narrow the clinician's search, individualized programming may still be required in order to reach optimal therapeutic benefit.

Based on the results of both the UPDRS and IGS-180 motion capture system it is evident that DBS procedure coupled with clinical programming over consecutive iterations is an effective way to reduce tremor in Parkinson patients, as tremor was significantly reduced in patients at 6 months following surgery. Based on the results of the GDS it can be concluded that mood was not affected in any way during the course of the study.

Similarly, based on the PDQ-8 score results it can be concluded that patient perceived quality of life was improved at one and two months following surgery. These results could be attributed to the device finally being turned on. However, in our PD group PDQ-8 scores declined thereafter to match baseline scores indicating a drop in patient perceived health related quality of life. This indicates that improvements in tremor may not have improved patient quality of life. This finding is inconsistent with the current literature.

PD is associated with reduced health related quality of life, reduced emotional well-being, social functioning and is often co-morbid with mental illness (Louis and Machado, 2015; Lageman, Cash and Mickens, 2014; Schrag, 2006). Several longitudinal studies have aimed to investigate the influence that DBS has on patient quality of life and caretaker burden and have found that DBS has a positive effect on health related quality of life (Lageman, Cash and Mickens, 2014; Lyons and Pahwa, 2005). In one such study by Oyama et al. (2014) examined the effect of DBS in 275 PD patients. In this group, DBS was found to improve patient quality of life but did not impact caregiver burden. However, studies have previously found that patients with severe axial symptoms, often who are non-dominant for tremor have significantly lower PDQ scores than patients with tremor dominant symptoms and mild to moderate axial symptoms (Appleman, Stavitsky and Cronin-Golomb, 2010). Rahman et al. (2008) previously reported that health related quality of life improves if axial symptoms improve and that improvement in axial

symptoms was more predictive of better quality of life following DBS than improvement in tremor severity. It may be the case that even though our PD group experienced reduced tremor following DBS programming other axial symptoms such as postural stability, gait and freezing episodes were not alleviated by the DBS treatment. These symptoms have a profound impact on measures of functional mobility and personal independence (Rahman et al., 2008). Thesetwo features have been strongly associated with measures of patient perceived quality of life (Appleman, Stavitsky and Cronin-Golomb, 2010; Lezcano et al., 2004; Martinez-Martin et al., 2002). Examining the impact of DBS on axial symptoms further and subsequently correlating their relationship to quality of life is one of the possible next steps for this study and others like it.

Another feature of clinical research that is well noted and often unavoidable is the inherent variability within the given study population. There is a great deal of variability between patients in term of length of diagnosis, dominant symptoms, symptom severity, medication regiment and dosing and all of which may have an impact on individual health outcomes. Even with a specific inclusion criteria applied patient variability exists whether it be in regards to disease characteristics or outcomes. Increasing the sample size may allow for the findings to be more representative of the population in question. According to Central Limit Theorem, increasing the sample size causes the mean to approach the sampling distribution of the mean. Patient recruitment was also challenging since STN-DBS surgeries are not terribly frequent and some patients may not be willing to participate in the study even of given the opportunity. The small number of study participants included in this study limits our ability to apply the findings to the STN-DBS population as a whole. The aim of statistical testing is to uncover a significant difference when it actually exists within a given population or group and this can only be

achieved with a larger and more representative sample size coupled with respective control measures. Increasing the number of study participants would increase the power of the results. Therefore the study protocol must be refined and new data must continue to be collected. Another limitation that should be noted is that the length of time patients were kept on each predefined setting. All patients were left on the a predefined setting for 1 hour before being tested however this length of time may not have been ideal to elicit a representative clinical response. Re-testing the same patients on the 18 predetermined settings for more extended periods of time and at different times of the day could ameliorate this current study limitation and provide us with further comparison data.

PD patients fluctuate throughout the day (in terms of how well they feel and their symptoms) a phenomenon known as on-off periods (Groisse et al., 2009). Symptom fluctuations could have an impact on the outcomes of the results. Therefore, it may be ideal to test the patients on a specific setting for a longer duration of time and on the sample setting at multiple time points.

3.1 Future Directions

Given the multifaceted nature of the IGS-180 system we have been able to collect data from a series of other tasks that examine other cardinal symptoms of PD, including gait, posture, bradykinesia and dyskinesia. The next step would be to continue analysing the current data set to identify the effect of clinical programming on these symptoms of PD and examine whether or not any of the predefined settings resulted in a significant or superior clinical benefit. Further patient recruitment is also necessary and will allow for the generalizability of future findings. Once a larger cohort has been recruited, tested and analyzed the protocol may be refined to

further test a subset of the 18 settings which have been identified to elicit the greatest clinical benefit for each of the clinical settings. The next study would test these settings on multiple occasions to eliminate the effect of on-off periods, fatigue, or ordering effects. In future this protocol could be used or expanded by other research facilities in order to generate a large database of kinematic and scale based information which could potentially help clinicians identify a kinematic profile of each of their patients and further cater DBS programming based on this.

The hope is that one day a more dynamic system will be available to clinicians who engage in the clinical programming process which will improve the health outcomes of patients. This has the potential to improve the quality of life of patients and improve their symptoms as well.

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Appendix A

Unified Parkinson's Disease Data Form

PD *workbook*
THE WE MOVE CLINICIANS' GUIDE TO PARKINSON'S DISEASE

Name_____   Unit Number_____

	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF
Date																
DOPA mg/day hrs DOPA lasts																
1. Mentation																
2. Thought Disorder																
3. Depression																
4. Motivation/Initiative																
Subtotal 1—4 (maximum = 16)																
5. Speech																
6. Salivation																
7. Swallowing																
8. Handwriting																
9. Cutting food																
10. Dressing																
11. Hygiene																
12. Turning in bed																
13. Falling																
14. Freezing																
15. Walking																
16. Tremor																
17. Sensory symptoms																
Subtotal 5—17 (maximum = 52)																
18 Speech																
19. Facial expression																
20. Tremor at rest: face,lips,chin																
Hands: right																
left																
Feet: right																
left																
21. Action tremor: right																
left																
22. Rigidity: neck																
Upper extremity: right																
left																
Lower extremity: right																
left																

Unified Parkinson's Disease Data Form

PD *workbook*
THE WE MOVE CLINICIANS' GUIDE TO PARKINSON'S DISEASE

Date	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF	ON	OFF
23. Finger taps: right																
left																
24. Hand grips: right																
left																
25. Hand pronate/supinate: right																
left																
26. Leg agility: right																
left																
27. Arise from chair																
28. Posture																
29. Gait																
30. Postural stability																
31. Body bradykinesia																
Sub-total:18–31 (maximum=108)																
Total points: 1–31 (max=176)																
32. Dyskinesia (duration)																
33. Dyskinesia (disability)																
34. Dyskinesia (pain)																
35. Early morning dystonia																
36. "Offs" (predictable)																
37. "Offs" (unpredictable)																
38. "Offs" (sudden)																
39. "Offs" (duration)																
40. Anorexia, nausea, vomiting																
41. Sleep disturbance																
42. Symptomatic orthostasis																
Blood Pressure: seated																
supine																
standing																
Weight																
Pulse: seated																
standing																
Name of Examiner																

	BEST	WORST	BEST	WORST	BEST	WORST	BEST	WORST	BEST	WORST	BEST	WORST	BEST	WORST	BEST	WORST
Hoehn & Yahr Stage																
% ADL Score (PD)																
% ADL (with dyskinesia)																

Fahn S, Elton R, Members of the UPDRS Development Committee. In: Fahn S, Marsden CD, Calne DB, Goldstein M, eds. Recent Developments in Parkinson's Disease, Vol 2. Florham Park, NJ. Macmillan Health Care Information 1987, pp 153–163, 293–304

DBS Project
Contact Monitoring Session

Patient ID: DBS-   - V
Date:

Left STN

#	Contacts (+/-) Case / C0 / C1/ C2 / C3	Voltage	Check for side effects such as: Double Vision – Facial Dystonia – Hand Dystonia – Numbness – Tingling – Headache

DBS Project
Contact Monitoring Session

Patient ID: DBS-   - V
Date:

Right STN

#	Contacts (+/-) Case / C8 / C9 / C10 / C11	Voltage	Check for side effects such as: Double Vision – Facial Dystonia – Hand Dystonia – Numbness – Tingling – Headache

Kinematic Task Symptom Monitoring

Patient ID: DBS - …….. - V …..
Date: ………………………………..
Researcher's Initials: ……………
Notes:
For every session, ask if Patient feels medication-wise is: ON orOFF
Symptoms: T: Tremor - D: Dyskinesia - B: Bradykinesia - F: Freezing - BL: Balance

Symptoms / Tasks	S0 Patient: ON / OFF Start time End time:					S1 Patient: ON / OFF Start: End:					S2 Patient: ON / OFF Start: End:					S3 Patient: ON / OFF Start: End:					S4 Patient: ON / OFF Start: End:				
	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL
Speech	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL
Relaxed1	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL
Posture1	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL
Pro/Sup1	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL
Relaxed2	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL
Posture2	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL
Pro/Sup2	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL
N-TUG1	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL
N-TUG2	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL
F-TUG1	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL
F-TUG2	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL
S-TUG1	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL
S-TUG2	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL
Turn	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL
Balance	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL	T	D	B	F	BL
Remarks: Mood Cognition Fatigue																									

PATIENT ID: *DBS* _____ *V*_____   DATE:_____

MOOD ASSESSMENT SCALE

1. Are you basically satisfied with your life? _____

2. Have you dropped many of your activities and interests? _____

3. Do you feel that your life is empty? _____

4. Do you often get bored? _____

5. Are you hopeful about the future? _____

6. Are you bothered by thoughts you can't get out of your head? _____

7. Are you in good spirits most of the time? _____

8. Are you afraid that something bad is going to happen to you? _____

9. Do you feel happy most of the time? _____

10. Do you often feel helpless? _____

11. Do you often get restless and fidgety? _____

12. Do you prefer to stay at home, rather than going out and doing new things? _____

13. Do you frequently worry about the future? _____

14. Do you feel you have more problems with memory than most? _____

15. Do you think it is wonderful to be alive now? _____

16. Do you often feel downhearted and blue? _____

17. Do you feel pretty worthless the way you are now? _____

18. Do you worry a lot about the past? _____

19. Do you find life very exciting? _____

20. Is it hard for you to get started on new projects? _____

21. Do you feel full of energy? _____

22. Do you feel that your situation is hopeless? _____

23. Do you think that most people are better off than you are? _____

24. Do you frequently get upset over little things? _____

25. Do you frequently feel like crying? _____

26. Do you have trouble concentrating? _____

27. Do you enjoy getting up in the morning? _____

28. Do you prefer to avoid social gatherings? _____

29. Is it easy for you to make decisions? _____

30. Is your mind as clear as it used to be? _____

PDQ-8

PATIENT ID: *DBS* _____ *V*_____   DATE:_____

7. Had difficulty getting around in public?

Never   Occasionally   Sometimes   Often   Always

12. Had difficulty dressing yourself?

Never   Occasionally   Sometimes   Often   Always

17. Felt depressed?

Never   Occasionally   Sometimes   Often   Always

25. Felt embarrassed in public due to having Parkinson's disease?

Never   Occasionally   Sometimes   Often   Always

27. Had problems with your close personal relationships?

Never   Occasionally   Sometimes   Often   Always

31. Had problems with your concentration, e.g. when reading or watching TV?

Never   Occasionally   Sometimes   Often   Always

35. Felt unable to communicate with people properly?

Never   Occasionally   Sometimes   Often   Always

37. Had painful muscle cramps or spasms?

Never   Occasionally   Sometimes   Often   Always

Curriculum Vitae

Name: Kristina Ognjanovic

Post-secondary   McMaster University

Education and   Hamilton, Ontario, Canada

Degrees: 2009-2013 HBSc.

The University of Western Ontario

London, Ontario, Canada

2013-2015 M.Sc.

Related Work   Teaching Assistant and Proctor

Experience   The University of Western Ontario

2013-2015

Publications: **IEEE Conference,** December 2014

M. Delrobaei, **K. Ognjanovic**, G. Gilmore, F. Rahimi, S. Tran, S. Xian, K. McIsaac, M. Jog, "Quantifying the Short-term Effects of Deep Brain Stimulation Surgery on Bradykinesia in Parkinson's Disease Patients."

SONA 34th Annual Meeting, May 5 - 34 2014 - London

G. Gilmore**, K. Ognjanovic**, M. Delrobaei, F. Rahimi, S. Tran, S. Xian, K. McIsaac, M. Jog, "Motor assessment of Parkinson Disease patients following deep brain stimulation surgery using kinematic analysis technology."

CAN 8th Annual Meeting, May 25 - 28 *2014* - Montréal

G. Gilmore**, K. Ognjanovic**, M. Delrobaei, F. Rahimi, S. Tran, S. Xian, K. McIsaac, M. Jog, "Optimization of deep brain stimulation parameters for PD patients using objective measures."

2014 ISPGR World Conference,June 29 - July 3 2014 - Vancouver

K. Ognjanovic, M. Delrobaei, G. Gilmore, F. Rahimi, S. Tran, S. Xian, K. McIsaac, M. Jog, "Assessment of postural stability and balance in Parkinson disease patients after deep brain stimulation surgery using full body motion capture suit."

K. Ognjanovic, M. Delrobaei, G. Gilmore, F. Rahimi, S. Tran, S. Xian, K. McIsaac, M. Jog, "Motor assessment of Parkinson Disease patients following deep brain stimulation surgery using gait analysis technology."

Society for Neuroscience Conference, November 2014- Washington

M. Delrobaei, **K. Ognjanovic**, G. Gilmore, F. Rahimi, S. Tran, S. Xian, K. McIsaac, M. Jog, "Quantifying the short-term effects of Subthalamic deep brain stimulation surgery on bradykinesia in Parkinson's disease patients,"SFN Conference, Washington DC, Nov. 2014.