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# Deep brain stimulation and its effects on Parkinson disease spatiotemporal gait parameters.

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Graduate Program in Neuroscience

A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science

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DEEP BRAIN STIMULATION AND ITS EFFECT ON PARKINSON DISEASE  
SPATIOTEMPORAL GAIT PARAMETERS

(Thesis format: Integrated Article)

by

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Graduate Program in Neuroscience

A thesis submitted in partial fulfillment  
of the requirements for the degree of  
Masters of Science

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## **Abstract**

Subthalamic (STN) deep brain stimulation (DBS) alleviates common appendicular PD symptoms, such as: tremor, rigidity and bradykinesia. However, the effect STN-DBS has on modulating axial gait features has not been properly quantified objectively. The purpose of the present thesis was to investigate the role STN-DBS plays in modulating specific gait features such as pace, asymmetry, variability, rhythm and postural control. It is hypothesized that axial gait function is regulated predominantly by non-dopaminergic control systems. In the acute immediate post-operative phase a surgical effect, named the microlesion effect (MLE), is thought to produce a transient improvement of appendicular and axial symptoms. It was hypothesized the MLE is a surgical effect, having a non-specific influence on both appendicular and axial symptoms. Following surgical recovery and 6 months of clinically optimized STN-DBS, it was expected that the true STN-DBS effects would be presented. It was hypothesized that STN-DBS plays an important role in the dopaminergic basal ganglia circuit and a lesser role in the non-dopaminergic system. 10 individuals with PD who were approved for STN-DBS along with 11 healthy age-matched controls were used in the study. The participants were asked to walk across a 7 metre long gait analysis carpet at a self-selected paced walk (SELF) and a fast-as-possible walk (FAST). However, in the current study we found no improvement on Unified Parkinson's Disease Rating scale (UPDRS) appendicular scores and axial gait features at baseline, 1 week post-operation and 2 weeks post-operation. At 6 months, it was found that UPDRS scores improved for appendicular items but remained unchanged in the axial items. Furthermore, axial gait features remained unchanged in the SELF and FAST walks. Overall, axial gait function failed to improve from the MLE and STN-DBS. While the sample size was small, this finding may suggest an influence of regions outside the STN on axial function. Further analysis with more subjects should be conducted to verify the current findings.

## Keywords

Parkinson disease, deep brain stimulation, microlesion effect, axial symptoms, appendicular symptoms, gait parameters

## List of Abbreviations

ABC	Activities Balance Confidence Scale
DBS	Deep Brain Stimulation
DST	Double Support Time
FAST	Fast as possible gait speed
FOG-Q	Freezing of Gait Questionnaire
GDS	Geriatric Depression Scale
GPI	Globus Pallidus Internus
GPe	Globus Pallidus Externus
LID	Levodopa Induced Dyskinesia
MLE	Microlesion Effect
MoCA	Montreal Cognitive Assessment
PD	Parkinson disease
SELF	Self-selected “normal” gait speed
SNC	Substantia Nigra pars compacta
SNr	Substantia Nigra pars reticulata
SST	Single Support Time
STN	Subthalamic Nucleus
TEED	Total Electrical Energy Delivered
UPDRS	Unified Parkinson’s Disease Rating Scale

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## Preface

Parkinson disease (PD) is a debilitating movement disorder that results in increased immobility and decreased quality of life. Individuals suffering from PD are given pharmaceuticals that have a therapeutic window of around 10 years (Aquino & Fox, 2015). New treatment approaches need to be investigated to treat these PD individuals who no longer respond optimally to pharmaceuticals. Deep brain stimulation (DBS) is an accepted therapy being implemented for the treatment of PD; however the exact effect it has on gait is uncertain. This thesis examines gait impairments, which afflict many Parkinson disease (PD) patients. An acute and chronic change in gait induced by DBS was monitored to elucidate the effectiveness of this approach as a treatment for PD gait dysfunction.

**Chapter 1** outlines current background literature associated with PD and gait. This chapter summarizes the established knowledge on PD gait and defines the basic research tools associated with the following chapters, which present the current research.

**Chapters 2 and 3** present the research done as part of the completion of my Master's thesis related to the acute and chronic change in gait parameters following subthalamic deep brain stimulation (STN-DBS) for PD. Chapter 2 explores the acute microlesion effect, which has been thought to contribute the efficacy of DBS. Chapter 3 explores chronic DBS efficacy and its effect on PD gait.

**Chapter 4** summarizes the research presented in **Chapters 2 and 3** and provides a synthesis of significance and implications of the research findings.

# 1. Introduction

## 1.1 Parkinson disease: symptoms and etiology

Parkinson disease (PD) is one of the most common neurodegenerative disorders, second only to Alzheimer's disease (de Lau & Breteler., 2006). The prevalence of PD is about 1% in the population over 60 years of age, with approximately 10% of PD occurring in people 50 years or less (de Lau & Breteler, 2006). The primary pathophysiological cause of PD causing motor symptomatology, is the neurodegeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) within the Basal Ganglia (BG) (Burke & O'Malley., 2013). One of the key features of the PD motor symptoms is that they are manifest when there is a 60-80% loss of dopaminergic neurons within the SNc (Burke & O'Malley, 2013). The second hallmark pathophysiological sign of PD, although not in every case, is the presence of Lewy bodies. Lewy bodies are aggregates of the protein alpha-synuclein, which accumulate within surviving dopaminergic neurons. The exact mechanistic cascade underlying PD pathophysiology is currently unknown.

The loss of dopamine producing neurons and the formation of Lewy bodies contribute significantly to the onset and progression of PD. However, in the past decade the explanation of PD pathophysiology has shifted from altered neuronal discharge rates to altered synchronization of activity across populations of neurons. Neuronal oscillations stem from the rhythmic and repetitive nature of neural activity within the central nervous system. In a healthy brain, oscillatory pattern changes depending on the activity performed and cognitive demand. Lower frequency oscillations, such as theta (4-8hz) and alpha (8-13Hz), are associated with sleeping (Marzano et al., 2011). When a healthy, aroused and mentally active brain is engaged in activities, there is an increase in  $\beta$ -wave forms (13-30 Hz) (Little & Brown., 2014). Several studies have provided evidence that abnormal  $\beta$ -wave oscillations within the BG contribute, in part, to the pathophysiology of PD (Florin et al., 2013; Weinberger et al., 2006). How the aberrant activity of the oscillations leads to the motor deficits in PD remains elusive.

A number of common motor features have been determined and used in the diagnosis of PD. Some common motor symptoms associated with the onset of PD are akinesia, bradykinesia (slow movement), tremor, rigidity, gait impairments and loss of automatic movements (Pahwa & Lyons., 2010). PD is complicated further by frequently observed comorbid non-motor symptoms, such as depression, cognitive deficits and sleep disturbances (Gunn, Naismith, & Lewis., 2010; Lindgren & Dunnett., 2012). The non-motor symptoms arise from neurodegeneration within other areas including the cortex and locus coeruleus (Bonnet, Jutras, Czernecki, Corvol, & Vidailhet., 2012). The spectrum of motor and non-motor symptoms varies from person to person, and tends to become increasingly disabling as the disease progresses.

### **1.1.1 Axial and appendicular symptoms in PD**

Motor features of PD can be divided into two different categories: appendicular and axial. Appendicular impairments include all symptoms presenting in the limbs of the body. The standard, accepted BG structures such as the striatum, pallidum, thalamus and subthalamic nucleus (STN) along with the nigro-striatal pathway are likely responsible for the control of appendicular movements (Steiger, Thompson, & Marsden., 1996). These symptoms tend to respond well to dopaminergic medication intervention (see section 1.1.2). Furthermore, several research groups have reported improvements in appendicular symptoms following neurostimulation of the STN (Anderson, Burchiel, Hogarth, Favre, & Hammerstad., 2006; Krack et al., 2003).

Axial motor features tend to dominate the PD symptomatology in more advanced disease, contributing to the loss of mobility in PD individuals (Hely, Morris, Reid, & Trafficante., 2005). Axial motor features are a complex collection of body biomechanics, which involve muscles that support the head, spine, ribs and sternum. Thus, axial muscles play an important role in postural stability, gait, and speech impairments. In later stages of disease, axial motor features contribute to the majority of PD disability, including reduced mobility, loss of independence and increasing falls leading to other injuries. The reticulospinal/ vestibulospinal tracts control the axial movements (Steiger et al., 1996). Pharmacotherapies play an important role in improving gait in walking tasks in the short-

term (Bryant, Rintala, Hou, Lai, & Protas., 2011). However, in the long-term gait impairments still proceed and tend to worsen as the disease progresses (Galna, Lord, Burn, & Rochester., 2015). This suggests that gait may be influenced by other brain regions as well, which do not involve the common dopaminergic pathology (Galna et al., 2015; Lord, Baker, Nieuwboer, Burn, & Rochester., 2011).

Axial motor symptoms tend to be dopamine non-responsive and 10-15 years from diagnosis, axial symptoms are the dominant feature in most PD patients (Hely et al., 2005). The onset of appendicular symptoms early in the disease hints at a BG influence, while the later onset of axial symptoms hints at further degeneration in other brain regions. Various regions play a role in gait function and have been shown to degenerate at later time points in PD. These brain areas include the pedunculopontine nucleus (PPN), frontal regions and connections from frontal regions to the BG and PPN. It is hypothesized, in this thesis, that the axial control systems are predominantly non-dopaminergic. Therefore it is expected that STN-DBS intervention will do little to improve axial gait features, much like the common levodopa therapies.

### **1.1.2 Pharmacotherapy for PD**

Various treatment options exist that may be used to alleviate some of the symptoms associated with PD. The two general classes of treatment include pharmacological and surgical. The former treatment approach is that of oral pharmacotherapies while the latter is concerned with surgical alteration of the brain regions associated with PD (Tarazi, Sahli, Wolny, & Mousa., 2014). Oral pharmacotherapies always precede surgical interventions by many years. The treatment options are titrated over the years and the initial oral pharmacotherapy chosen is highly dependent on the demographics of the patient: age, disease stage, cognitive abilities and dominant symptoms. Medical intervention is always attempted first, and remains the mainstay of treatment for 90 percent of patients (Tarazi et al., 2014). Surgical therapies are tried in well selected patients approximately 8-10% of times (Tarazi et al., 2014).

Pharmacotherapies are commonly associated with monoamine neurotransmitter imbalances, most notably dopamine. Drug therapies seek to correct the imbalances in

dopaminergic producing neurons within the BG in PD patients. There are several drug classes of dopamine modifying medications that seek to alleviate the motor impairments in PD, such as: carbidopa/levodopa (Sinemet) and dopamine agonists (pramipexole and ropinirole) (Kalinderi, Fidani, Katsarou, & Bostantjopoulou., 2011; Tarazi et al., 2014). While pharmacotherapies are effective in the short-term, side effects manifest later including levodopa induced dyskinesias (LIDs) (Aquino & Fox., 2015). Furthermore, patients tend to experience increasing motor fluctuations leading to more frequent “wearing off” periods at optimized dosages (Poewe & Mahlkecht., 2009).

Pharmacotherapies are generally prescribed to treat common appendicular motor symptoms, including rigidity, tremor and bradykinesia. Indeed these appendicular symptoms of the upper and lower limbs do respond to standard dopaminergic medications well for many years. However, axial symptoms, such as those affecting speech and oral motor control and gait, balance and stability, are not responsive to the dopaminergic medications over an extended period (Tarazi et al., 2014). Wright *et al.* (2007) studied the difference in levodopa response to axial and appendicular rigidity in 12 PD participants. This group found that levodopa was ineffective at improving rigidity in the axial systems (trunk, torso) but improved in the appendicular system (knees, arms, wrists) (Wright, Gurfinkel, Nutt, Horak, & Cordo., 2007). Axial rigidity is an important feature for proper gait function, without treatment this symptom contributes to the maintained gait impairment.

These differences in appendicular versus axial symptoms and their response to medications may be related to their underlying pathophysiological basis and different control systems. Early on in PD it is thought that the pathophysiology is restricted to the dopaminergic systems in the basal ganglia (Connolly & Lang., 2014). As the disease progresses other non-dopaminergic systems are affected such as the cerebellum, frontal cortex and PPN (Maillet, Pollak, & Debu., 2012). Thus, appendicular symptoms present early in the disease followed by non-dopaminergic axial symptoms (Connolly & Lang., 2014). A recent study of eight PD participants found that gait dysfunction may be precipitated by decrease activation in motor and frontal associative areas, basal ganglia, thalamus and cerebellum (Maillet et al., 2012). Axial symptoms directly affect mobility

and are of great importance to the patients overall quality of life. Hence, the need to understand the aspects of axial symptoms and the effects of intervention, especially surgical intervention is great. The possibility of replacing the patients' oral medications with a surgical implanted device would provide a much needed improvement in the quality of life. Ferrara *et al.* (2010) studied the healthy related quality of life in 21 PD participants who underwent STN-DBS surgery and found a significant improvement in the energy levels, enjoyment of life, independence from help and controllability of movement following 1 year post-operation (Ferrara et al., 2010). It is postulated that the quality of life is improved due to the neurostimulation in conjunction with the reduction in quantity of medications consumed (Ferrara et al., 2010).

## **1.2 Neural Circuitry involved in PD**

The following section reviews the important aspects of the basal ganglia and other circuits in PD, relating it to the idea of the differences between axial (gait) and appendicular symptoms. This will shed light on why gait effects of interventions are unique and why they need to be carefully studied as a way of understanding non-dopaminergic aspects of motor control.

### **1.2.1 Dopaminergic circuitry: appendicular influence**

The appendicular symptoms in PD have been attributed to the reduction in dopaminergic activity within the BG. The BG is a group of nuclei found at the base of the prosencephalon (forebrain) and is strongly connected to the thalamus and cerebral cortex. The organization of the cortico-basal ganglionic circuits is much more complex than the summary here (Figure 1-1). However, it is important to have a basic understanding of the various structures and the role they play in the pathology of PD. The striatum is the primary afferent structure of the BG, receiving glutamatergic input from the cerebral cortex. The striatum consists of the nucleus accumbens, caudate nucleus and the putamen (Kandel & Schwartz., 2013). The lentiform nucleus consists of the globus pallidus (GP) and the putamen. The GP is further divided into the external (GPe) and internal (GPi) segments. The substantia nigra (SN) is further broken down into the substantia nigra reticulata (SNr) and the SNc, which are both part of the mesencephalon (Kandel &

Schwartz., 2013). The GPi and the SNr are the main efferent nuclei of the BG (Squire., 2013). The STN is a structure, which relays information from the striatum to the output nuclei of the BG.

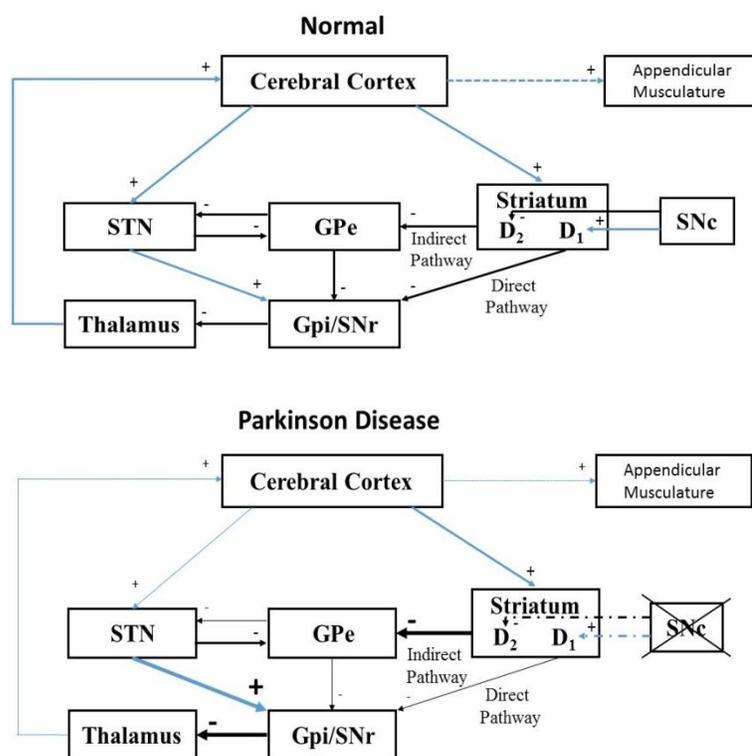
As previously stated appendicular and axial motor features of PD respond differently to treatment interventions, which may stem from the structural organization of the central nervous system. The appendicular motor features tend to be controlled by the influence of dopamine on the striato-pallidal circuit.

### *1.2.2 Dopaminergic effect in the Basal Ganglia*

Striatal projections from the medium spiny neurons are GABAergic and connect to the output nuclei (GPi and SNr) in two distinct ways: the “direct” and “indirect” pathways (Squire., 2013). The direct pathway involves the striatum sending convergent inhibitory projections to the output nuclei. The neurons in the direct pathway contain D1 dopamine receptors and co-express the proteins substance-P and dynorphin (Squire., 2013). The indirect pathway involves striatal projections to the output nuclei indirectly through the GPe and the STN. The neurons in the indirect pathway contain D2 dopamine receptors and co-express the protein enkephalin (Squire., 2013). The dopamine effect, modulated by the SNc releasing dopamine into the striatum, on these two types of receptors is two-fold: exciting D1 receptors while inhibiting the D2 receptors (Penney & Young., 1983). Therefore, the two circuits have differing effects on the output nuclei. The direct pathway tends to inhibit the output nuclei, while the indirect pathway tends to excite the output nuclei. These output nuclei send inhibitory projections to motor areas in the thalamus and brainstem. As previously stated this depiction of the BG is oversimplified. Its detailed structure and organization is far more complex. For instance, there is a hyper direct pathway that projects directly from the cortex to the STN (Brunenberg et al., 2012).

In the PD brain, dopamine depletion mediates the cardinal symptomatology presented in the onset and duration of the disorder (see Figure 1-1). The lack of dopamine input into the BG, a result of the degradation of SNc neurons, leads to the over activity in the indirect pathway and a hypoactivity in the direct pathway (Hirsch et al., 2000). This causes an excessive inhibition of thalamic and brainstem motor nuclei through the indirect

pathway (DeLong., 1990; Hirsch et al., 2000). Dopaminergic treatment is highly effective in the treatment of appendicular symptoms of PD such as rigidity, bradykinesia and tremor in all limbs. In early PD, axial symptoms are predominantly related to the effects of appendicular symptoms on the trunk and lower limbs. Moreover, the appendicular symptoms directly result in axial impairments leading to negative locomotor effects on gait and posture. When the appendicular symptoms respond to levodopa, the axial symptoms will apparently improve for a considerable period. However, primary axial dysfunction, which may be unrelated to dopamine, will continue to advance and become predominant, and unresponsive as discussed previously/below.



**Figure 1-1.** Basal ganglia-thalamo-cortical circuit schematic in a normal and parkinsonian state. The thickness of the arrows describes the strength of the connection. The + indicates excitation while the - indicates inhibition. Loss of SNc neurons leads to increased thalamic inhibition.

### 1.2.3 Non-dopaminergic circuitry: axial influence

The STN is a unique structure in the BG because it contains mostly excitatory glutamatergic neurons, unlike the other BG structures (Kandel & Schwartz., 2013). It is postulated that a hyperactivity of the STN pathway plays a role in the onset of PD motor symptoms. The STN glutamatergic efferent pathways project to important brain areas such as pallidum and the pedunculopontine tegmental nucleus (PPN).

The PPN is located in the brainstem, caudal to the SN. The PPN provides the majority of cholinergic input to the thalamus, with projections to the striatum, cerebellum and brain stem (Yarnall, Rochester, & Burn., 2011). The PPN is divided into two parts: the pars compacta (PPNc) and the pars dissipates (PPNd) (Devos, Defebvre, & Bordet., 2010). The PPNc contains the majority of the cholinergic neurons within the PPN, while the PPNd contains more glutamatergic neurons (Devos et al., 2010). The PPN receives projections from all areas of the BG, with the exception of the SNc (Devos et al., 2010). The PPN has been shown to play an important role in gait and postural control (Pahapill & Lozano., 2000).

Bohnen *et al.* (2009) studied the cholinergic activity of the PPN in 44 PD participants with a history of falls (Bohnen et al., 2009). This group found a 12.3% reduction in acetylcholine levels compared with controls (Bohnen et al., 2009). It was concluded from this study that gait impairments are not caused by the nigrostriatal dopaminergic denervation but by cholinergic hypofunction.

An increase incidence of cognitive decline has been linked to postural instability in PD (Barbas., 2006). The dorsolateral pre-frontal cortex is important for proper cognitive performance, decreased activity of this region has been linked to the progression of PD (Kikuchi et al., 2001). Furthermore, a recent fMRI study by Prodoehl *et al.* (2013) demonstrated a decrease in pre-frontal cortex activity in individuals who had gait dysfunction dominant PD compared with tremor dominant PD (Prodoehl et al., 2013).

The PPN is highly connected with the BG and the pre-frontal cortex (Nocera et al., 2010). A recent review suggests, based on previous literature, that dysfunction of the PPN modifies pre-frontal cortex and BG activity leading to increased postural instability and gait dysfunction (Yarnall et al., 2011). Thus, the non-dopaminergic circuitry are thought to be mostly responsible for the control of gait. Since it is dopamine independent, it is predicted that gait will be unresponsive to STN-DBS intervention.

#### **1.2.4 Dopaminergic effect on axial features**

Evidence for a non-dopaminergic influence on axial features stems from past research studying the effect of levodopa on gait parameters. It is understood, as discussed above, axial gait function is not a single network but requires the input of multiple systems. These various systems have varying response to levodopa treatment.

A recent report by Curtze *et al.* (2015) found gait parameters associated with pace improved following administration of levodopa in 104 PD participants (Curtze, Nutt, Carlson-Kuhta, Mancini, & Horak., 2015). However, they found that gait parameters associated with rhythm and postural control worsened following levodopa treatment (Curtze et al., 2015). This group did not directly measure the gait parameters; they employed 6 body sensors from which they interrelated the gait characteristics. Furthermore, they provided a small subset of gait parameters. Postural control is an important feature of gait that is affected in the progression of PD. A recent study by de Kam *et al.* (2014) studied the effects of stepping patterns and postural control in 12 PD participants OFF and ON levodopa medication. This group found that these axial features were unresponsive to levodopa treatment (de Kam et al., 2014). The inability of axial gait function to respond adequately to levodopa means new treatment approaches need to be explored.

### **1.3 Neurosurgical treatments for PD**

Highly select groups of patients are eligible for neurosurgical intervention, namely deep brain stimulation. Bilateral DBS of the subthalamic nucleus (STN-DBS) is performed on patients that are levodopa responsive but have persistent motor symptoms despite optimal

medical therapy (Okun et al., 2012). The inclusion criteria for DBS surgery includes 1) motor complications that are refractory to best medical treatment, 2) are levodopa responsive, 3) no mental health issues (dementia, depression), 4) have had PD for greater than 7 years (Grimes et al., 2012).

The idea of stimulating the brain for treatment of motor impairments was first explored in 1987 by Alim Benabid. Benabid hypothesized that thalamic stimulation could alleviate tremor symptoms in individuals with PD. In 1993 Benabid *et al.* demonstrated that high-frequency stimulation of the STN was effective in a person with advanced PD (Benabid et al., 1994). In the post-operation phase, the DBS device is turned on and current is increased as the medication is adjusted and reduced to maintain symptom benefit. In this post-operative period, literature has shown a maintained benefit of appendicular symptoms such as rigidity, bradykinesia and tremor following STN-DBS (Benabid et al., 1994; Moro et al., 1999; Weaver et al., 2009). However, there is an unclear consensus about the maintained benefit of axial symptoms following STN-DBS.

While several mechanistic hypotheses for the efficacy of DBS in the treatment of PD exist, the true mechanism of effect remains elusive. It is known that the electrical current delivered creates a field that can be modified by adjusting the pulse generator parameters (voltage, pulse width and frequency). Eusebio *et al.* (2011) demonstrated that high frequency STN-DBS stimulation suppressed the excessive  $\beta$ -frequency synchronization in 16 PD participants (Eusebio et al., 2011). Furthermore, it has been demonstrated that levodopa has a similar effect to reduction of the synchronous  $\beta$ -frequency waveforms (Kühn, Tsui, Aziz, Ray, & Brücke., 2009; Kühn, Kupsch, Schneider, & Brown., 2006; Weinberger et al., 2006). McNeely *et al.* (2013) propose that STN-DBS and levodopa improve motor function by influencing similar neural pathways (McNeely & Earhart., 2013). This group examined 12 PD participants and found similar responses on the Unified Parkinson's disease rating scale (UPDRS), although STN-DBS effects were slightly stronger (McNeely & Earhart., 2013).

It is well established that appendicular symptoms improve following STN-DBS intervention such as tremor (Kim et al., 2010), rigidity (Shapiro et al., 2007) and

bradykinesia (St. George, Nutt, Burchiel, & Horak., 2010). However, the effect on axial gait function is less clear and will be discussed further. A recent meta-analysis determined appendicular symptoms remain improved at 5 years post-operation while axial function remains worsened (St. George et al., 2010). In order to understand the axial gait response to STN-DBS a quantitative assessment needs to be conducted that better defines the specific gait features that remain impaired in the post-operation state. Appendicular symptoms are divided into various features, axial gait features should be as well (see section 1.5.2).

#### **1.4 DBS and axial symptoms**

To date few studies have examined changes in gait parameters following STN-DBS intervention. Most studies have monitored gait post-surgery using clinical rating scales, mainly the UPDRS, to assess the responsiveness (see Appendix. D). A number of research groups have shown that bilateral STN-DBS maintains axial gait benefits following STN-DBS intervention (Cantinioux et al., 2010; Hausdorff, Gruendlinger, Scollins, O'Herron, & Tarsy., 2009; Piper, Abrams, & Marks., 2005). Moreover, several groups have found axial gait features do not respond to STN-DBS and continue to worsen post-operation (Hariz, Rehnroona, Quinn, Speelman, & Wensing., 2008; Kelly et al., 2010).

A recent review by Collomb-Clerc *et al.* (2015) examined several studies that reported on gait parameter changes following STN-DBS intervention for PD. This review provided a brief synopsis of the outcome of these studies by providing all the gait parameter changes in a single table. The table is complex, making conclusions about the pattern of gait parameter changes very difficult. The significant studies exploring gait parameter changes will be briefly explored, along with an explanation of their weaknesses. It is important to know this is not meant to be an exhaustive list but to provide an insight into the current understand of gait and STN-DBS.

### **1.4.1 Studies finding axial improvement**

Ferrarin *et al.* (2005) assessed gait parameter changes in 10 PD participants following STN-DBS surgery. This group was the first to explore gait parameters quantitatively, finding improvement in various parameters such as stride length, velocity and stance time (Ferrarin *et al.*, 2005). This group did not consider asymmetry or variability of gait parameters. Furthermore, they only assessed at 10 months post-operation and did not have pre-operative measures.

Cantinaux *et al.* (2010) showed response of 3 gait parameters to STN-DBS intervention (gait velocity, step length and cadence). They found an improvement in velocity, stemming from an improvement in step length. They examined 11 patients OFF stimulation followed by ON stimulation at an unknown time-point post-operation.

Hausdorff *et al.* (2009) measured 13 PD participants in 4 states, in this order: OFF medication/ON DBS, OFF medication/OFF DBS, ON medication/OFF DBS and ON medication/ON DBS. They found a significant improvement in UPDRS subscores such as tremor, rigidity and bradykinesia comparing OFF medication/OFF DBS to ON medication/ON DBS. It was also found, in this comparison that gait speed and stride length improved. However, the time in which patients were assessed was not adequate making carry over effects of stimulation and medication possible. The ideal ON medication state is about 1 hour, making these assessment of patients biased.

Piper *et al.* (2005) studied 15 PD participants undergoing STN-DBS surgery pre-operation, 3 months post-operation and 3-4 years post-operation. They assessed patients using a motion capture camera system. They found an improvement in gait velocity and stride length up to 4 years post-operation. However, they only explored 3 gait parameters and did not consider the asymmetry/variability of those gait parameters.

Altug *et al.* (2014) demonstrated a significant improvement on several clinical rating scales in 19 PD participants 6 months post-operation. This group reported a significant decrease in UPDRS subscores for gait and postural stability 6 months post-operation (Altug, Acar, Acar, & Cavlak., 2012). The specific gait parameter changes

were unknown and therefore parameters that are unable to be detected by observation may have been affected.

#### **1.4.2 Studies finding no axial improvement**

Kelly *et al.* (2010) examined gait function 6 months post STN-DBS surgery in 8 PD participants. There was no significant improvement in total UPDRS scores or gait subscores following 6 months of stimulation (Kelly *et al.*, 2010). Furthermore, gait speed and stride time variability were not significantly changed 6 months post-operation (Kelly *et al.*, 2010).

A recent meta-analysis of the long-term effect of STN-DBS on motor outcome in PD determined axial function remains impaired at 5 years post-operation (St. George *et al.*, 2010). This group determined the long-term efficacy of STN-DBS on balance and gait function are not maintained to the same extent as the appendicular symptoms (St. George *et al.*, 2010). However, this meta-analysis considered only studies that used the UPDRS to rate motor function. The inter-rater reliability of the UPDRS is a concern, especially when comparing across various research sites (Klucken *et al.*, 2013).

#### **1.4.3 Shortfalls of previous studies**

Several of the above-mentioned studies examined axial function by reporting gait subscores of the UPDRS. Stating that gait worsens or improves, as assessed with one UPDRS item ranking, is not sufficient when attempting to provide a detailed overview of the specifics of axial gait dysfunction. The conflicting results of the mentioned studies may stem from the assessment tool being used.

A few of the studies explored a more in depth analysis of gait function, reporting on the change in various gait parameters. However, simply stating the change in gait parameters does not elucidate the relationship between the gait parameters. Understanding that various gait parameters increase or decrease has little clinical relevance/implications. The current thesis explores the change in various gait parameters, following STN-DBS intervention, in a more systematic manner. Employing an organized system for examining gait parameter changes allows for a better understanding of the

relationship between different parameters. The objective is to provide detailed information about the parameters and classify them into various features of gait.

## **1.5 Gait Dysfunction and Parameters in Parkinson Disease**

### **1.5.1 Gait dysfunction in PD**

The apparent simplicity of gait, stemming from its automatic and rhythmic nature, overshadows the true complexity of the task. As previously discussed, the act of walking employs the complex integration of cortical, subcortical, brainstem and spinal cord neural networks with external sensory information (Nutt, Marsden, & Thompson., 1993). Pathology can affect single or multiple levels of this integration system, producing motor impairments. Furthermore, each brain region has differing population of neurons that contribute to axial motor symptoms. It is clear that gait impairments arise from several brain regions, and is thought to have a significant non-dopaminergic influence (Pahapill & Lozano., 2000).

Gait is defined as the sequence of leg movements for a stride cycle, which tends to be impaired in individuals afflicted with PD. A stride cycle is the most common unit studied in gait metrics, spanning from the placement of the heel of one foot onto the ground to the placement of the same foot in succession. A step length is half a stride length, spanning the distance of the heel of one foot to the heel of the other foot in succession (explained in more detail in Section 2.2.5). Classically, affected gait in PD presents as slowness (reduced limb velocity), reduced arm swing, shorter stride lengths, shorter step lengths, stooped posture and increased double support time (Morris, Huxham, McGinley, Dodd, & Iansek., 2001; Sofuwa et al., 2005).

Proper assessment of gait parameters can inform clinicians about early pathology (Baltadjieva, Giladi, Gruendlinger, Peretz, & Hausdorff., 2006), predict cognitive decline (Verghese et al., 2008) and risk of falls (Verghese, Holtzer, Lipton, & Wang., 2009). To date a limited selection of gait parameters are used to assess gait function in PD. Furthermore, the average value for the gait parameters are often reported and used to illustrate gait changes. However, average values from gait parameters only explain a

portion of the dysfunction; variability and asymmetry in gait parameters are also important measures. Moreover, stating average values does not address the relationship between various gait parameters. An organized assessment profile of various gait parameters would better elucidate the specific features of gait that are impaired

### **1.5.2 Exploring gait feature models for PD**

Several research groups have addressed the issue of the organization of gait parameter changes in elderly and patient populations. There is inconsistency, in current literature, on the appropriate selection of gait parameters to be used for analysis and the conclusions drawn from changes in these gait parameters. Displaying gait changes without context does not provide a good assessment of gait function response to treatment. As previously discussed, axial gait features tend to worsen in PD regardless of dopaminergic medication intake (Galna et al., 2015). Implementing a detailed assessment profile of gait parameters for PD will aid in elucidating axial gait response to STN-DBS.

Verghese *et al.* (2008) formulated a predictive model for gait in patients with mild cognitive impairment, providing three gait feature categories for various gait parameters: pace, rhythmicity and variability (Verghese et al., 2008). Hollman *et al.* (2011) expanded on this model by adding more gait parameters into the three gait feature categories and adding two new feature categories: phase and base of support (Hollman, McDade, & Petersen., 2011). A recent principle component analysis was conducted which sought to expand on these two previous models and apply the model to a PD population. Rochester *et al.* (2013) formulated a concise model with the gait feature categories: pace, rhythm, variability, asymmetry and postural control (Lord, Galna, & Rochester., 2013). These five features provide an understanding of key gait parameters with respect to their purpose and role in pathology. This model has been validated in a PD population and will be used for the current research (Galna et al., 2015).

#### ***Pace***

Pace refers to the speed at which a person walks and mainly associated with the gait parameters of step velocity and step length. When PD participants are OFF and ON

dopaminergic medications, pace remains significantly impaired compared with controls (Hass et al., 2012; Morris, Ianssek, Matyas, & Summers., 1994). Galna *et al.* (2015) found that following 18 months of levodopa treatment the pace feature continued to decline (Galna et al., 2015).

### ***Rhythm***

Gait rhythmicity is important for safe walking in humans. Rhythmic gait involves the temporal aspects of the stride cycle. The timing of each phase of the stride cycle determines the rhythmic nature of the walk. In PD rhythmicity tends to become impaired giving rise to increased temporal variability, asymmetry and instability in gait (Galna et al., 2015). Most of the literature on the neural basis of left-right gait coordination comes from animal models. These studies suggest that locomotor rhythmicity activity relies on central pattern generators (CPG) within the nervous system (Marder & Calabrese., 1996). In animals, the CPGs reside in the cervical and lumbar regions of the spinal cord. These generate basic motor output patterns responsible for rhythmic contractions of antagonistic flexor-extensor groups of muscles in the limbs of the animal (Yogev, Plotnik, Peretz, Giladi, & Hausdorff., 2007). There is some evidence to suggest that limb coordination during human locomotion is controlled and organized similar to quadrupeds (Dietz., 2002). Thus in humans there may be an influence of CPGs in the production of rhythmic and symmetric gait.

### ***Variability***

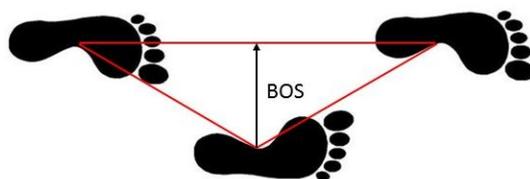
The measures of gait, like most physiological signals, are not constant but rather fluctuate with time and from one step to the next. Variability is the term used to describe these step-to-step fluctuations. In healthy subjects the variability in their gait parameters remains low (Hausdorff, Cudkowicz, & Firtion., 1998). In PD pathology, gait variability tends to increase as the disease progresses (Hausdorff et al., 1998). The increase in variability has been attributed to an inherent increase in the variability of muscle force production (Stelmach, Teasdale, Phillips, & Worringham., 1989).

## *Asymmetry*

Parkinson disease motor symptoms often begin asymmetrically on one side of the body and then progress to involve the other side as the disease advances (Hoehn & Yahr., 1967). While patients present with symptoms bilaterally, the severity of the symptoms may not be symmetrical (Marinus & van Hilten., 2015). The cause of asymmetry is unknown and it does not have any known environmental, genetic or neurochemical etiology (Djaldetti, Ziv, & Melamed., 2006; Marinus & van Hilten., 2015). However, the unequal limb symptoms such as rigidity in one leg versus the other may contribute to the asymmetry seen in the gait parameters.

## *Postural control*

The base of support for human walking is the area beneath them that includes every point of contact the person makes with the supporting surface (see Figure 1-2). Postural control is the ability return and keep the center of body mass over the base of support (Horak., 1987).



**Figure 1-2.** Base of support used for postural control.

## **1.6 DBS microlesion effect**

A transient lesion is created during the DBS surgery; it has been named the microlesion effect (MLE). This is an acute (short-lasting) lesion, which, on its own, is thought to cause a cessation of many of the appendicular and axial PD symptoms. Jech *et al.* (2012) investigated the formation of the MLE using fMRI in twelve individuals undergoing STN-DBS surgery. This group found, in addition to neuronal death, the formation of an edema within the motor network. The MLE is thought to be a surgical effect, differing from the known effects of neurostimulation and levodopa (Jech *et al.*, 2012).

To date there have been very few studies that have examined the effect of the MLE on PD motor symptoms, the ones that have explored the MLE using the UPDRS (Granziera et al., 2008; Maltête et al., 2008; Mann et al., 2009). Granziera *et al.* (2008) showed PD symptoms improved for 1 month post-operation and then immediately worsened. This group termed this phenomenon as a “delayed failure” of appendicular and axial symptoms, assessed using the UPDRS, up to 1 month post-operation. This group postulated the symptom improvement from the MLE masks the effect of the STN-DBS. Moreover, they found a subset of participants (10%) had delayed failure of symptoms meaning the MLE masked improper electrode placement (Granziera et al., 2008). Maltete *et al.* (2008) examined 30 STN-DBS participants and found that improvement in UPDRS scores began at 4 days post-operation (Maltête et al., 2008). The former group reported the presence of the MLE is troublesome while the latter group reported the MLE to be a sign of good electrode placement. However, both these groups examined the MLE effect while the STN-DBS stimulator was ON immediately post-operation. The MLE was not adequately examined in these studies due to the presence of the STN-DBS stimulation. The symptom improvement found in these studies may have been a synergistic effect of STN stimulation and the MLE. Furthermore, these studies did not report the specific gait parameter changes previously discussed (see section 1.5.2). A detailed analysis of axial gait changes in response to the MLE has not been conducted.

An accurate examination of the MLE would require the DBS stimulator to be OFF and dopaminergic medications to remain consistent. Controlling for these variables allows for a more sensitive examination of the MLE. Furthermore, assessing the MLE at two different time-points, with the stimulator OFF, would provide a more detailed progression of the MLE on axial features. In the present thesis it is hypothesized that the MLE is a surgical effect, having an effect on both dopamine and non-dopamine systems. Thus, it is expected that there will be an immediate post-operation improvement in appendicular and axial gait features in the absence of STN-DBS stimulation. Demonstration of this in the STN-DBS OFF state will negate the possible influence of STN stimulation.

## 1.7 Measuring clinical outcome

### 1.7.1 A comparison of gait assessment tools

Monitoring PD motor symptoms provides invaluable feedback on the effectiveness of various therapeutic interventions. Presently, the assessments of appendicular and axial PD symptoms are often carried out using standardized clinical scales, such as: the UPDRS. The appendicular limb symptoms are better represented on the UPDRS than the axial symptoms. As previously discussed, a more detailed investigation of axial gait feature defects in PD could be used as a reference for therapeutic efficacy.

For motor symptoms in particular, the UPDRS Part III is the most commonly used scale to rate such symptoms in PD (Goetz et al., 2008). The UPDRS, maintains an intrinsic subjectivity limiting its value as a measure in clinical diagnosis and research (Chien et al., 2006). Individual clinician UPDRS ratings can vary, causing low inter-rater reliability. More specifically, the UPDRS contains an integer rating scale (0-4) to assess severity of motor functions instead of using a more ratio-based quantitative approach (Klucken et al., 2013). The UPDRS contains only one item specifically for gait (item 29) and a few other items for other axial features (item 18 and 30). Therefore the UPDRS has low specificity when examining axial gait features because providing a single integer rating for gait does not provide detailed information about aspects of the gait are impaired. A recent study by Yogev *et al.* (2007) found that UPDRS asymmetry was not associated with gait asymmetry (Yogev et al., 2007). Moreover, asymmetric motor symptoms such as tremor and rigidity do not fully account for the existence of gait asymmetry (Yogev et al., 2007).

Researchers have improved reliability of disease ratings through the increased use of objective and quantitative data collection tools over the past few years. The advancement of more complex interventions accentuated the need for improved assessment measures for many disorders. The question of “man versus machine”, increasing the use of technology to counter subjectivity, has become more prevalent in current literature looking to assess and quantify patient symptom profiles (Egerton, Thingstad, & Helbostad., 2014; Heldman et al., 2011; Mera, Heldman, Espay, Payne, &

Giuffrida., 2012; Zampieri et al., 2010). The interest in the current thesis is to extract a more detailed profile of the axial gait feature changes following STN-DBS surgery.

### **1.7.2 Gait speed changes**

Several research groups have studied the effect of gait speed on the bilateral coordination of gait using treadmill machines (Ivanenko, Cappellini, Poppele, & Lacquaniti., 2008; Seay, Haddad, van Emmerik, & Hamill., 2006). In these studies, they focused on the transition from walking to running and few studies have examined the coordination of gait parameters within the walking speed range. Furthermore, the use of treadmills instead of over ground walking removes the conscious control over gait speed. The current thesis will provide a more realistic environment in which patients will perform walking tasks above ground. Gait speed changes will be an important component of the research presented in Chapters 2 and 3.

The ensuing Chapters will investigate the effects self-dictated normal and fast gait have on the coordination of the left-right stepping pattern. The self-selected gait speed (SELF) of people with PD has been associated with disability level on the UPDRS (Tan, Danoudis, McGinley, & Morris., 2012). The fast as possible (FAST) gait speed has not been well documented but plays an important role in measuring one's ability to adapt gait speed to environmental demands. Furthermore, SELF and FAST gait speed has been shown to predict community ambulation and risk of falling in individuals with PD (Elbers, Van Wegen, Verhoef, & Kwakkel., 2013; Paul et al., 2013).

### **1.7.3 Clinical scales**

As previously mentioned there are common non-motor features associated with PD. While not in every case, some individuals with PD present with cognitive deficits and affective symptoms. Depression, a common affective disorder, has been show to appear in a subset of PD cases (Ceravolo et al., 2013; Spalletta et al., 2014). Furthermore, depression has been shown to occur before clinical diagnosis of PD was made in a cohort of individuals (Schuurman et al., 2002). The onset of depression is thought to occur due to the disruption to the dopamine system. This effect may be further exacerbated by

administration on levodopa treatment (Eskow Jaunarajs, Angoa-Perez, Kuhn, & Bishop., 2011). Cognitive deficits have been shown to occur in PD and tend to worsen as the disease progresses (Yarnall et al., 2014). The exact physiological underpinnings of this are not clear but there may be a role of the collection of cortical Lewy bodies (Lashley et al., 2008) and cholinergic dysfunction (Tiraboschi et al., 2000). PD subjects with cognitive deficits have been shown to have a greater incidence of co-morbid depression, compared to PD subjects without cognitive impairment (Yarnall et al., 2014).

Healthy cognitive functioning plays an important role in proper gait function and impaired cognition in PD has been demonstrated to contribute to the presenting gait impairments (Maillet et al., 2012). Due to the co-morbidity of cognition and depression in PD, both non-motor features will be measured for possible confounds in the current research. The Montreal Cognitive Assessment Scale (MoCA) is an accurate measure of global cognition (Nasreddine et al., 2005), and has been validated in the PD population (Hoops et al., 2009). The Geriatric Depression Rating Scale (GDS) accurately measures mild to moderate depression and has been validated in the PD population (Leentjens et al., 2008). A recent multicenter study found that STN-DBS does not reduce overall cognition and affectivity in PD (Witt et al., 2008).

## **1.8 Rationale**

The current thesis investigates the response of axial gait features to STN-DBS intervention. The aim was to provide a more detailed and systematic assessment of axial gait function than has been studied previously. As previously discussed, studies have examined gait function using the UPDRS and various gait parameters. These methods do not provide an explanation for the variable response of gait parameters to STN-DBS. The current thesis adopts a recent principle component analysis to explore an explanation for the changes in gait parameters following STN-DBS.

The examination of these gait parameters during a preferred pace and fast-paced walking condition has not been previously explored. The former walking condition is less cognitively demanding than the latter walking condition. It is thought that the faster walking condition is more cognitively and motorically demanding.

The overall objective is to determine the features that remain unresponsive to STN-DBS intervention. This information may be used in two ways 1) provide a better treatment for continued gait dysfunction by allowing a more fine-tuned titration of the STN-DBS device 2) monitor the addition of another therapeutic treatment to improve the unresponsive gait features.

## **1.9 Summary**

The role STN-DBS has in modulating PD gait features remains unclear, due in part to the use of subjective and qualitative clinical rating scales. A more detailed assessment of gait features will elucidate the specific effect STN-DBS has on gait features such as: pace, asymmetry, variability, rhythm and postural control. It is hypothesized that axial gait function is predominantly regulated by non-dopaminergic systems.

The second chapter of the current thesis explores a proposed immediate post-operative symptom improvement, which is thought to be due to the MLE. While previous studies examined the MLE with the STN-DBS stimulator turned on, the current study will examine the MLE with the stimulator OFF. In the absence of modified dopaminergic medication and without the DBS device being turned on it is thought that the true MLE will be evaluated. It is hypothesized that the MLE is a surgical effect, having little selectivity for the various dopaminergic and non-dopaminergic control systems. The immediate post-operative improvement is thought to occur in all symptoms, regardless of the dopaminergic and non-dopaminergic systems. It is expected that an improvement will be found in both appendicular and axial symptoms. The current thesis will quantify this acute surgical effect and its potential role in STN-DBS effectiveness.

The third chapter of the current thesis explores the 6 month clinically optimized STN-DBS state. Subsequently, following surgical recovery, the DBS device is turned on and clinically optimized while the medication is reduced. At the 6 month time point it is expected that the real effects of DBS will be seen. It is hypothesized that axial gait function is primarily regulated by non-dopaminergic systems. Thus, it is predicted that because STN-DBS has a stronger dopaminergic network influence, axial gait function will remain impaired following 6 months of STN-DBS. At 6 months post-operation it is

expected that the participants will have recovered from the surgical effect and their DBS device will be at a clinically optimized setting.

Overall, it is hypothesized that axial gait features are controlled predominantly by non-dopaminergic control systems. Previous work has demonstrated STN-DBS acts mainly on the dopaminergic BG system, in turn leaving axial gait features untreated. The specific features of gait that are non-responsive to STN-DBS have not been elucidated. In the ensuing chapters gait feature changes will be quantified and investigated under various walking conditions. It is predicted that the MLE will induce a global improvement in appendicular and axial symptoms through a non-specific surgical effect. Following surgical recovery, gait features are predicted to worsen due to STN-DBS effect in the dopaminergic BG circuit.

## 1.10 References

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## **2. Parkinson disease motor symptom response to the microlesion effect immediately post-operation.**

### **2.1 Introduction**

Parkinson disease (PD) is a neurodegenerative disorder that presents with appendicular (limb) and axial motor deficits such as rigidity, resting tremor, akinesia, bradykinesia and gait impairments. As PD progresses the severity of symptomatology increases and the response to pharmaceutical treatments decreases. Bilateral STN-DBS with multipolar electrodes and a subcutaneous pacemaker has become standard practice for advanced PD (Deuschl et al., 2006). STN-DBS targets PD symptoms that have been previously responsive to the levodopa treatment. The mechanism by which STN-DBS intervention impacts PD symptoms remains elusive (Miocinovic, Somayajula, Chitnis, & Vitek, 2013). Recent literature points to a possible contribution from the immediate post-operative microlesion effect (MLE) in the prediction of the long term effectiveness of STN-DBS (Maltête et al., 2008; Tykocki, Nauman, Koziara, & Mandat., 2013). While the effect of the MLE is thought to be surgical (global improvement), the improvement in appendicular symptoms suggests proper implantation within the STN. In this respect, studying the MLE is becoming increasingly important.

Interestingly, after DBS lead implantation and before the device is turned on for stimulation, many individuals present with improved symptoms. This improvement, thought to be a result of the MLE, produces a transient cessation of PD symptoms lasting a few weeks following surgery (Granziera et al., 2008; Kondziolka, & Lee., 2004; Mann et al., 2009). Several studies have reported the MLE occurring in various DBS targeted brain regions following electrode placement, such as: GPi (Mann et al., 2009), ventral intermediate nucleus of the thalamus (Morishita et al., 2010) and STN (Maltête et al., 2008). Following the routine surgical implantation of the electrode leads, brain tissue damage occurs resulting in a hemorrhage, edema and disruption of cells (Morishita et al., 2010). The MLE has been shown to cause clinical improvement immediately following surgery, with a range of improvements (Granziera et al., 2008). Tykocki *et al.* (2013) found that PD participants experience a greater MLE than others depending on disease

duration (Tykocki et al., 2013). Moreover, it was found that individuals with a shorter PD duration may experience a greater MLE than individuals with a longer PD duration (Tykocki et al., 2013). Current literature has demonstrated improvement from the MLE using the UPDRS for measure outcome (Derrey et al., 2010; Morishita et al., 2010; Tykocki et al., 2013). While this data has proven useful, a quantitative approach may reveal specific axial gait improvements which are poorly assessed with the UPDRS.

The current chapter examines differences in axial gait parameters up to 2 weeks post-operation. As previously established in Chapter 1, appendicular symptoms may have a different control mechanism that is regulated by and disrupted due to dopamine dysregulation while axial symptoms tend to arise, at least in part, from more non-dopaminergic systems. Axial features have been shown to be less responsive to dopaminergic medications (Hely, Morris, Reid, & Trafficante, 2005). The MLE has been shown to improve both appendicular and axial symptoms immediately following STN-DBS surgery in individuals with PD (Maltête et al., 2008; Tykocki et al., 2013). The improvement in PD symptoms, without much change in dopaminergic medication immediately post-operation, is thought to have surgical shock like response to the system. This shock is global and not specific for the dopaminergic or non-dopaminergic pathways. In the MLE state, the individual has the same medication dosing as preoperative and yet experiences an improvement of appendicular and axial symptoms. It is not clear how long these effects last, only that they tend to diminish a few weeks post-operation (Maltête et al., 2008; Mann et al., 2009; Tykocki et al., 2013). Thus it is hypothesized that there will be an acute improvement in axial gait parameters immediately post-operation due to the MLE. This study is the first to explore quantitative data elucidating the influence of MLE on axial gait features.

## **2.2 Methods**

### **2.2.1 Study Participants**

Ten PD participants undergoing bilateral STN-DBS were included in this analysis (Table 2-4.). Inclusion criteria for the PD participants included: 1) diagnosis of PD with debilitating symptoms (tremor, stiffness) for whom medications have begun to lose effectiveness 2) severe motor fluctuations with disabling off periods and dyskinesia during on phases 3) physiological eligibility for the DBS procedure. Exclusion criteria for the PD participants included: 1) lack of English proficiency 2) dementia or psychiatric abnormalities. Furthermore, PD participants were required to be on a steady state of their medications, with no change in the past year as assessed from chart reviews. This study was approved by the Human Subjects Research Ethics Board (HSREB) (Western University Ethics (WUE) # 103928), and all participants provided informed consent.

### **2.2.2 STN-DBS Surgical Procedure**

The DBS surgical procedure differs slightly between centers but follows similar steps previously reviewed (Benabid, Chabardes, Mitrofanis, & Pollak., 2009). A pre-operative MRI scan was completed to determine the best location for target stimulation. Further pre-operative planning was conducted, including choosing the best entry site, path, and approach to avoid blood vessels. Once the plan was established, a stereotactic head frame was placed on the patient to allow proper placement of the electrodes.

Electrophysiological exploration was carried out by using microelectrodes and various tracks. Some centers conduct the exploration one track at a time, others investigate multiple tracks at once. The microelectrodes recorded the activity of the neurons as it was lowered down toward the target STN. The neural activity was projected through a set of speakers, which allowed the neurosurgical team to listen for the typical firing pattern of the STN. The STN has asymmetrical spiking pattern at a high frequency with bursting patterns (Benabid et al., 2009). There were also proprioceptive responses to passive movements made by the neurosurgeon.

Once the microelectrodes were implanted, a full symptoms review was completed by stimulation of each microelectrode independently. This review established the location of each microelectrode in relation to the STN. It is important to determine where each microelectrode is placed: e.g. within the STN, around the STN border and outside the STN (Benabid et al., 2009). Tremor and rigidity are the two most common symptoms used to assess which microelectrode produces the best symptom relief (Benabid et al., 2009). The track that produced the most beneficial effects and fewest side effects was determined. All microelectrodes were removed and a chronic lead (DBS 3389, 1.5 mm contact length, 0.5 spacing, 1.27 mm diameter) was permanently implanted into the selected track. The pulse generator was implanted subcutaneously into the subclavicular area.

The pulse generator was turned on at 2 weeks post-operation and it was optimally programmed for symptomatic relief as well as avoidance of undesirable side-effects, such as dysarthria, blurred vision or pain. There are several programmable components on the device that determine how the electrical impulses are delivered to the brain. These include stimulation frequency, pulse width, and pulse voltage. A high frequency (130Hz) STN-DBS stimulation and a narrow pulse width (60-90  $\mu$ s) has been shown to be beneficial in alleviation of both appendicular and axial motor symptoms in PD (Eusebio et al., 2011; Sidiropoulos et al., 2013). Initial programming uses a frequency of 130 Hz and a pulse width of 90  $\mu$ s. The pulse generator was set to have a positive polarity while both electrode leads had contact points that were set to a negative polarity. Each contact point (numbered zero for the distal contact and three for the proximal contact) was investigated independently. The voltage was increased from zero to a maximum of 5 volts, while looking for symptom relief as well as unwanted side effects: eye deviation, dysarthria, dyskinesia and muscular contraction (usually the face). Having the contact point negative and the pulse generator as positive is termed monopolar and is usually the first selection used. However, if the lead is sub-optimally placed a review of bipolar setting (one contact point is positive while another is negative) may be investigated.

The current produced by the lead creates an electrical field, which causes stimulation of the STN and possibly surrounding areas. Monopolar settings tend to

produce a larger electrical field and bipolar settings produce a narrower electrical field (Kuncel & Grill., 2004). The best setting is typically: monopolar, 2-2.5 volts, 130 Hz and 90  $\mu$ s (Benabid et al., 2009; Kuncel & Grill., 2004). Initially the voltage was set to 1.5 volts and was gradually increased over a few months post-operation to a clinically optimized level. Titration of levodopa was also conducted post-operation; lowering oral dosages to levels that do not induce dyskinesia but avoid apathy and other related withdrawal symptoms.

### **2.2.3 Clinical Scales Assessment**

STN-DBS participants underwent neuropsychological testing before the surgery. During the research appointments STN-DBS participants completed several standardized clinical scales (see Table 2-1.). The scales given to the STN-DBS participants were: the Montreal Cognitive Assessment (MoCA) scale, activities-specific balance confidence (ABC) scale, the geriatric depression scale (GDS), the UPDRS and the freezing of gait questionnaire (FOG-Q) (see appendix D-H). The MoCA test was used to assess levels of cognitive impairment and has been validated in the PD population (Hoops et al., 2009; Nasreddine et al., 2005). The MoCA test has a total score of 30 and a score below 25 is considered cognitively impaired (Nasreddine et al., 2005). The ABC scale is a 16 item self-report questionnaire that rates balance confidence on various tasks and has been validated in a PD population with excellent test-retest reliability (Bello-Haas, Klassen, Sheppard, & Metcalfe., 2011). The GDS scale is a 30 item self-report questionnaire used to assess levels of depression in an elderly population and has been validated in a PD population with high test-retest reliability (Ertan, Ertan, Kiziltan, & Uyguçgil., 2005). The FOG-Q is a 6 item scale used to assess freezing of gait and has been validated in a PD population (Giladi et al., 2009).

All STN-DBS participants were assessed by the UPDRS-III in the ON state at the beginning of each visit. For the purpose of the current study, scores derived from the UPDRS-III were used to assess appendicular and axial symptoms. The appendicular items were rigidity (sum of item 22) and akinesia (sum of items 23-26). Rigidity was further divided into upper limb (neck and arms) and lower limb (legs). Akinesia was also

divided into upper limb (sum of item 23-25) and lower limb (sum of item 26). Axial items were gait (sum of item 29-30), speech (item 18) and body bradykinesia (item 31).

**Table 2-1.** The clinical rating scales used during each visit to the research facility.

<b>Clinical Questionnaires</b>
Unified Parkinson Disease Rating Scale (UPDRS)
Activities-specific Balance Confidence Scale (ABC)
Freezing of Gait Questionnaire (FOG-Q)
Montreal Cognitive Assessment (MoCA)
Geriatric Depression Scale (GDS)

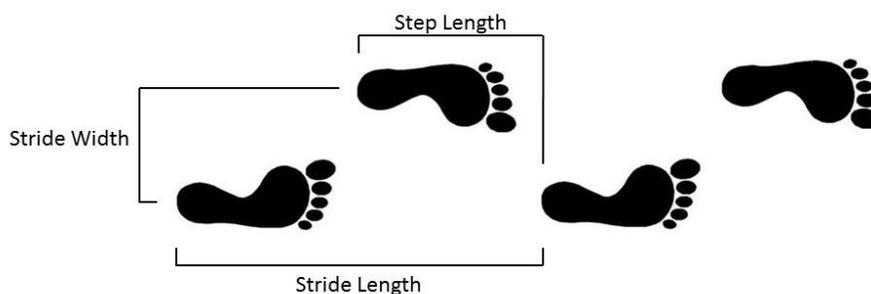
#### **2.2.4 Quantitative Gait Assessments**

Various gait assessment tools exist to quantify axial gait parameters but an efficient and effective system is the Zeno walkway (Zenometrics LLC, Peekskill, NY) with ProtoKinetics Movement Analysis Software (PKMAS) analysis system software (PKMAS, Harvertown, PA, version 8.1). The Zeno walkway is a portable 7 metre long carpet with embedded pressure sensors. The sensors detect each footfall made by the participant while walking and relay the information to a computer for analysis. The PKMAS software system captures each footfall on the Zeno walkway and provides accurate measurement of various gait parameters (Bilney, Morris, & Webster., 2003; Menz, Latt, Tiedemann, Kwan, & Lord., 2004). The validity and reliability of the PKMAS system has been shown in many studies to date (Chien et al., 2006; McDonough, Batavia, Chen, Kwon, & Ziai., 2001; Nelson et al., 2002; van Uden & Besser., 2004). The PKMAS analysis system allows the patient's gait performance to be quantified in an efficient manner, allowing post-hoc analysis to be conducted (Egerton, Thingstad, & Helbostad, 2014). The ability to extract gait parameters during a patients walk in real-time has advanced the way in which treatment regimens are assessed. Obtaining these gait parameters can elucidate the identification of disease (Egerton, Williams, & Iansek., 2012; Lord, Galna, Coleman, Burn, & Rochester., 2013), the prediction of falls (Verghese, Holtzer, Lipton, & Wang, 2009) and contribute to defining gait patterns in the progression of PD (Hass et al., 2012). With respect to the present work the PKMAS system provides insight into the effectiveness of STN-DBS intervention for PD gait patterns.

Gait was assessed while participants conducted a walking task at preferred pace (SELF) and fast as possible (FAST) gait speeds. For the SELF task participants were asked to walk at their preferred pace. For the FAST task participants were asked to walk at their fast-as-possible gait speed. Each walking condition was performed twice. Participants began seated in a chair at one end of the 7 meter long walkway, 2 meters from the start of the walkway. There was an X on the floor 2 meters past the end of the walkway where the participant was informed to walk to. Once they walked across the walkway and reached the X they had to turn around to return to the chair. Ample space was provided on either end of the carpet to avoid recording acceleration/deceleration of the walks.

### **2.2.5 Axial gait parameters**

Seven spatiotemporal gait parameters were extracted using the PKMAS system these include: step velocity, step length, single support time, double support time, step time, stance time and stride width. The average values of each parameter, over the walking trial, were used along with the variability and asymmetry of these parameters. The measure for variability was obtained by calculating the mean of the standard deviation between the left and right steps. The measure for asymmetry was obtained by calculating the absolute difference between the left and right steps. These calculated gait parameters are divided into five general gait features: pace, variability, rhythm, asymmetry and postural control (see Table 2-2.). These features, and their respective gait parameters, have been established and validated previously in a PD population (Galna, Lord, & Rochester., 2013; Lord, Galna, Verghese, et al., 2013). For the purpose of the study these parameters will be used to fully quantify axial gait changes.



**Figure 2-1.** Spatiotemporal gait parameters used to assess quality of walking.

### ***Step Velocity***

Velocity of the step was measured by calculating the distance travelled in a period of time. As PD progresses the step velocity tends to decrease. Step velocity is the largest contributing factor to failure in obstacle avoidance in PD (e.g. avoiding raised curbs or crossing a busy street) (Hass et al., 2012).

### ***Step Length***

The length of the step was measured by finding the distance between the heel of one foot to the heel of the successive opposite foot (see Figure 2-1.). Step length is related to stride length in that there are two step lengths in one stride length. Stride length is measured by finding the distance between the heel of one foot to the heel of the same foot in a gait cycle (see Figure 2-1.). Step length tends to be shorter in the PD population during gait initiation and during the SELF gait speed task with an asymmetrical presentation over time (Bovonsunthonchai, Vachalathiti, Pisanpong, Khobhun, & Hiengkaew., 2014). A reduction in stride length may be due to an asymmetry, which can be detected by examining the step length.

### ***Single support time***

Single support time is the phase in the gait cycle where the body is supported by one limb. This is the length of time one foot is raised up off the ground lifted upward and forwards during a stride. In the PD population single support time tends to remain

consistent as the disease progresses (Hass et al., 2012; Hollman, McDade, & Petersen, 2011).

### ***Double support time***

Double support time is the length of time in the gait cycle where the body is supported by both limbs. This is the phase where both feet are planted on the ground and a stride length has just been completed. This parameter is speed dependent, as walking speed increase double support time tends to decrease. It is this phase that individuals with PD use to compensate for increased instability (Cole, Silburn, Wood, Worringham, & Kerr., 2010). If an individual with PD feels less stable they tend to compensate by increasing the time spent in the double support phase, instead of the single support phase. In this way the double support time tends to be increased in a PD population when compared to healthy age-matched controls (Hass et al., 2012; Hollman et al., 2011).

### ***Step Time***

Step time is the amount of time required to complete a step length. Compared to healthy subjects, individuals with PD tend to have an increase in step time (Bovonsunthonchai et al., 2014).

### ***Stance Time***

The stance time of the walking cycle is the amount of time the body is supported by single or double feet. The phase in which one foot or both feet contact the floor.

### ***Stride Width***

The width of the stride is the distance between the midline of one footfall and the midline of the successive footfall (see Figure 2-1.). PD stride width tends to remain similar to healthy age matched (Bovonsunthonchai et al., 2014; Okada, Fukumoto, Takatori, Nagino, & Hiraoka., 2011).

**Table 2-2.** Description of the gait parameters and their respective gait feature categories.

<b>Gait Feature/Parameter</b>	<b>Description of parameters</b>
<b>Pace</b>	
Step Velocity	Measure of distance travelled in period of time.
Step Length	Distance between heel strike of one foot to the heel strike of the successive foot
<b>Variability</b>	
Step Time SD	Step-to-step variability in the time required to complete a step length.
Step Length SD	Step-to-step variability in the length of each step.
Step Vel. SD	Step-to-step variability of distance travelled in period of time.
<b>Rhythm</b>	
Step Time	Total time required to complete a step length.
Stance Time	Total time when both limbs are on the ground.
SST	The phase in the step cycle where the body is supported by one limb.
<b>Asymmetry</b>	
Step Time Asymm	Step-to-step asymmetry in the time required to make complete a step length
Stance Time Asymm	Step-to-step asymmetry in the time both limbs are on the ground
SST Asymm	Step-to-step asymmetry in the time spent support by one limb.
DST Asymm	Step-to-step asymmetry in the time spent support by both limbs.
<b>Postural Control</b>	
Step Length Asymm	Step-to-step asymmetry in the length of each step.
Step Width	The distance between the midline of one footfall and the midline of the successive footfall.
DST	The phase in the step cycle where the body is supported by both limbs.
Step Width SD	Step-to-step variability in the width of each step.

SST, single support time; DST, double support time; the gait features and associated gait parameters were extracted from previous literature (Lord, Galna, & Rochester., 2013).

### **2.2.6 Experimental Timeline**

Gait data was extracted from 3 of the 9 visits (V0-V2) the PD participants made to the research facility (see Table 2-3.). The STN-DBS participants came to the research facility pre-operation, 1 week post-operation, 2 weeks post-operation and then once a month for 6 months. However, to assess the MLE only V0, V1 and V2 were used. Following the assessment at two weeks post-operation, the DBS device was turned on. The walking tasks in the current study did not provide a possibility for a learning effect due to the nature of the task itself. Participants were requested to walk at their SELF and FAST pace, a task they perform on a daily basis. Walking is an inherently learned task, and a learning effect was not expected. Furthermore, gait assessments and the PKMAS system have proven test re-test reliability in multiple studies to date (Meldrum, Shouldice, Conroy, Jones, & Forward., 2014; Steffen & Seney., 2008; Stolze, Kuhtz-Buschbeck, Mondwurf, Jöhnk, & Friege., 1998).

**Table 2-3.** Summary of each visit to the research facility.

<b>Visit#</b>	<b>Weeks Post-op</b>	<b>Task</b>
<b>V0</b>	Pre-op	Motor kinematic measurements + Clinical rating scales
<b>V1</b>	1 (Post)	Motor kinematic measurements + Clinical rating scales
<b>V2</b>	2	Motor kinematic measurements + Clinical rating scales + Device Turn On
<b>V3</b>	4	Motor kinematic measurements + Clinical rating scales
<b>V4</b>	8	Motor kinematic measurements + Clinical rating scales
<b>V5</b>	12	Motor kinematic measurements + Clinical rating scales
<b>V6</b>	16	Motor kinematic measurements + Clinical rating scales
<b>V7</b>	20	Motor kinematic measurements + Clinical rating scales
<b>V8</b>	24	Motor kinematic measurements + Clinical rating scales

### 2.2.7 Data Analysis

Demographic and clinical characteristics were summarized using means and standard deviations. Between-group demographic comparisons were made with independent-samples t-tests. Descriptive statistics were calculated for the spatiotemporal gait parameters based on the raw scores exported from the PKMAS software system. Gait parameters were expressed as (a) mean spatiotemporal characteristics, (b) step-to-step variability (calculated by combining the average of left and right standard deviations) and (c) asymmetry (calculated by finding the absolute difference between left and right steps on each parameter). No extreme outliers were found in the data, assessed using boxplots. All data met Shapiro-Wilks test for normality and a repeated measures ANOVA was used to compare baseline values to 1 and 2 weeks post-operation. Statistical significance was set at  $p < .05$  (two-sided). Post-hoc comparisons were performed using a Bonferonni correction. All statistics were conducted using SPSS (v21.0, IBM Corporation, Chicago, IL).

## 2.3 Results

### 2.3.1 Study Participants: clinical outcomes

Ten PD participants undergoing bilateral STN-DBS (Age: 63.9 yrs ( $\pm 5.65$  yrs), Females: 4 (40%), PD duration: 10.6 yrs ( $\pm 3.30$  yrs)) were included in the analysis. Demographic and clinical characteristics are presented in Table 2-4. There was no significant change in medication intake immediately post-operation. The overall UPDRS score was not significantly different comparing pre-operation to 1 and 2 weeks post-operation. UPDRS subscores showed that akinesia in the upper body was significantly improved 2 weeks post-operation (see Table 2-4.).

**Table 2-4.** STN-DBS participant demographics. UPDRS items were divided into appendicular and axial ratings. Data are displayed for STN-DBS participants at pre-operation, 1 week and 2 weeks post-operation.

	STN-DBS participants				
	Baseline (n=10)	1 week post-operation (n=10)	P <sub>1</sub> Value	2 weeks post-operation (n=10)	P <sub>2</sub> Value
Age (yrs)	63.91 ( $\pm 5.65$ )	---	---	---	---
Females, n (%)	4 (40%)	---	---	---	---
PD Duration (yrs)	10.61 ( $\pm 3.30$ )	---	---	---	---
LED (mg/day)	1417.88 ( $\pm 452.26$ )	1055.38 ( $\pm 240.57$ )	.105	1005.00 ( $\pm 311.59$ )	.199
UPDRS ON score	22.10 (14.08)	15.55 (10.41)	.071	15.35 (9.55)	.285
<b>Appendicular Subscores</b>					
Tremor (item 20-21)	3.50 (3.13)	2.25 (1.78)	.287	3.20 (2.74)	1.00
Rigidity (item 22)	4.95 (3.81)	3.85 (2.98)	.386	3.70 (1.26)	.772
Upper Limb	3.05 (2.03)	2.2 (1.42)	.248	2.35 (2.12)	.499
Lower Limb	1.90 (2.07)	1.65 (2.00)	1.00	1.35 (1.16)	1.00
Bradykinesia (item 23-26)	8.05 (5.49)	6.45 (5.56)	.198	4.8 (5.67)	.085
Upper Limb	5.5 (4.08)	4.55 (4.66)	.381	3.15 (4.10)	<b>.043</b>
Lower Limb	2.55 (1.96)	1.9 (1.33)	.810	1.65 (2.00)	.855
<b>Axial Subscores</b>					
Speech (item 18)	0.90 (1.26)	0.45 (0.83)	.512	0.30 (0.48)	.400
Gait (item 29-30)	1.80 (1.39)	1.4 (0.81)	.630	1.35 (1.11)	1.00
Body bradykinesia (item 31)	0.60 (1.07)	0.2 (0.42)	.669	0.15 (0.34)	.704

SD, standard deviation; LED, levodopa equivalency dose; UPDRS, Unified Parkinson's Disease Rating Scale; Calculation for LED was based on a standardized formula from literature by Tomlinson *et al.* (2010) (Tomlinson et al., 2010); p<sub>1</sub> represents the difference in the STN-DBS group from baseline to 1 week post-operation using a repeated measures ANOVA; p<sub>2</sub> represents the difference in the STN-DBS group from baseline to 2 weeks post-operation using a repeated measures ANOVA; Post-hoc comparisons were conducted using bonferonni corrections; Significance was set to  $p < .05$ ; means are displayed with standard deviation in brackets.

Interestingly, the STN-DBS participants performed significantly worse on the MoCA test 1 week ( $p = .006$ ) and 2 ( $p = .007$ ) weeks post-operation (see Table 2-5.). As to be expected with the MLE, the ABC and FOG-Q scores were significantly improved at 1 week post-operation ( $p = .006$  and  $p = .041$  respectively) but returned to pre-operation levels at 2 weeks post-operation.

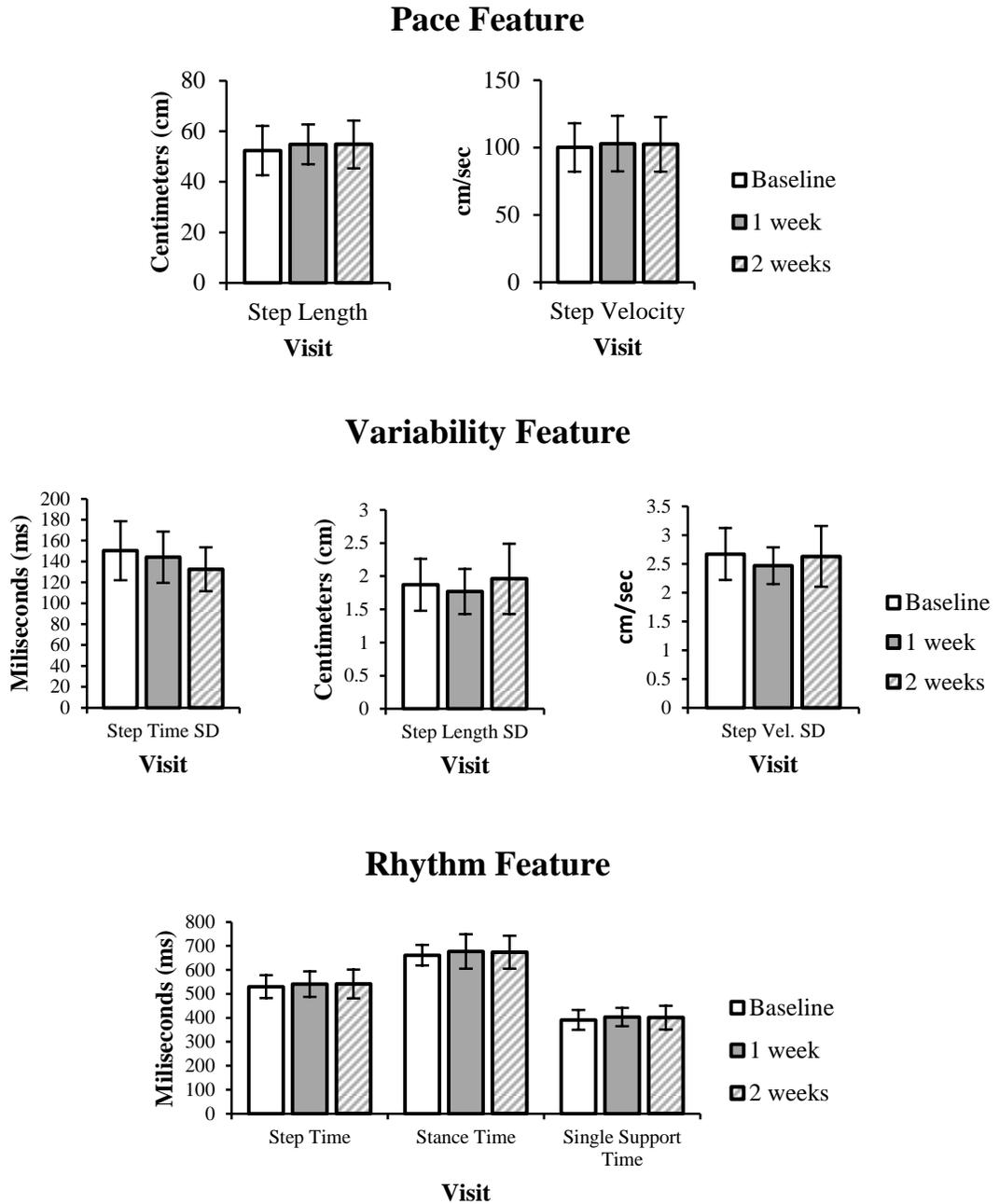
**Table 2-5.** Scores from the clinical rating scales and questionnaires. Scores are displayed for STN-DBS participants at the pre-operative, 1 week and 2 weeks post-operation.

Clinical Scales	STN-DBS Participants				
	Baseline (n=10)	1 week post-operation (n=10)	P <sub>1</sub> value	2 weeks post-operation (n=10)	P <sub>2</sub> value
MoCA	26.70 (2.41)	23.10 (3.54)	.006	22.55 (4.28)	.007
GDS	9.50 (7.57)	9.1 (8.76)	1.00	8.60 (8.23)	1.00
ABC	63.25 (14.40)	79.25 (15.32)	.006	72.34 (20.63)	.308
FOG-Q	12.00 (6.11)	6.8 (5.84)	.041	10.40 (8.59)	1.00

p<sub>1</sub> represents the difference in the STN-DBS group from baseline to 1 week post-operation using a repeated measures ANOVA; p<sub>2</sub> represents the difference in the STN-DBS group from baseline to 2 weeks post-operation using a repeated measures ANOVA; Post-hoc comparisons were conducted using bonferonni corrections; Significance was set to p = < .05; means are shown with standard deviation in brackets.

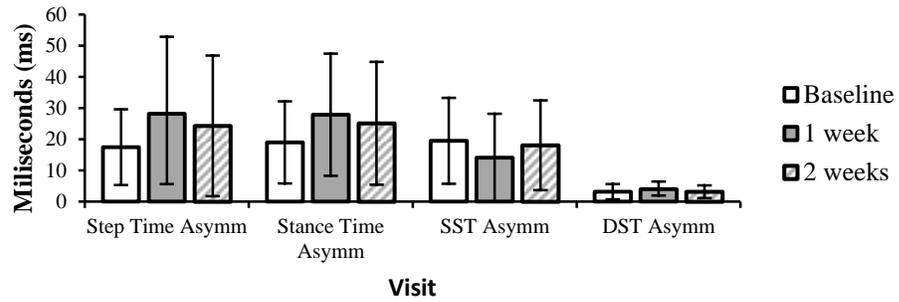
### **2.3.2 Gait parameter changes during the normal walk (SELF)**

Assessment of axial gait performance, during the SELF walking task, showed no significant improvement in any of the spatiotemporal gait parameters at 1 week and 2 weeks post-operation (see Figure 2-2. and Figure 2-3.). While these results were not significant, there were some general trends that were observed in the data set. Overall a few parameters trended toward improvement at 1 week post-operation. These parameters were associated with the gait features: pace, variability and postural control. These features trended toward improvement 1 week post-operation but worsened again 2 weeks post-operation (see Figure 2-2. and Figure 2-3.).

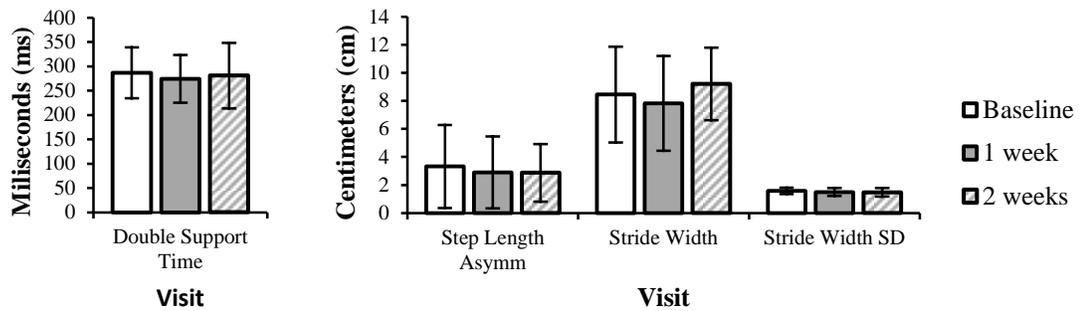


**Figure 2-2. Gait features pace, variability, rhythm and the respective gait parameter outcomes at pre-operation, 1 week post-operation and 2 weeks post-operation on the SELF gait task.** The difference between pre-operation, 1 week post-operation and 2 weeks post-operation in the STN-DBS group was assessed using repeated measures ANOVA. All post-hoc comparisons were conducted using bonferroni corrections. The mean values are displayed in the bar graph with standard deviation as the error bars.

### Asymmetry Feature



### Postural Control Feature

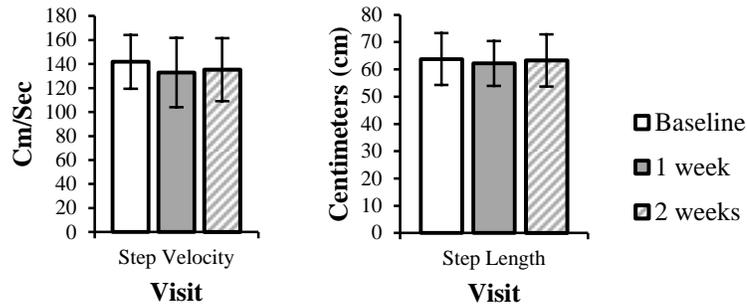


**Figure 2-3. Gait features asymmetry, postural control and the respective gait parameter outcomes at pre-operation, 1 week and 2 weeks post-operation on the SELF gait task.** The difference between pre-operation, 1 week post-operation and 2 weeks post-operation in the STN-DBS group was assessed using repeated measures ANOVA. All post-hoc comparisons were conducted using bonferroni corrections. The mean values are displayed in the bar graph with standard deviation as the error bars.

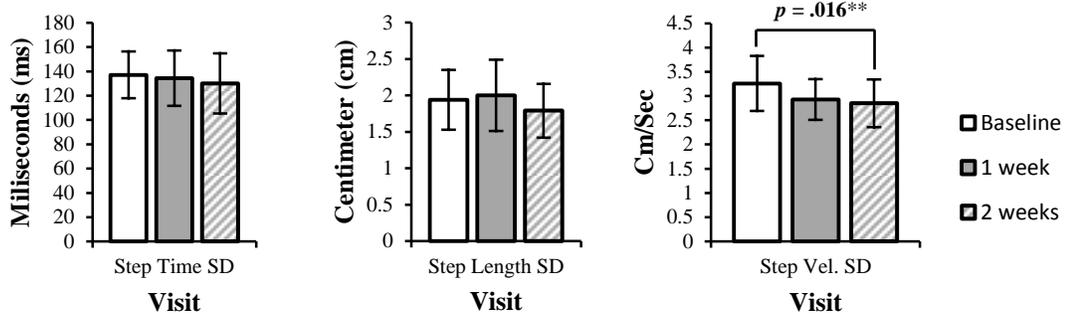
### **2.3.3 Difference in gait parameters in the fast walk (FAST)**

When STN-DBS participants were asked to walk at their FAST gait speed it was found that a few gait parameters significantly worsened post-operation (see Figure 2-4. and Figure 2-5.). At 1 week post-operation stance time ( $p = .021$ ) and double support time ( $p = .021$ ) significantly worsened from pre-operation scores ( $p = .021$ ). At 2 weeks post-operation double support time was no longer significantly worse from pre-operation. However, stance time remained significantly worse from pre-operation scores ( $p = .002$ ). Furthermore, step velocity variability improved ( $p = .016$ ) while step time worsened ( $p = .023$ ) at 2 weeks post-operation. There were some general trends noticed in the data set. There was a trend toward worsening in the pace, asymmetry postural control at 1 week and 2 weeks post-operation. However, variability trended toward improvement 1 week and 2 weeks post-operation.

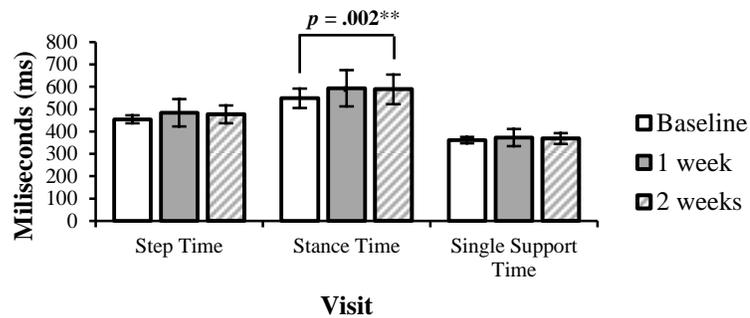
## Pace Feature



## Variability Feature

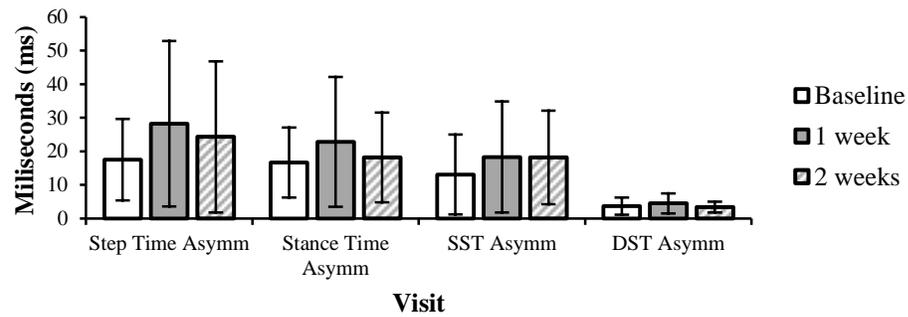


## Rhythm Feature

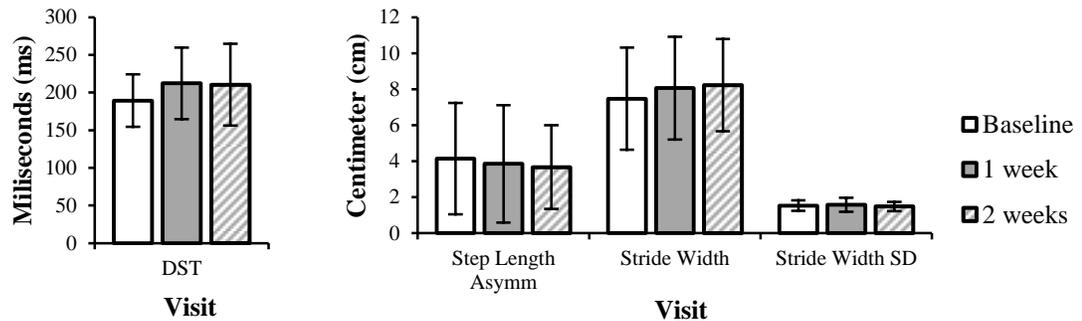


**Figure 2-4. Gait features pace, variability, rhythm and the respective gait parameter outcomes at pre-operation, 1 week and 2 weeks post-operation on the FAST gait task.** The difference between pre-operation, 1 week post-operation and 2 weeks post-operation in the STN-DBS group was assessed using repeated measures ANOVA. All post-hoc comparisons were conducted using bonferroni corrections. Corrections were made for multiple comparisons by dividing the p-value by the number of parameters in each feature: \*\* indicates  $p < .016$ . Only bold p-values are significant following corrections. The mean values are displayed in the bar graph with standard deviation as the error bars.

## Asymmetry Feature



## Postural Control Feature



**Figure 2-5.** Gait features asymmetry, postural control and the respective gait parameter outcomes at pre-operation, 1 week and 2 weeks post-operation on the FAST gait task. The difference between pre-operation, 1 week post-operation and 2 weeks post-operation in the STN-DBS group was assessed using repeated measures ANOVA. All post-hoc comparisons were conducted using bonferroni corrections. The mean values are displayed in the bar graph with standard deviation as the error bars.

## 2.4 Discussion

In the present study, the aim was to determine change in gait features due to the MLE. It was hypothesized that the MLE would cause an overall improvement in appendicular and axial symptoms. This improvement would stem from an acute system level post-surgical effect as has been seen in other studies. As such the improvements that have been suggested previously would occur in both control systems, namely appendicular and axial. This improvement would be seen while the medication doses would not be significantly modified during this acute period as per clinical protocol. Such improvement would then be termed the “microlesion effect”. However, in this research, no MLE was demonstrated on either the appendicular or the axial gait scores immediately following STN-DBS operation. Gait performance was unchanged on the SELF gait task and worsened on the FAST gait task. Furthermore, improvement on appendicular measures was not found. As previously stated the study may have been under powered with only 10 PD participants.

In the next few sections the current finding that appendicular and axial gait features fail to improve immediately post-operation will be discussed. Previous literature has suggested that the MLE promotes transient improvement in appendicular and axial PD symptoms immediately post-operation. This contradiction will be discussed and explanations of the findings will be explored. The effect on the UPDRS will be first, followed by the PKMAS results.

### **2.4.1 UPDRS: appendicular and axial symptoms**

The current study found no significant improvement in appendicular symptoms with the exception of upper body akinesia as assessed by the UPDRS. This finding contradicts previous studies that found improvement on the UPDRS scores immediately post-operation in both appendicular and axial domains (Derrey et al., 2010; Jech et al., 2012). Jech *et al.* (2012) found a significant reduction 4 days post-operation in rigidity, akinesia and axial scores (Jech et al., 2012). Maltete *et al.* (2008) reported a 27% improvement in rigidity, tremor and bradykinesia 7 days post-operation (Maltête et al., 2008).

The MLE occurs in every individual undergoing STN-DBS surgery but there is a gradient in the extent of the MLE and the subsequent symptom improvement experienced. Early neurostimulation research has shown that the MLE improvements vary among the population. A study by Tasker (1998) demonstrated that 53% of the PD participants in the study (n=19) experienced improvement from the MLE immediately following DBS electrode implantation (Tasker., 1998). It has also been demonstrated by Benabid *et al.* (1996) that 20.5% of their PD participants experienced improvement from the MLE (n=117) following DBS electrode implantation (Benabid et al., 1996). However this implies that 80% of the population did not see a MLE. Dividing STN-DBS participants into separate groups, based on the presence or absence of improvement from the MLE, has been previously conducted by several groups using UPDRS motor scores (Pourfar et al., 2009; Tykocki et al., 2013). Such regression analysis could be carried out with our data if the sample size were larger. It may then be possible to show that subgroup of patients show an improvement and thus a MLE immediately post-operatively.

An important variable in post-surgical effect is the location of the electrode. Microelectrode recordings are carried out during the operation which allows the surgeon and the physiologist to determine the target that they are implanting. However the physiological data is not analysed in terms of the localization of the electrode within the STN. This placement is quite varied in each patient and may produce a MLE in different parts of the STN. Although the data is preliminary, somatotopic organization of the input-output of the STN has been known to exist. Therefore, it is possible that the MLE also varies substantially between patients based upon the location of the stimulation electrode.

Secondary effects of the surgery such as hemorrhage, edema and mechanical disruption of pathways is also likely to be anatomically different among patients. Unfortunately, magnetic resonance imaging (MRI) is not possible after implantation to delineate these effects. Therefore, one can conjecture that the MLE can be highly variable and therefore should not be counted upon as being consistent across patients.

No improvements in appendicular or axial domains were found from the UPDRS assessment 1 week and 2 weeks post-operation. The UPDRS is subjective and qualitative in nature having only a few items related to axial gait symptoms (Klucken et al., 2013). Thus, axial symptoms were further assessed in different walking tasks using a quantitative and objective approach.

#### **2.4.2 Gait tasks: axial symptoms**

It should be mentioned from the outset that no other study to date has explored axial gait parameter changes in response to the MLE at two visits immediately post-operation. The current study found that the performance of STN-DBS participants on the SELF gait speed task, immediately post-operation, remained unchanged from pre-operation measures. Furthermore, performance on the FAST gait speed task worsened immediately post-operation. There are several explanations as to why the axial gait features did not change in the SELF gait speed task and worsened in the FAST gait task.

Quantitative monitoring of axial gait parameters has not been conducted in the literature but a general analysis of gait function has been reported on. Jech *et al.* (2012) studied the MLE and found an improvement on axial domains of the UPDRS 4 days following STN-DBS surgery (Jech et al., 2012). In contrast, Granzoera *et al.* (2008) found that an axial gait failure, assessed with the UPDRS, occurred 1 month post-operation (Granziera et al., 2008). The present study examined STN-DBS participants 1 week and 2 weeks post-operation. The two assessments may have been conducted at a point where the MLE had peaked and was diminishing. However, if this were accurate, the axial gait parameters would have declined in the self and fast gait tasks equally. However, the fact that the fast walk was somewhat more affected could imply that the mechanisms for control of self-paced and fast walk are different. As seen in chapter 3 with long term effects of DBS, the self-paced versus fast walk effects are significantly different.

Another explanation for non-axial improvement could be due to electrode placement within the STN. Physiological mapping of the movement-related neurons within the STN has been localized to the dorsal two-thirds of the STN. The specific

organization of the STN is complex and its physiology was not studied in the current study. However, the somatotopic organization of the STN implies precise electrode placement is important for proper response to STN-DBS. Granziera *et al.* (2008) found STN-DBS participants who developed gait difficulties immediately after surgery had improper electrode placement (Granziera *et al.*, 2008). Furthermore, the MLE may spread to surrounding STN regions, impairing function. The lenticular fasciculus is a tract which houses pedunculopallidal fibers that connects the GPi with the PPN (Devos, Defebvre, & Bordet, 2010). The PPN is important in the initiation and modulation of gait (Pahapill & Lozano., 2000). It has been postulated that the MLE occurring within the STN causes a reduction in STN hyperactivity, contributed to improvement in appendicular symptoms. However, if the MLE spreads or occurs outside the STN it may interfere with other brain regions. Spread to the pedunculopallidal fiber tract may interfere with PPN activity, resulting in abnormal gait performance.

The sustained rigidity and lower limb akinesia may have contributed to the worse performance in the FAST gait task (Chien *et al.*, 2006). The combination of reduced LED values and the unchanged appendicular symptoms immediately post-operation may have prevented the STN-DBS participants from walking at a FAST gait speed.

#### **2.4.3 Decline in global cognition: link to gait dysfunction**

Interestingly, immediately post-operation, global cognition significantly decreased as assessed by the MoCA test. This finding agrees with previous work showing cognitive decline up to 6 months post-operation (Kim *et al.*, 2013). Kim *et al.* (2013) conjecture that the decline up to 6 months post-operation is due to reduction of levodopa equivalent dose (LED) (Kim *et al.*, 2013). The current study found a cognitive decline occurring 1 week post-operation. At this time-point (V1) the LED values were 25% reduced from pre-operation levels (V0) and may contribute to the decline in cognition. Cools *et al.* (2002) showed that L-dopa ameliorates high-level cognitive deficits in individuals with PD by increasing blood flow to the pre-frontal cortex (Cools, Stefanova, Barker, Robbins, & Owen, 2002). A reduction in LED, although not significant, may explain the rapid decline in cognition immediately post-operation.

The decline in global cognition may also stem from the implantation of the electrodes. The trajectory of the electrode during surgery may be associated with decline in global cognition. Witt *et al.* (2013) found if the electrode passed through the caudate nucleus the individual experienced greater decline in global cognition (Witt *et al.*, 2013). The caudate nucleus is part of the cortical-sub-cortical loop system involved in aspects of executive functioning and working memory performance (Marklund *et al.*, 2009). The decline seen in the current study may be related to the trajectory of the electrodes which form the MLE. However, this is only theoretical as the trajectory of the electrodes was not measured in the current study.

Walking is considered a normal automatic task in younger individuals but the cognitive component of gait becomes more important with ageing. It is known that cognition and physical function decline is common in older individuals. Atrophy of the temporal lobe and prefrontal areas has been linked to gait and mobility deficits (Rosano, Aizenstein, Studenski, & Newman., 2007). Furthermore, global cognition and gait difficulty have been linked to atrophy of the corpus callosum (Ryberg *et al.*, 2007). While atrophy of various brain regions is not a surgical side effect, it is important to understand that global cognition and motor function are linked. This study has shown that post-operatively, global cognition declined immediately following surgery and this may have played a role in the poor performance on the fast walking task.

#### **2.4.4 Other clinical scales**

The significant improvement on the FOG-Q and ABC scale may stem from a surgery-related placebo-effect as described by several groups (Granziera *et al.*, 2008; Rodriguez-Oroz., 2005). A recent report by de la Fuente-Fernandez (2004) suggested the improvement immediately post-operation may be due to a placebo effect in which participants assume they will get better immediately following the surgery (de la Fuente-Fernández., 2004). This placebo effect has been reported to having a magnitude of around 40% (de la Fuente-Fernández., 2004). It is interesting that the subjective rating scales showed improvement, while the objective measures showed no improvement. Furthermore, in order to control for a potential placebo-effect, all study participants in the

study were pre-informed that the stimulation would remain OFF until two weeks post-operation. Under these conditions, the influence of the placebo effect should be minimized substantially during the evaluation of the MLE. If correct assessment of the true placebo effect were to be conducted, a sham DBS operation would be required. This type of operation would not be approved for ethical reasons.

Notwithstanding the above mentioned placebo-effect, the improvement on the clinical scales may suggest that the objective kinematic technology does not provide all the information required for clinical improvement. This finding suggests having a subjective input from the participant, in conjunction with the objective kinematic technology, may be more beneficial than relying on the technology alone.

#### **2.4.5 Limitations**

The current study has several limitations that should be addressed. The most significant limitation is that with few subjects, there might not have been power to detect true differences that might have occurred. The current study was unable to replicate findings that generally arise owing to MLE on appendicular symptoms, which could be due to insufficient power. Furthermore, recruiting more participants into the study would allow the division of participants into MLE gradient groups. It is known that the MLE may be greater in some individuals while less extensive in others. Tykocki *et al.* (2012) used the distribution of the MLE results to determine cut off points to separate each participant into low, medium and high response to the MLE (Tykocki et al., 2013). Thus, the non-significant results in this study may stem from the grouping of participants. Separating STN-DBS participants into gradients of MLE would allow for a more detailed review.

Another limitation is the lack of imaging to obtain the placement of the electrodes within the STN. Obtaining proper localization of the DBS lead within the STN would help to further elucidate the mechanism of the MLE. Subsequently, imaging the MLE would allow a better understanding of the mechanism. However, as discussed above, it is currently not possible to obtain proper MRI scans on implanted patients due to safety reasons.

The baseline used in the current study may have imposed a limitation as well. The baseline was conducted within 2 weeks before the surgery. However, an inclusion criterion for DBS surgery is an increase in negative side effects of PD medications. PD participants may therefore be on lower medication dosages and thus the baseline may not be their best optimized medication state.

Medication induced dyskinesias may hinder the gait results during the ON state assessments. Moreover, at the baseline visit patients are asked to come into the research laboratory about 1 hour after taking their medications - clinically defined as their “ON” state. However, patients undergoing DBS surgery tend to experience LIDs and the onset of dyskinesias may hinder the gait data. The dyskinesia is a result of medication and not the disease. The reduction in medication from baseline to 1 week post-operation may have impeded the effects expected from the MLE. There was a 25% reduction in medication from V0 to V1, which may have masked the MLE effects and contributed to the non-significant findings. Future studies should keep medication consistent when examining the MLE.

Corrections for multiple comparisons were conducted to attempt to correct for multiple comparisons. Corrections were made by dividing the p-value by the number of gait parameters within each gait feature. However, a stringent correction may support a Type II error (giving a “false negative” result). These corrections were done to decrease the risk of a type 1 error, despite this research having exploratory components.

#### **2.4.6 Strengths/Implications**

The current study was the first to quantitatively and objectively examine the response of axial gait features to the MLE. This method of analysis allows for a much more detailed review of the specific gait features and parameters that may respond to the MLE. Furthermore, the current study examined participants at two different time-points following surgery. This allowed a better examination of the pattern of the MLE. Previous studies chose only one time point for the MLE analysis, which does not provide enough detail to assess the MLE. Furthermore, past studies examined the MLE while the DBS

device was turned on. This may have caused a false positive result in the previous research.

Proper assessment of the MLE may allow it to be used as a predictive factor for STN-DBS efficacy. Several studies have suggested using the MLE to predict outcome from STN-DBS (Maltête et al., 2008; Tykocki et al., 2013). However, the current findings do not support this notion as no significant result was found.

## **2.5 Conclusion**

In summary, there was no improvement in appendicular or axial gait parameters in response to the MLE. The current study had few participants and a true effect may not have been found due to the underpowered study. On the walking tasks the STN-DBS participants were able to maintain performance at a preferred pace but performed significantly worse at a fast pace immediately after surgery. The poorer performance on the FAST gait speed task may be due to the reduction in global cognition and maintained bradykinesia. This study is the first to demonstrate that the MLE may not produce an improvement in appendicular or axial symptoms. The MLE must occur in every surgery due to the insertion of a foreign object into brain tissue, causing edema. However, the MLE is an ephemeral phenomenon and may not play a role in improving axial features post-operation. Any improvement found may be due to a post-operative placebo effect. The current research approach should be applied to a larger population to explore the MLE with greater power.

## 2.6 References

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### **3. Long-term STN-DBS and the response of axial gait features.**

#### **3.1 Introduction**

Gait difficulties are reported to be one of the most common and severe symptoms experienced by individuals with PD (Hammarlund, Andersson, Andersson, Nilsson, & Hagell., 2014; Kelly et al., 2010). As the pathology progresses gait impairments worsen and lead to increased risk of falling, reduced independence, and are directly related to a decline in the individuals' quality of life (Forsaa, Larsen, Wentzel-Larsen, Herlofson, & Alves., 2008). Gait in PD is characterized by impairments in several axial gait parameters such as shorter step lengths, shorter stride lengths, lowered walking speed and the tendency toward a longer duration in double-support time when compared with controls (Morris et al., 1994; Sofuwa et al., 2005). Furthermore, it is well established that PD is a unilateral disorder, which contributes directly to increased variability and asymmetry in PD gait patterns (Marinus & van Hilten., 2015).

Despite the development of many pharmaceutical treatments for PD, levodopa remains the most effective medication. However, prolonged use of levodopa results in motor fluctuations and levodopa induced dyskinesias (LIDs) which reduce the quality of life in PD. Furthermore, gait dysfunction seems to be unresponsive to these medications and worsens as the disease progresses. As an alternative, high frequency DBS of the STN is a current intervention being implemented in individuals with PD who are no longer seeing benefits from their current pharmacotherapy. STN-DBS has proven to be effective at alleviating various appendicular PD symptoms such as tremor, bradykinesia, dyskinesia and rigidity. Following STN-DBS most patients require significantly less pharmaceuticals and thus significantly reduced motor fluctuations, contributing to an increase in the quality of life.

Current literature provides conflicting reports on the response of gait to STN-DBS. While some research groups have provided data documenting an improvement in gait with long term STN-DBS (Krack et al., 2003; Piboolnurak et al., 2007; Zibetti et al., 2011), others have shown a continued worsening of gait (Janssen et al., 2014; Kelly et al., 2010). This conflicting data on gait may stem from differing gait analysis methods. Currently, the UPDRS is used to track the response of motor symptoms to STN-DBS intervention. The UPDRS is a standardized test used for monitoring and measuring global body functioning in PD. Part III of the UPDRS is used to assess the motor performance of PD: normal (0), mild (1), moderate (2), severe (3) and unable to perform task (4) (Goetz et al., 2008). The low resolution and subjective nature of this rating scale may hinder the evaluation of the effectiveness of STN-DBS in PD. Furthermore, there is only one item (item 29) on the UPDRS that relates specifically to gait: in UPDRS part III, an overall score is given to rate the participant's gait performance. The UPDRS provides an overview of motor disability, but is limited in its quantitative and objective assessments of motor impairments (Tavares et al., 2005). In order to track the changes in the gait features that are affected in PD, the current study employed a more objective and quantitative assessment tool (Tavares et al., 2005).

The PKMAS system was used to extract important gait parameters from PD individuals during above ground varied gait speed walking tasks. The system provides a large set of parameters that will be grouped and analyzed according to a well published gait feature model (Galna et al., 2015; Galna et al., 2013; Lord et al., 2013). Lord *et al.* (2013) published a principle component analysis, which grouped 16 gait parameters into five general features of gait: pace, rhythm, asymmetry, variability and postural control.

The current chapter examines the change in gait parameters, between levodopa and STN-DBS treatment conditions, on varied gait speed tasks. It is hypothesized that gait function is predominantly regulated by non-dopaminergic systems. Thus it is predicted that the gait features will continue to worsen following STN-DBS in both walking conditions. This study will provide, for the first time, a quantitative and objective assessment of the specific gait feature changes affected by long-term STN-DBS

stimulation in individuals diagnosed with PD. This quantification will shed light on the features of gait that continue to worsen following implantation.

## **3.2 Methods**

### **3.2.1 Participants**

The same PD participants were used in the ensuing chapter as in Chapter 2. The PD participants had all been diagnosed previously by a movement disorder neurologist, and were recruited from the Movement Disorder Clinic at Western University Hospital in London, Ontario, Canada. PD inclusion criteria comprised (1) Diagnosis of idiopathic PD; (2) approved for implantation of bilateral STN-DBS stimulating electrodes; (3) cognitively stable (assessed with Mini-Mental State Exam [MMSE]); (4) sufficient knowledge of the English language.

Control participants were healthy and age-matched to the PD participants. They were recruited from the general public. Control inclusion criteria comprised (1) between ages of 50-70 years ; (2) ability to walk without gait aid (e.g. cane or walker). Exclusion criteria for all participants included (1) any neurological disorder with residual motor deficits; (2) history of limb/joint damage, or hip/knee replacements that may affect gait performance. All PD participants were enrolled prior to their DBS surgery, allowing pre-assessment before implantation. Human Subjects Research Ethics Board (HSREB) (Western University Ethics [WUE] [# 103928]) approved the study. All participants provided informed consent.

**Table 3-1.** Participant demographics for study. Controls compared with STN-DBS participants on various demographics.

	Participant Groups		
	Control ( <i>n</i> =11)	STN-DBS ( <i>n</i> =10)	P <sub>1</sub> value
Age (yrs)	63.72 (±5.52)	63.91 (±5.65)	.944
Females, <i>n</i> (%)	7 (63%)	4 (40%)	.302
PD Duration (yrs)	—	10.61 (±3.30)	—
LED (Pre-op) (mg/day)	—	1374.13 (±477.34)	—
LED (6 months post-op) (mg/day)	—	414.75 (±248.26)	—
UPDRS ON score (Pre-op)	—	22.10 (± 14.08)	—
UPDRS ON score (6 months post-op)	—	11.25 (± 4.08)	—

SD, standard deviation; LED, levodopa equivalency dosage; p-value corresponds to independent samples t-tests for differences between controls and PD participants; significance was set to  $p < .05$ ; Calculation for LED was based on a standardized formula from literature by Tomlinson *et al.* (2010) (Tomlinson *et al.*, 2010); means are displayed with standard deviation in brackets.

### **3.2.2 Clinical outcomes and gait assessment**

The same standardized questionnaires and clinical scales that were used in Chapter 2 were used in the current chapter (see Table 2-1.). Gait assessments were conducted in the same manner as Chapter 2 (see section 2.2.4.). The same gait parameters were collected based on the previously mentioned gait model (see Table 2-2.). Gait parameters are expressed as mean values. Variability is calculated by calculating the mean of the standard deviation between the left and right steps. The asymmetry is calculated by taking the absolute difference between the left and right steps.

### **3.2.3 Calculation of total electrical energy delivered**

A major determinant of tissue stimulation by the DBS lead is the electrode impedance. The impedance is the opposition to current flow, effectively the ratio of current delivered for a given voltage, measured in ohms. A main characteristic of impedance is that it is assessed at a specified frequency, e.g. 1kHz or some other frequency (a sine wave of voltage is used for the test). This distinguishes it from resistance, which is the ratio of constant current delivered for a constant voltage. Higher impedance signifies a lower therapeutic efficacy due to lower current being delivered to brain tissue. Impedance is

modified in two ways: 1) foreign body encapsulation around the electrode 2) electrical properties of brain tissue (grey and white matter) (Satzer, Maurer, Lanctin, Guan, & Abosch., 2014). With regards to the operation the impedance would also inform the programmer that the electrodes and leads are intact. Infinite impedance indicates the lead is broken. Therefore, impedance measurements were also used in the selection process of optimal contact points for current delivery.

The various combinations of settings on the DBS device make comparisons between STN-DBS participants challenging. The total electrical energy delivered (TEED) value provides a standardized output measure which allows comparisons to be made between patients. TEED was calculated by using the programmed DBS parameters (voltage, frequency and pulse width) along with the measured system impedance. Koss *et al.* (2005) present the formula which had been derived from equations of basic electronics (Koss et al., 2005).

$$\text{TEED} = \frac{V^2 \cdot pw \cdot f}{R} \quad (1s)$$

Where  $V$  is the voltage (volts),  $pw$  is the pulse width ( $\mu s$ ),  $f$  is the frequency (Hz) and  $R$  is the impedance ( $\Omega$ ). Based on this formula the output measure estimates the total energy being delivered by the stimulator ( $\mu J$ ).

### **3.2.4 Experimental Timeline**

The timeline used in the current chapter was also used in Chapter 2. Chapter 3 examines the other visits not explored in chapter 2 (V0-V8). Briefly, the PD participants came to the facility 1 week pre-operation, 1 week post-operation, 2 weeks post-operation and then up to 6 months post-operatively (see Table 2-3.). The pre-operation time point was defined as the date where the PD participants have reached their best clinically optimized medication dosages, which optimally alleviated their symptoms. This optimized time point required PD participants to be on a stable dosage of medications, without any change in the past year. This optimized dosage was assessed and quantified by a trained movement disorder neurologist. Participants were brought into the research facility one week pre-operatively to collect a baseline measure of their ON medication

state. The 6 month post-operation time point was defined as the date where the PD participants experienced their best clinically optimized DBS stimulator settings, which optimally alleviated their symptoms determined by a trained movement disorder neurologist.

### **3.2.5 Data Analysis**

Demographic and clinical characteristics were summarized using means and standard deviations. Between-group demographic comparisons were made with independent-samples t-tests. Descriptive statistics were calculated for the spatiotemporal gait parameters based on the raw scores exported from the PKMAS software system. Gait parameters were expressed as (a) mean spatiotemporal characteristics, (b) step-to-step variability (calculated by combining the average of left and right standard deviations) and (c) asymmetry (calculated by finding the absolute difference between left and right steps on each parameter). No extreme outliers were found in the data, assessed using boxplots. All data met Shapiro-Wilks test for normality and parametric paired-samples t-tests were used to compare baseline values to 6 months post-operation. Furthermore, the independent samples t-test was used to compare the STN-DBS participants with control participants. Statistical significance was set at  $p < .05$  (two-sided). Corrections were made for multiple comparisons within each gait feature category (related gait parameters): two parameters in gait feature ( $p < .025$ ), three parameters in gait feature ( $p < .016$ ). A Pearson correlation was conducted to examine the relationship between the change in TEED and the change in gait parameters. It was thought that changes in gait parameters may stem from changing the TEED over the 6 month study. All statistical analyses were conducted using SPSS (v21.0, IBM Corporation, Chicago, IL).

## **3.3 Results**

### **3.3.1 Demographic and Clinical Assessments**

Twenty-one participants, 10 with bilateral STN-DBS (Age: 63.9 ( $\pm 5.65$ ), Females: 4 (40%), PD duration: 10.6 ( $\pm 3.30$ )) and 11 age-matched healthy controls (Age: 63.72 ( $\pm 5.52$ ), Females: 7 (63%)), were included in the analysis.

Demographic and clinical characteristics are presented in Table 3-1. Compared with the control group, the STN-DBS participants were the same age and had proportionately equal number of males and females. Clinical assessments are presented in Table 3-2. The STN-DBS group had no significant change in the GDS, ABC or FOG-Q questionnaires between the pre-operative and 6 months post-operative visits. The ABC and GOD-Q scales measure axial improvement, this result is to be expected. The maintained GDS scale score is an interesting finding that was not expected and will be discussed further. Compared with the control group, the STN-DBS group scored worse on the GDS and ABC questionnaires' at pre-operation and 6 months post-operation. In the STN-DBS group there was no significant decrease in global cognition from pre-operation to 6 months post-operation. In the STN-DBS group, the UPDRS ON scores (see Table 3-3.) and LED (see Table 3-2.) significantly decreased from pre-operation to 6 months post-operation.

**Table 3-2.** Scores from the clinical rating scales and questionnaires. Scores are displayed for STN-DBS participants at the pre-operative and 6-months post-operation visits. Control participants are also displayed. Mean scores and standard deviations are shown.

Clinical Scales	Controls (n=11)	STN-DBS Participants					
		Baseline (n=10)	P <sub>1</sub> value	6 Months (n=10)	P <sub>2</sub> value	Change in Scores (n=10)	P <sub>3</sub> value
MoCA	27.20 (1.79)	26.70 (2.41)	.690	23.60 (6.09)	.111	- 3.10 (5.34)	.100
GDS	3.50 (2.65)	9.50 (7.57)	<b>.049</b>	11.8 (8.59)	<b>.018</b>	2.30 (6.83)	.156
ABC	96.25 (1.69)	63.25 (14.40)	<b>.000</b>	67.50 (20.45)	<b>.002</b>	4.25 (29.80)	.633
FOG-Q	—	12.00 (6.11)	—	6.90 (6.05)	—	- 5.10 (7.88)	.071
LED (mg/day)	—	1374.13 (477.34)	—	414.75 (248.27)	—	- 975.38 (498.79)	<b>.000</b>
TEED (μJ)	—	13.03 (11.53)*	—	90.31 (25.70)	—	77.28 (23.73)	<b>.000</b>

TEED, total electrical energy delivered; \*TEED baseline is from device turn on at 2 weeks post-operation (V2); p<sub>1</sub> represents the difference in the STN-DBS group from V0 to V8 using paired-samples t-tests; p<sub>2</sub> represents the difference between the STN-DBS group and the control group using independent-samples t-tests; TEED baseline is at V2 (device turn on); Significance was set to p = < .05; means are shown with standard deviation in brackets.

**Table 3-3.** UPDRS subscores divided into appendicular and axial ratings. Scores are displayed for STN-DBS participants at the pre-operative and 6-months post-operation visits. Mean scores and standard deviations are shown.

Clinical Scales	STN-DBS Participants			
	Baseline (n=10)	6 Months (n=10)	Change in Scores (n=10)	P <sub>1</sub> value
<b>UPDRS ON Total</b>	22.10 (14.08)	11.25 (4.29)	- 10.85 (12.84)	<b>.026</b>
<b>Appendicular Subscores</b>				
Rigidity (item 22)	4.95 (3.81)	1.75 (1.14)	- 3.20 (3.86)	<b>.028</b>
Upper Limb	3.05 (2.03)	0.70 (0.67)	-2.35 (1.97)	<b>.004</b>
Lower Limb	1.90 (2.07)	1.05 (0.80)	-0.85 (2.33)	.279
Akinesia (item 23-26)	8.05 (5.49)	4.55 (3.18)	- 3.5 (4.67)	<b>.042</b>
Upper Limb	5.5 (4.08)	3.45 (2.87)	2.05 (3.39)	.089
Lower Limb	2.55 (1.96)	1.10 (0.94)	1.45 (2.47)	.097
<b>Axial Subscores</b>				
Gait (item 29-30)	1.80 (1.39)	1.65 (0.57)	- 0.15 (1.56)	.812
Speech (item 18)	0.90 (1.26)	0.15 (0.24)	- 0.75 (1.25)	.104
Bradykinesia (item 31)	0.60 (1.07)	0.25 (0.42)	- 0.35 (1.29)	.458

UPDRS, Unified Parkinson's Disease Rating Scale; p<sub>1</sub> represents the UPDRS score difference, in the STN-DBS group, from baseline to 6 months post-operation using paired-samples t-tests; Significance was set to p = < .05; means are shown with standard deviation in brackets.

### **3.3.2 DBS stimulator settings**

The DBS stimulator was switched on at 2 weeks post-operation. All STN-DBS participants were set to the same initial DBS settings (1.5 volts, 90  $\mu$ s, 130 Hz). The DBS stimulator was set to a monopolar stimulation setting in two STN-DBS participants. All other STN-DBS participants were set to bipolar stimulation (see Table 3-4.). While the TEED values were different on either side, the values were not significantly higher on the left side compared with the right ( $p = .079$ ).

**Table 3-4.** Initial stimulator settings for each STN-DBS participant at 2 weeks post-operation. DBS settings include contacts used (C+ indicates pulse generator case as cathode), voltage (V), pulse width ( $\mu$ s) and frequency (Hz). Monopolar settings use C+ as a contact point, while bipolar settings do not.

<b>STN-DBS participants at device turn on</b>										
<b>Subjects</b>	<b>Left STN</b>					<b>Right STN</b>				
	<b>Contacts</b>	<b>V</b>	<b>PW</b>	<b>F</b>	<b>TEED</b>	<b>Contacts</b>	<b>V</b>	<b>PW</b>	<b>F</b>	<b>TEED</b>
DBS-01	C+2-	1.5	90	130	6.63	9+10-	1.5	90	130	4.08
DBS-02	1-2+	1.5	90	130	31.35	9-10+	1.5	90	130	17.84
DBS-03	2-3+	1.5	90	130	51.29	C+10-	1.5	90	130	23.54
DBS-04	1-3+	1.5	90	130	2.22	10-11+	1.5	90	130	5.01
DBS-05	C+2-	1.5	90	130	12.54	C+10-	1.5	90	130	12.51
DBS-06	1-3+	1.5	90	130	10.11	8-11+	1.5	90	130	6.99
DBS-08	C+10-	1.5	90	130	4.48	C+2-	1.5	90	130	5.07
DBS-09	1-2+	1.5	90	130	4.71	9-10+	1.5	90	130	3.31
DBS-11	1-2+	1.5	90	130	35.51	9-11+	1.5	90	130	10.98
DBS-12	1-2+	1.5	90	130	6.09	9-11+	1.5	90	130	6.31
<b>Average</b>		<b>1.5</b>	<b>90</b>	<b>130</b>	<b>16.49 (16.81)</b>		<b>1.5</b>	<b>90</b>	<b>130</b>	<b>9.57 (6.68)</b>

TEED, total electrical energy delivered measured in  $\mu$ s; V, voltage measured in volts; PW, pulse width measured in  $\mu$ s; F, frequency measured in Hz. Average = means of the values with standard deviation in brackets.

At 6 months post-operation, the two monopolar STN-DBS participants had only their right DBS lead switched to bipolar while the left remained monopolar (see Table 3-5.). Participant 3 had their left STN bipolar contact locations changed as well. The changes occurred due to insufficient symptom improvement at the monopolar setting, assessed by a trained movement disorder neurologist. All STN-DBS participants received an increase in voltage over the 6 month period as a standard clinical practice in DBS stimulation. A registered movement disorder neurologist completed these changes in settings at scheduled clinic visits. The TEED values were not significantly higher on the left side compared with the right ( $p = .695$ ).

**Table 3-5.** Final stimulator settings for each STN-DBS participant at 6 months post-operation. DBS settings include contacts used (C+ indicates pulse generator case as cathode), voltage (V), pulse width ( $\mu$ s) and frequency (Hz). Monopolar settings use C+ as a contact point, while bipolar settings do not.

<b>STN-DBS participants at 6 months post-operation</b>										
<b>Subjects</b>	<b>Left STN</b>					<b>Right STN</b>				
	<b>Contacts</b>	<b>V</b>	<b>PW</b>	<b>F</b>	<b>TEED</b>	<b>Contacts</b>	<b>V</b>	<b>PW</b>	<b>F</b>	<b>TEED</b>
DBS-01	C+2-	3.9	90	100	91.02	9+10-	3.9	90	100	92.74
DBS-02	1-2+	3.8	90	100	103.81	9-10+	3.8	90	100	121.69
DBS-03	0-3+	3.6	90	130	107.89	9-11+	4.6	90	130	73.18
DBS-04	1-3+	3.4	90	130	50.58	10-11+	3.8	90	130	105.59
DBS-05	C+2-	4.0	90	130	154.97	8+11-	4.1	90	130	101.33
DBS-06	1-3+	2.5	90	130	50.40	8-11+	2.5	90	130	34.59
DBS-08	C+10-	3.0	90	130	80.69	C+2-	2.7	90	130	68.34
DBS-09	1-2+	3.0	90	130	63.13	9-10+	3.4	90	130	69.32
DBS-11	1-2+	3.5	90	130	132.95	9-11+	3.9	90	130	92.64
DBS-12	1-2+	3.0	90	120	89.39	9-11+	3.5	90	120	121.98
<b>Average</b>		<b>3.37</b>	<b>90</b>	<b>123</b>	<b>92.48 (34.07)</b>		<b>3.62</b>	<b>90</b>	<b>123</b>	<b>88.14 (27.14)</b>

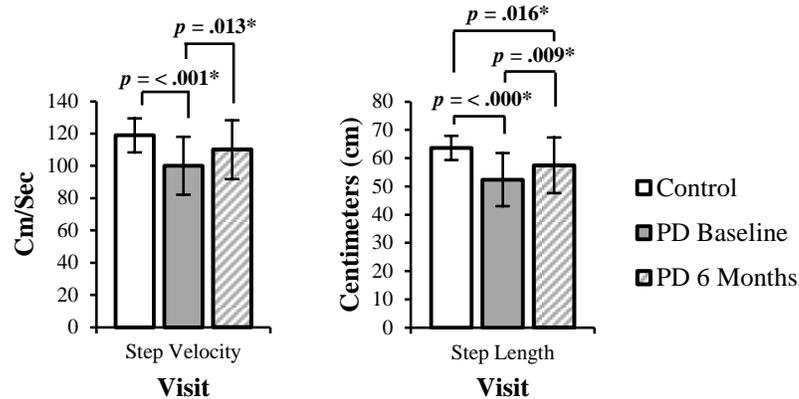
TEED, total electrical energy delivered measured in  $\mu$ s; V, voltage measured in volts; PW, pulse width measured in  $\mu$ s; F, frequency measured in Hz. Average = means of the values with standard deviation in brackets.

### **3.3.3 Difference in gait parameters in the normal walk (SELF)**

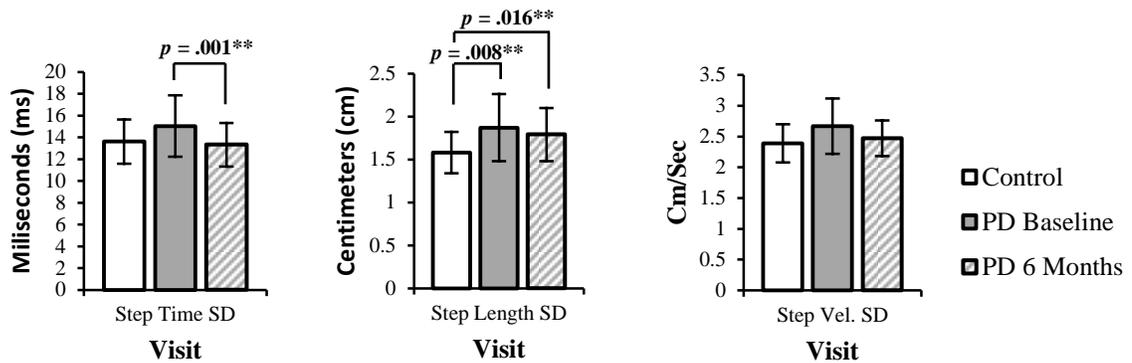
When compared with the control group at pre-operation, the STN-DBS showed impairment in 6 out of the 16 gait parameters related to pace (velocity and step length), variability (step length SD), asymmetry (step time and single support time) and postural control (step width SD) (see Figure 3-1. and Figure 3-2.). Rhythm remained the same across groups at pre-operation. Following 6 months of stimulation, the STN-DBS group only differed from the control group on 3 parameters related to pace (step length), variability (step length SD) and asymmetry (step time). Two parameters, rhythm and postural control, remained unchanged across groups 6 months post-operation.

Within the STN-DBS group there was improvement in 4 parameters associated with pace (velocity and step length), variability (step time SD) and postural control (double support time). Two parameters, rhythm and asymmetry, remained unchanged within the STN-DBS group 6 months post-operation.

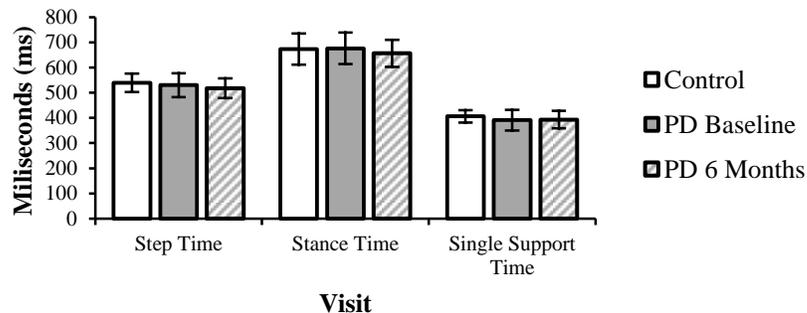
## Pace Feature



## Variability Feature

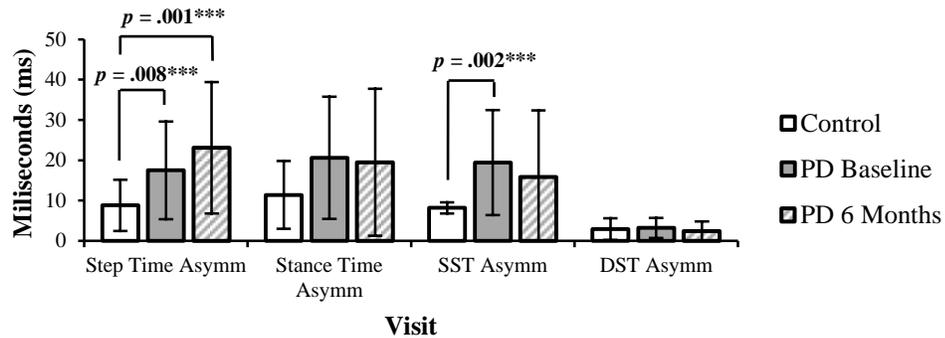


## Rhythm Feature

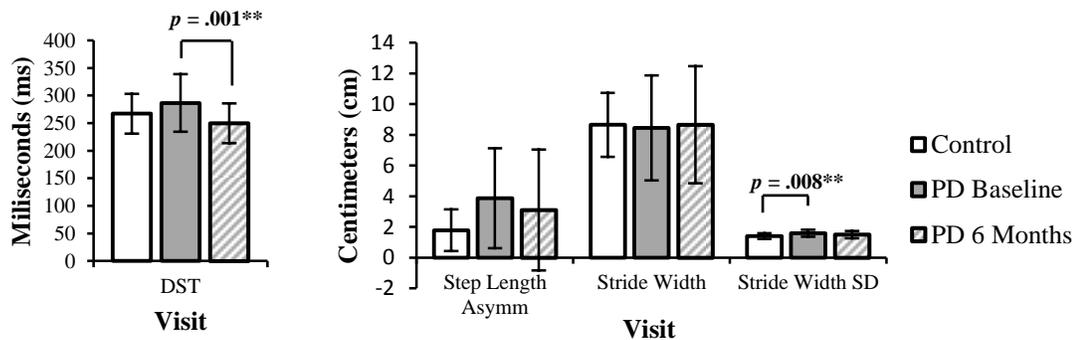


**Figure 3-1. Gait features pace, variability, rhythm and the respective gait parameter outcomes pre-operation and 6 months post-operation on the SELF gait task.** The difference between controls and the PD group was assessed using independent-samples t-tests. The difference within the PD group from baseline to 6 months of STN-DBS stimulation was assessed using a paired-samples t-test. Corrections for multiple comparisons were conducted by dividing the p-value by the number of parameters in each feature: \* indicates  $p < .025$ , \*\* indicates  $p < .016$ . The mean values are displayed in the bar graph with standard deviation as the error bars.

## Asymmetry Feature



## Postural Control Feature



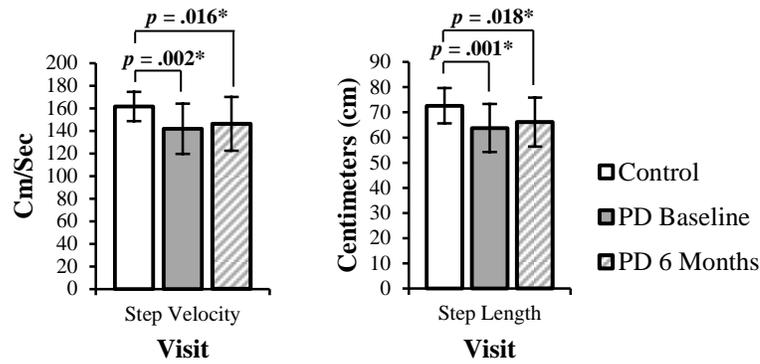
**Figure 3-2. Gait features asymmetry, postural control and the respective gait parameter outcomes pre-operation and 6 months post-operation on the SELF gait task.** The difference between controls and the PD group was assessed using independent-samples t-tests. The difference within the PD group from baseline to 6 months of STN-DBS stimulation was assessed using a paired-samples t-test. Corrections for multiple comparisons were conducted by dividing the p-value by the number of parameters in each feature: \*\* indicates  $p < .016$ , \*\*\* indicates  $p < .013$ . The mean values are displayed in the bar graph with standard deviation as the error bars.

### **3.3.4 Difference in gait parameters in the fast walk (FAST)**

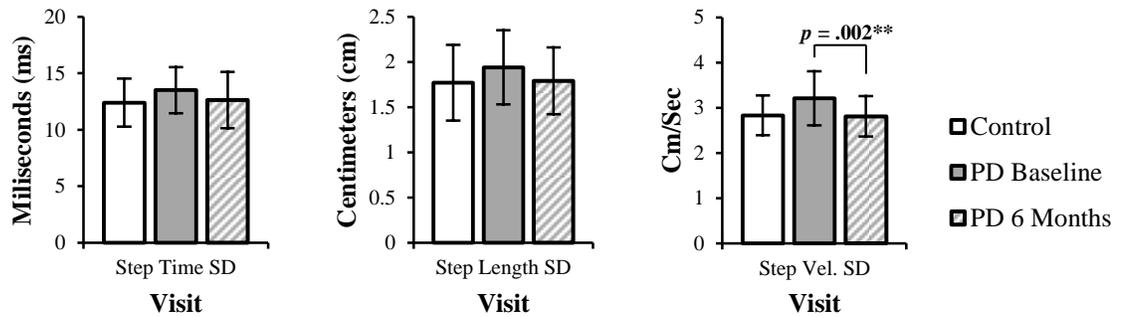
When compared with the control group at pre-operation, the STN-DBS showed impairment in 4 out of the 16 gait parameters related to pace (velocity and step length), asymmetry (stance time) and postural control (step length asymmetry) (see Figure 3-3. and Figure 3-4.). Variability and rhythm remained the same across groups at pre-operation. Following 6 months of stimulation, the STN-DBS group differed from the control group on 2 parameters related to pace (velocity and step length). All other parameters remained unchanged across groups following 6 months of STN-DBS intervention.

Within the STN-DBS group there was improvement in 2 parameters associated with variability (step velocity SD) and postural control (step length asymmetry). Pace, rhythm and asymmetry did not change between pre-operation and 6 months post-operation within the STN-DBS group.

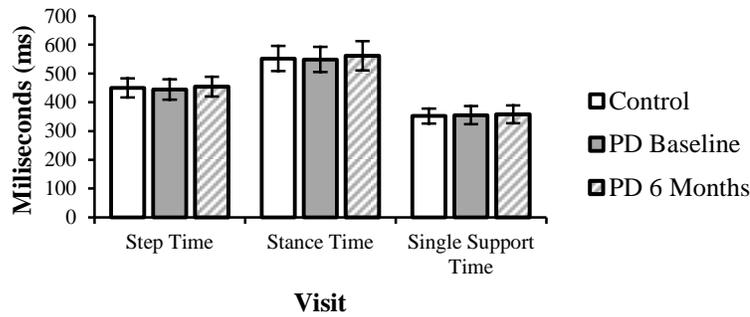
### Pace Feature



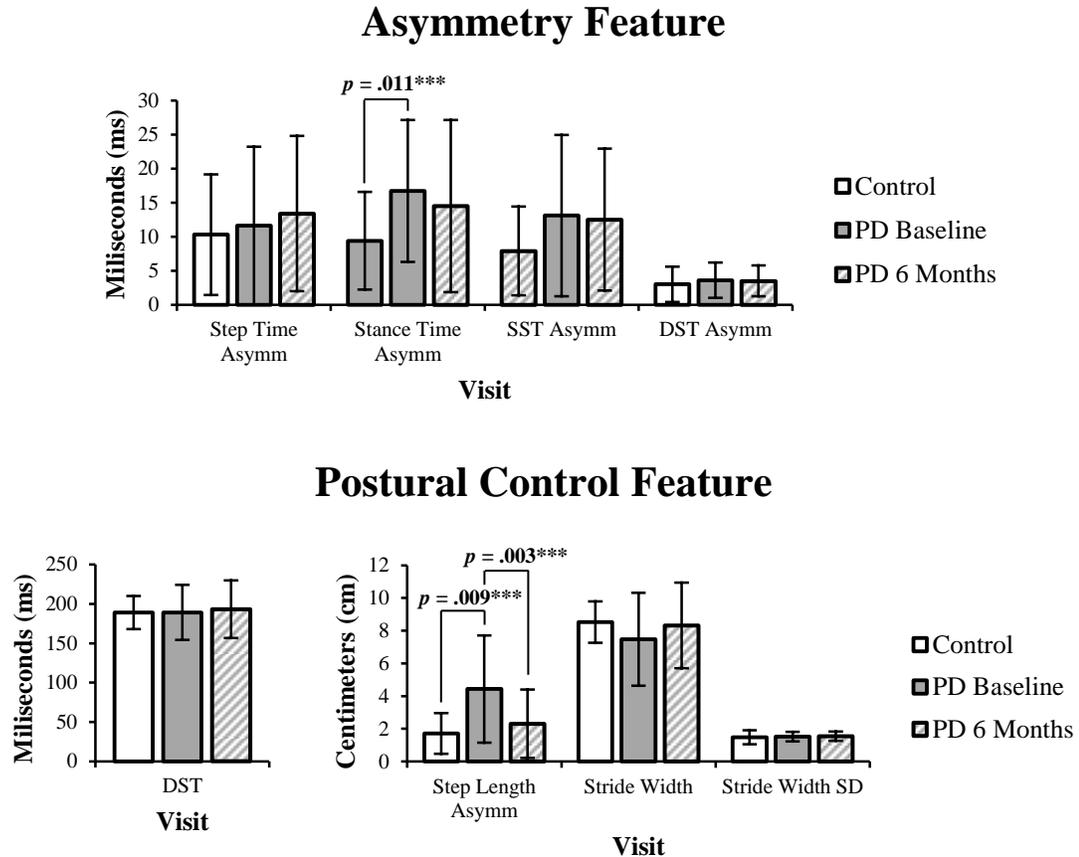
### Variability Feature



### Rhythm Feature



**Figure 3-3. Gait features pace, variability, rhythm and the respective gait parameter outcomes pre-operation and 6 months post-operation on the FAST gait task.** The difference between controls and the PD group was assessed using independent-samples t-tests. The difference within the PD group from baseline to 6 months of STN-DBS stimulation was assessed using a paired-samples t-test. Corrections for multiple comparisons were conducted by dividing the p-value by the number of parameters in each feature: \* indicates  $p < .025$ , \*\* indicates  $p < .016$ . The mean values are displayed in the bar graph with standard deviation as the error bars.



**Figure 3-4. Gait features asymmetry, postural control and the respective gait parameter outcomes pre-operation and 6 months post-operation on the FAST gait task.** The difference between controls and the PD group was assessed using independent-samples t-tests. The difference within the PD group from baseline to 6 months of STN-DBS stimulation was assessed using a paired-samples t-test. Corrections for multiple comparisons were conducted by dividing the p-value by the number of parameters in each feature: \*\*\* indicates  $p < .013$ . The mean values are displayed in the bar graph with standard deviation as the error bars.

### 3.3.5 Correlation of TEED values to gait parameter changes

The correlation of TEED to the gait parameters signified which parameters were related to the increase in TEED (see Table 3-6.). It was found that in the SELF walking task all parameters that were significantly improved after 6 months of STN-DBS stimulation were correlated with an increase in TEED. In the FAST walking task only step length asymmetry was correlated with an increase in TEED. With a decreased LED it seems that a higher TEED value is positively correlated with an improvement in pace for SELF walking and postural control in FAST walking.

**Table 3-6.** Correlation between the change in gait parameters and the change in TEED values. Change in parameters were measured in SELF and FAST gait speed tasks.

Gait Feature/Parameter	STN-DBS Participants			
	Change in SELF ( <i>n</i> =10)	Correlation with change in TEED <i>r</i> ( <i>p</i> <sub>1</sub> )	Change in FAST ( <i>n</i> =10)	Correlation with change in TEED <i>r</i> ( <i>p</i> <sub>2</sub> )
<b>Pace</b>				
Step Velocity (cm/sec)	10.02 (16.49)	-.571 (.009)*	4.48 (13.46)	-.407 (.075)
Step Length (cm)	5.09 (7.87)	.509 (.022)*	2.41 (8.19)	.222 (.346)
<b>Variability</b>				
Step Time SD (ms)	- 1.71 (1.9)	-.411 (.072)	- 0.87 (2.60)	-.009 (.972)
Step Length SD (cm)	- 0.08 (0.38)	-.363 (.115)	- 0.15 (0.38)	-.383 (.095)
Step Vel. SD (cm/sec)	-0.20 (0.42)	.108 (.650)	- 0.39 (0.49)	-.242 (.304)
<b>Rhythm</b>				
Step Time (ms)	- 12.60 (51.05)	.366 (.113)	10.5 (44.50)	.305 (.191)
Stance Time (ms)	- 20.10 (59.22)	.253 (.282)	12.95 (40.00)	.208 (.379)
SST (ms)	2.00 (45.83)	.444 (.050)	3.00 (45.70)	.168 (.479)
<b>Asymmetry</b>				
Step Time Asymm (ms)	8.0 (15.05)	-.355 (.124)	0.90 (11.65)	-.075 (.754)
Stance Time Asymm (ms)	- 1.15 (22.57)	-.393 (.086)	2.20 (13.22)	-.032 (.894)
SST Asymm (ms)	- 3.50 (17.78)	-.264 (.261)	- 0.60 (11.80)	-.160 (.499)
DST Asymm (ms)	- 0.80 (3.71)	.087 (.724)	- 0.10 (3.83)	-.060 (.802)
<b>Postural Control</b>				
Step Length Asymm (cm)	-0.76 (3.28)	.486 (.030)	- 2.13 (2.78)	.550 (.012)***
Stride Width (cm)	0.21 (3.31)	-.455 (.044)	0.85 (2.24)	-.476 (.034)
DST (ms)	- 36.6 (41.57)	-.539 (.013)***	4.1 (31.92)	-.261 (.266)
Stride Width SD (cm)	-0.09 (.24)	-.017 (.945)	0.02 (0.41)	-.008 (.973)

SST, single support time; DST, double support time; *p*<sub>1</sub> represents the correlation between the change in SELF gait parameters and the change in TEED values using a bivariate Pearson correlation; *p*<sub>2</sub> represents the correlation between the change in FAST gait parameters and the change in TEED values using a bivariate Pearson correlation; corrections for multiple comparisons: \* indicates *p*< .025, \*\*\* indicates *p*< .013; means are shown with standard deviation in brackets for change values.

### 3.4 Discussion

In the present study, the aim was to determine the change in gait features following STN-DBS intervention in PD. It was hypothesized that axial gait function is controlled predominately by a non-dopaminergic system. Thus it was predicted that STN-DBS, acting through the BG dopaminergic system, would not improve gait features following 6 months of stimulation. Furthermore, it was also predicted that appendicular symptoms would improve significantly and would continue to stay improved. This is the first study, to our knowledge, to examine extensive gait parameters in individuals with PD undergoing STN-DBS stimulation. The results show little improvement in axial gait function following intervention with STN-DBS regardless of walking task. While the study may have been underpowered, the results support the differences between the axial versus the appendicular control of movement that contributes to gait dysfunction in PD.

In the next few sections appendicular and axial PD symptoms outcome will be discussed. The discussion will first examine PD participant performance with the performance of the controls, developing an understanding of the impaired features in the PD population. The discussion will shift toward axial gait outcome following 6 months of STN-DBS in both a preferred walking speed and fast walking speed task. Finally, improvements in non-motor features of the STN-DBS population were found and will be discussed. The discussion begins with defining the two time-points studied in the current paper.

#### **3.4.1 Defining time points: optimized medication vs. optimized STN-DBS**

In order to examine the main question stated above, STN-DBS participants were assessed in the pre-operative and longer term (6 month) period. The 6 month time period was chosen based on previous literature, which demonstrates a significant improvement in DBS motor symptoms at this time point (Niu et al., 2012; Weaver et al., 2009). Anderson *et al.* (2006) studied 96 STN-DBS participants for the maximal improvement in UPDRS off medication/STN-DBS versus on medication states/STN-DBS. This group explored 6 months and 12 months post-operation. They found that 6 months produced a 50% improvement in UPDRS scores between OFF and ON states. At 12 months post-

operation there was a 48% improvement in the UPDRS scores between OFF and On states.

Prior to the surgery each PD participant had been treated with pharmacotherapies for several years. The pre-operative time point was considered to be the PD participants' stabilized medication state to control his or her symptoms. The trained movement disorder neurologist assessed this optimized dosage of dopaminergic medication. The MLE was examined at immediate post-operative period when the patients were on all the medications that they were taking pre-operatively and the DBS device had not been turned on. This effect was discussed in chapter 2. Following 6 months of STN-DBS device titration, by the same trained movement disorder neurologist, the STN-DBS participants are at a clinically stabilized setting on their device based on their symptoms. At this time point dopaminergic medications have been reduced and some participants were off all medications. It should be mentioned that the reduction in medication is a requirement when increasing the stimulator and it is recognized to be a confounding variable.

#### **3.4.2 Between group gait impairments: control compared with PD ON medication**

Overall, PD participants ON medication had a significant amount of axial gait impairments, compared with controls, at the SELF walking speed pre-operation. Specifically, PD participants had significantly worse pace, variability, asymmetry and postural control compared to controls. These findings are in agreement with previous literature that demonstrates PD participants have significantly worse pace (Hass et al., 2012; Vokaer, Azar, & de Beyl., 2003), variability (Baltadjieva, Giladi, Gruendlinger, Peretz, & Hausdorff, 2006), and asymmetry (Yogev, Plotnik, Peretz, Giladi, & Hausdorff, 2007) in the medication state at the SELF gait speed task when compared with controls. The recruited PD participants had an average disease duration of 10 years, which is when axial symptoms become the dominant symptom (Hely, Morris, Reid, & Trafficante, 2005).

A few parameters maintained impairment in the PD group, when compared with controls, regardless of the gait speed in the ON medication pre-operation state. These

parameters were velocity and step length. The reduction in step length and velocity in PD participants ON medication, compared with controls has been well established in the literature (Hass et al., 2012; Morris, Iannsek, Matyas, & Summers., 1996; O'Shea, Morris, & Iannsek., 2002). Morris *et al.* (1996) postulated that the step length is directly related to the reduction in gait velocity (Morris et al., 1996). Thus, when velocity is significantly decreased it is expected that step length will also be reduced. Interestingly it was found that step length variability was significantly impaired at the SELF walking speed task, but improved when PD participants walked at their FAST gait speed. While the mechanism for this improvement is not understood fully, it matched previous findings in literature (Vieregge, Stolze, Klein, & Heberlein., 1997). The improvement in asymmetry when PD participants walked at FAST compared with SELF has been reported in literature (Yogev et al., 2007). Axial gait impairments continue to persist even when ON medication. Interestingly, the results suggest that at higher gait speeds some gait parameters are improved, compared to controls, ON medication. However, this may not be an actual improvement since this increased speed for example may actually represent tachykinesia, which increases fall risk.

The exact underpinning of gait parameter impairment during medication state is not known, but various explanations have been postulated. The BG is important for the planning and execution of self-initiated movements (Boecker, Jankowski, Ditter, & Scheef., 2008). The supplementary motor area (SMA) stores learned motor sequences (such as walking) for execution when needed (Grafton, Woods, & Tyszka., 1994; Tanji & Shima., 1994). A recent study by Wu *et al.* (2011) found there is a reduced functional connectivity between the BG and SMA during performance of self-initiated tasks in PD participants (Wu et al., 2011). This reduced connectivity may play a role in the increase in variability and the impairment in pace. The increase in asymmetry in PD gait has been associated with an asymmetric activation of the SMA during walking (Shibasaki, Fukuyama, & Hanakawa., 2004). In this scenario, the role of dopamine is largely unknown and may include mechanisms of even attentional regulation.

### **3.4.3 Between group gait impairments: control compared with ON STN-DBS state**

In general, it was found that there were significant gait impairments in the STN-DBS group compared with controls. At the SELF gait speed, PD participants showed impairment in pace, variability and asymmetry. These impairments closely match those of the medication state.

As with the medication state, STN-DBS participants showed improvement in gait parameters when walking at their FAST gait speed, when compared with controls. The impairment in step length, regardless of gait speed task, has been documented previously in literature following STN-DBS operation (Rocchi et al., 2012). Overall, STN-DBS state showed slight impairment when compared with controls.

It is conceivable to conjecture that slow walking is a combination of appendicular and axial control systems and hence the effects of disease are manifested most when the speed is self-paced and thus slower. Following STN-DBS, the appendicular symptoms, although improved may not be able to sufficiently mask the effects of poorer axial symptom improvements. Hence the differences between controls, PD and post-DBS are most visible at this self-paced walking speed. At faster gait speeds the participants would have less time to make limb movement changes and their body inertia would be much greater (McGeer., 1993). In this state it may be that the PD individuals “lock” their trunk muscles, allowing the appendicular features to control the walking. However, this is only conjecture to explain the finding that fast gait did not differ significantly when compared with controls is interesting.

### **3.4.4 Within group gait impairments: medication state compared with STN-DBS state**

In general, STN-DBS provided an improvement in 4 of the 16 gait parameters associated with pace, variability and postural control when compared with medication state at the SELF gait speed. Interestingly, there were fewer axial gait parameter improvements in the FAST gait speed task compared to the SELF gait speed task. This would fit the hypothesis that the main improvements are appendicular and hence the gait

improvements are not due to the contributions of the improvement in axial symptom complex.

The main finding was that following 6 months of STN-DBS surgery, PD participants were able to walk faster than in the medication state on the SELF gait walking task. The improvement found in step velocity and step length, between medication and STN-DBS state, matches a previous study that showed this relationship in the SELF gait speed task (Lubik et al., 2006; Stolze et al., 2001). Interestingly it was found that this improvement in step velocity and step length was correlated with an increase in TEED (see Table 3-6.).

The finding that stride velocity and step length remained unchanged between medication state and STN-DBS state at FAST gait speed is novel. The inability of PD participants to receive similar improvement in the FAST gait speed task may be a result of unchanged body bradykinesia. As reported from the UPDRS, body bradykinesia and axial signs overall remained unchanged following 6 months of STN-DBS. Chien *et al.* (2006) found that various gait features (step velocity and step length) are accurate at measuring bradykinesia. Furthermore, this group found that PD participants were impaired in the FAST walking condition due to bradykinesia (Chien et al., 2006).

A possible explanation for the maintained impairment in FAST walking could be due to SMA activity. Harada *et al.* (2009) found that SMA activity, in healthy individuals, tends to increase during faster walking tasks (Harada, Miyai, Suzuki, & Kubota., 2009). As discussed above, the SMA region connectivity decreases in PD. Furthermore, this decrease in activity is thought to play a role in akinesia (loss of voluntary movement) (Wu et al., 2011). Thus, an individual with PD may have an impaired FAST walk due, in part, to the reduction of SMA activity.

While there was improvement in a few gait parameters following 6 months of STN-DBS it is not enough to confirm STN-DBS maintains benefit in axial gait features. The small difference between medication state and DBS state on axial gait features has been documented in literature using the UPDRS (McNeely & Earhart., 2013). STN-DBS intervention was successful at improving overall UPDRS motor scores, which highly

reflect appendicular motor symptoms of PD (Geurts et al., 2011). The finding that STN-DBS improved more of the appendicular symptoms but failed to improve axial gait symptoms may imply that STN-DBS has a similar dopaminergic effect to PD medications. McNeely *et al.* (2013) demonstrated this relationship in 16 PD participants. This group found that levodopa and STN-DBS improved rigidity, bradykinesia and tremor in a similar manner. Most interestingly, this highlights the different control systems that may be involved in axial versus appendicular symptoms (McNeely & Earhart., 2013).

The finding that STN-DBS does not improve gait feature impairments following 6 months of STN-DBS contradicts previous studies that found general improvement after 6 months (Lilleeng, Gjerstad, Baardsen, Dalen, & Larsen., 2014). However, a direct comparison is difficult to make due to the nature of the assessment tool. The contradiction may stem from the quantitative and objective review of gait in the present study and especially separating the appendicular versus axial control.

#### **3.4.5 Non-axial STN-DBS improvements**

It should be noted that while STN-DBS may not significantly improve axial gait features in PD, other non-motor features improve. For instance, a recent study found that STN-DBS intervention improved life expectancy in individuals with PD compared with medication state (Ngoga et al., 2013). Other studies have found an improvement in appendicular motor features and LIDs (Harries et al., 2012; Krack et al., 2003). In alignment with these previous studies, the current study reported a significant decrease in LED values and a significant improvement in UPDRS scores.

Appendicular symptoms such as rigidity and akinesia were significantly improved following STN-DBS as reported by the UPDRS (see Table 3-7.). This finding confirms the influence STN-DBS has on the appendicular and thus possibly those symptoms that are controlled by the dopaminergic system, allowing replacement of pharmaceuticals with the stimulator. The ability of PD participants to have lowered LED means fewer consumption of pills, a reduction in motor side effects and an improved quality of life. Since the majority of axial gait parameters did not improve compared to the optimized

medication state, other stimulation targets may be considered for proper targeting of the axial symptoms.

### **3.4.6 Limitations**

There are several limitations to the study that should be addressed. From the outset the study had a relatively small sample size and may have been underpowered. While it was not significant, the control participant group contained more females when compared to the STN-DBS participant group. The majority of studies find that men exhibit greater gait speed and stride lengths than females (Callisaya, Blizzard, Schmidt, McGinley, & Srikanth., 2010; Hollman et al., 2011). Therefore, when comparing the between groups it may appear that the STN-DBS participant group was performing better than they actually were on a few gait parameter measurements. If an exact equal number of males and females were used there may have been more parameters that are affected in the PD group compared with the controls. However, the size of the participant group did not lend itself to a study of the influence of gender factors.

The environment in which the tasks were conducted may have introduced a Hawthorne effect in our participant population. This effect is generally thought of as a modification or improvement in an individual's behavior in response to their awareness of being observed. The research area used was contrived and may not have captured the true gait impairments within the PD group within a natural setting. A recent study by Robles-Garcia *et al.* (2015) found that when PD participants were aware they were being tested they changed their walking strategy (Robles-García et al., 2015). Implementing a testing regime that incorporates a more "covert" testing period would be beneficial in examining gait patterns of the PD population over time.

Participants were told to withhold their medication during testing periods post-operation, but were not tested completely "off" medication. Participants were informed to not take their morning medications, which provided about 8-10 hours of OFF medication. However, following surgery the STN-DBS participants had reduced their medication and most participants were completely off medication 3 months post-operation. The reduction

in medication may have been produced a confounding result, as patient's may have suffered from drug withdrawal.

Repeating testing for 6 months may have introduced a learning effect, however if a learning effect did exist it would be expected there would have been an improvement in both SELF and FAST walking conditions. Furthermore, the tasks were simple walking tasks, a task that the participants carry out every day. However, control participants should have been brought in more than once to determine if they experienced any change.

### **3.4.7 Strengths**

The present study is the first to examine several axial gait feature changes quantitatively in prolonged STN-DBS state. Currently the effects of STN-DBS stimulation on axial gait symptoms are measured using the UPDRS. Recent studies have expressed the ability of the UPDRS to detect subtle gait changes is limited due to the small number of items and its ordinal rating system (Kelly et al., 2006; Klucken et al., 2013). The current study elucidated the change in several gait parameters following STN-DBS intervention.

The present study provided an improved method for assessing gait changes in response to STN-DBS. The data demonstrate the specific gait feature impairments that are found in both medication ON and STN-DBS On states. The study provides a framework for future research on viable treatment alternatives for axial symptom improvement in PD.

### **3.4.8 Implications**

The current research sheds light on the long-term effect STN-DBS intervention has on axial gait symptoms. STN-DBS was successful at improving appendicular symptoms of PD (rated by UPDRS-III) and reducing the total medication dosage of the participants. However, STN-DBS was not able to improve gait features associated with asymmetry, rhythm variability and postural control in the SELF task. This finding is important when considering the inclusion criteria for the STN-DBS surgery.

If a patient has significant gait impairments before surgery the current research suggests that other treatment options should be considered. A recent article describes the STN-DBS surgery as a “Pandora’s box” of complications post-operation (Galati & Stefani., 2015). While not every patient experiences these side effects, the risk is higher when proceeding with the STN-DBS operation. There are some manageable complications such as device dislocation and impaired wound healing, which impart temporary discomfort for the patient. However, there are more chronic complications such as anhedonia and cognitive impairment (Galati & Stefani., 2015). As discussed in chapter 2, cognition is an important factor in axial gait function.

The present study suggests that individuals with PD, who experience axial gait impairments as their primary symptom, may want to consider other treatments options to avoid unwanted complications. Further analysis with a larger sample size should be conducted to verify this claim. However, it has been currently shown that STN-DBS has little to improve axial gait features.

### **3.5 Conclusion**

The current study provides a specific quantitative assessment of various gait features changes in response to STN-DBS intervention. Overall, clinically optimized STN-DBS intervention at 6 months post-operation was only successful at improving pace in PD participants compared with medication state. The failure of STN-DBS to recover other axial gait features, but improves appendicular symptoms, implies that STN-DBS may work on similar dopaminergic systems as the commonplace PD medications. Axial gait parameters should be assessed and considered as inclusion criteria prior to STN-DBS surgery. Individuals with PD that have prevailing gait difficulties may not be ideal candidates for the STN-DBS surgery.

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## 4. General Discussion and Conclusion

The current thesis suggests that pre-operative/post-operative objective gait assessments should be conducted in order to help determine which specific gait features respond to the treatment. Together, there are 5 important features of proper gait function, which include pace, variability, rhythm, asymmetry and postural control. Determining the pre-operative gait features that are impaired may help to predict the outcome from STN-DBS. It was found that pre-operative gait feature impairments with variability, rhythm, asymmetry and postural control persisted following STN-DBS surgery. Pace was the only feature that improved significantly during the preferred walking task. The ability to predict the outcome of gait response to STN-DBS surgery would allow future individuals to make a more informed decision about pursuing STN-DBS surgery. It is suggested, from the current thesis, that if gait function impairment is the predominant symptom in an individual with PD then other treatment avenues should be explored.

The concept of predicting the outcome of STN-DBS surgery on motor symptoms has been explored in previous work. Tykocki *et al.* (2013) explored the notion that the MLE could be used as a predictive factor for STN-DBS efficacy. This group found a positive correlation between the MLE and the degree of improvement from STN-DBS. However, the improvement from the MLE is a gradient and differs between individuals (Tykocki, Nauman, Koziara, & Mandat, 2013). Jach *et al.* (2012) found the symmetry of the MLE is not consistent. They used fMRI and found that in 10 patients the MLE edema was formed in one hemisphere only and was nonexistent in another patient. In the present thesis the MLE was not found to improve either appendicular or axial gait symptoms. As discussed this result may be due to the small sample size used. However, using the MLE as a predictive factor for STN-DBS outcome may prove challenging due to the inconsistency of its occurrence.

Other avenues have been explored to provide a prediction to the efficacy of STN-DBS. Tsai *et al.* (2009) found that responsiveness to levodopa pre-operatively was unable to predict the long-term outcome (18 months) of STN-DBS in 36 PD participants. This group found that good cognitive function and tremor dominant symptoms are good

predictors of STN-DBS outcome. Individuals who are older and have axial dominant symptoms were found to have a poorer response to STN-DBS.

Interestingly the current thesis found that there were fewer improvements in the faster walking task. A faster walking speed fundamentally changes the dynamics of human gait. The increase in speed means the individual has less time to make limb movement changes in each step and the inertia of the body is much greater (McGeer., 1993). Research on individuals with spinal cord injuries revealed that faster walking speeds rely more on spinal reflex pathways and spinal neural networks (Beres-Jones & Harkema., 2004). Furthermore, Harada *et al.* (2009) found that faster walking speeds tended to increase activity in the prefrontal cortex and the SMA region (Harada, Miyai, Suzuki, & Kubota, 2009). In section 3.4.2 it was discussed that the SMA region connectivity decreases in PD, which is an area that is thought to play a role in akinesia (Wu *et al.*, 2011). Thus, it may be due to the decreased activity within the SMA region in PD that results in a less significant impact on faster gait speeds.

Exploring gait function performance at varied gait speeds allows a more detailed account of the gait impairments. The data presented indicates that if axial function is impaired prior to surgery it may continue to be impaired. It was hypothesized that axial gait function is regulated by predominantly non-dopaminergic systems. While the study may have been underpowered, it was found that STN-DBS did little to improve axial gait function. This finding supports past research that has suggested levodopa and STN-DBS act on similar neural networks, which axial gait function is non-responsive to.

Other regions of interest have been proposed to have a greater effect on axial gait function. A recent review by Follet *et al.* (2012) discussed the issue of STN-DBS efficacy on axial gait function. This review argued STN-DBS is efficient at improving appendicular symptoms such as rigidity, tremor and bradykinesia but falls short at treating axial gait dysfunction. A recent meta-analysis confirmed this finding that in the long-term appendicular symptoms maintain improvement but axial gait impairments continue to worsen (St. George, Nutt, Burchiel, & Horak, 2010). Follet *et al.* (2012) went on to discuss the PPN as a potential target for axial gait dysfunction.

As with the STN-DBS literature on axial gait function, the PPN literature on gait function is also controversial. As previously established the PPN is an important structure within the brainstem that is closely connected to the BG. The PPN also projects to the SMA, cerebellum and spinal cord (Aravamuthan, Muthusamy, Stein, Aziz, & Johansen-Berg., 2007). It has been proposed that the axial gait function may be due in part to the cholinergic PPNc and glutamatergic PPNd neuronal systems. Significant loss of cholinergic neurons within the PPNc has been documented in the pathology of PD (Pahapill & Lozano., 2000). Stefani *et al.* (2007) explored PPN-DBS with promising results in 6 PD participants. It was found that PPN-DBS, in conjunction with STN-DBS, improved UPDRS gait scores by 37% (compared to STN-DBS alone) (Stefani *et al.*, 2007). However, another study by Ferraye *et al.* (2010) found that UPDRS gait scores failed to improve in response to PPN-DBS in 6 PD participants with STN-DBS (Ferraye *et al.*, 2010). It can be stated, from the STN and PPN axial gait literature, that the subjectivity of the clinical rating scales may play a role in the conflicting reports. Establishing a more detailed and organized assessment of gait features will better elucidate the response of gait to these interventions.

In summary, this thesis was the first to provide a detailed and organized assessment of axial gait feature changes following STN-DBS intervention for PD. Future directions for the study will include a larger sample size and a longer follow-up period. The results should be interpreted with the knowledge that the study may have been underpowered due to the small number of PD participants ( $n=10$ ). Presently, it was found that the surgical MLE effect did not impart any significant improvement in appendicular and axial PD symptoms. The clinical improvement of axial gait features were minimal following 6 months of STN-DBS. This may hint at a predominantly non-dopaminergic control system for axial gait function. Other non-dopaminergic systems should be investigated for clinical improvement of axial gait function.

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## Appendix A: Ethics Approval



**Western  
Research**

Use of Human Participants - Revision Ethics Approval Notice

Research Ethics

**Principal Investigator:** Dr. Mandar Jog

**File Number:** 103928

**Review Level:** Delegated

**Protocol Title:** Optimization of Deep Brain Stimulation Parameters for PD Patients Using Objective Measures

**Department & Institution:** Schulich School of Medicine and Dentistry/Clinical Neurological Sciences, London Health Sciences Centre

**Sponsor:**

**Ethics Approval Date:** November 29, 2013 **Expiry Date:** August 31, 2015

**Documents Reviewed & Approved & Documents Received for Information:**

Document Name	Comments	Version Date
Revised Western University Protocol	Received Nov, 20, 2013	

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the University of Western Ontario Updated Approval Request Form.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

## Appendix B: Letter of Information

### Letter of Information

**Study Title:** Optimization of Deep Brain Stimulation Parameters for Parkinson Disease Patients using Objective Measures

**Principal investigator:** Dr. Mandar Jog, London Health Science Movement Disorders Clinic, UWO

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#### Introduction

We are inviting you to voluntarily participate in a research project designed to objectively assess the short-term effects of deep brain stimulation (DBS) of the subthalamic nucleus (STN) surgery on mobility changes, such as gait and posture, in a laboratory setting. Deep brain stimulation (DBS) is a surgical procedure to implant an impulse generator that sends electrical signals to brain areas related to control of body movement. Electrodes are placed deep in the brain and are connected to a programmable stimulator device. Similar to a heart pacemaker, the stimulator uses electric pulses to help regulate brain activity. The doctor tunes the stimulator settings with a wireless device and stimulation settings can be adjusted as a patient's condition changes over time. This procedure will have been clearly explained to you by your surgeon and neurologist and you will have already signed a separate consent form for this operation as part of the treatment of your Parkinson disease.

Currently, fine-tuning the stimulator is a lengthy process, and despite the large amount of time being spent, choosing the best setting is still largely accomplished by trial and error. The data collected will be used to develop a promising approach to optimizing STN-DBS parameters.

#### Background

Deep brain stimulation (DBS) is an important treatment option for patients with Parkinson disease (PD) whose medication has been ineffective. But, after more than a decade of clinical trials, choosing the best setting for the stimulator is still a trial and error practice.

Under the current standard of care for DBS, patients return to the clinic a few weeks after the surgery for the initial device tuning. DBS settings are adjusted by a doctor with expertise in programming. During this process, the participant will be examined and questioned to avoid any known side effects (such as speech problems, dizziness, and rigidity). If results are not satisfactory, then more stimulation combinations would be tested by trial and errors.

In this study, we attempt to use our lab expertise to begin the development of an intelligent DBS programming technology. We expect that once developed, PD patients undergoing DBS can be assessed using our assessment techniques and we would be able provide guidelines for other programmers. Improved quality of life, reduced programming time, and even better battery life could be some potential benefits of being in the study.

### **Study Funding**

The study is funded by a research grant from Movement Disorders lab at London Health Sciences Centre (LHSC).

### **Nature of the research project and tasks involved**

We are looking to investigate mobility changes in 24 persons with STN-DBS recruited from the Movement Disorders Clinic at London Health Sciences Centre (LHSC). This study requires you to attend a total of 9 visits (one pre- and one post-operative assessment and 7 follow-up programming sessions) over the course of 24 weeks.

At each visit, you will be required not to take your morning medication until after the study procedure is finished. As a result, you may experience some symptoms and side effects of your disease. However, the side effects should not be permanent and they should be relieved after you resume your routine medication schedule.

You are eligible for the study based on the following criteria:

1. Diagnosed Idiopathic Parkinson Disease
2. Movement disorders with debilitating symptoms (tremor, stiffness) while medications have begun to lose effectiveness.
3. Severe motor fluctuations with disabling off periods and dyskinesia during on phases
4. Assessed for eligibility for the DBS procedure
5. Able to give informed consent
6. Able to visit the clinic for assessment
7. No dementia or psychiatric abnormalities.

***Brain Surgery/Pacemaker:*** If you have had previous brain surgery or a cardiac pacemaker, you CANNOT BE IN THIS STUDY. Please notify the research team if you have experienced either of these conditions.

***Unstable Pharmacological Treatment:*** If you have moderately severe Parkinsonism such that your medication routine is unstable then you CANNOT BE IN THIS STUDY. Please notify the research team if this is the case.

***Dementia:*** If you have dementia (as assessed by your doctor), severe cognitive disturbances or severe psychiatric symptoms (in particular hallucinations and depression), then you CANNOT BE IN THIS STUDY. Please notify the research team if you have experienced or are experiencing these conditions.

The research visits will require you to come to Dr. Jog's research facilities located at South Street Hospital in London, Ontario.

The visits will be completed as outlined below:

Visit 1: One Week Pre-Operation

Clinical rating scales for movement difficulties and other difficulties (depression, etc.) such as the UPDRS and the MoCA will be administered in this visit. The Unified Parkinson's Disease Rating Scale (UPDRS) is a widely used measure of impairment and disability associated with Parkinson Disease (PD). The Montreal Cognitive Assessment (MoCA) test is a brief 30-question test which assesses different types of cognitive abilities such as short-term memory and concentration.

Following these scales, a whole-body mobility and gait assessment will be performed. This data is collected to analyze your condition before the surgery. This session may take roughly two hours.

Visit 2: One Week Post-Operation

The clinical rating scales, as well as the whole-body mobility and gait assessment will be conducted similar to Visit 1. Data will be collected over two periods of the day; each period will take roughly two hours.

The study doctor will select the best contact of the implanted electrode to produce more improvement in one targeted symptom, with fewer side effects.

Visits 3-9: 2, 3, 4, 8, 16, 20 and 24 Weeks Post-Operation

Once the best electrode contacts are chosen for each side, programming the DBS device will start on the third visit, two weeks after surgery. In this visit and all the follow-up visits, you will participate in a morning and afternoon programming session, each lasting approximately two and a half hours. During these sessions, there will be alternating movement assessment and device programming periods.

**Motor Function:**

During each visit, a researcher will complete the United Parkinson's Disease Rating Scale (UPDRS). This is the same assessment that your doctor completes with you during your routine clinic visit. It assesses the condition of your disease and the quality of your movements, including: stiffness, tremor, walking, activities of daily living, speech, etc. It is a non-invasive assessment and will take approximately 10 minutes to complete.

**Whole-body Mobility Assessment:**

The whole-body mobility is assessed using Animazoo IGS 180 system. You will be dressed in a lightweight, stretchable, and breathable Lycra suit over your regular clothing. You will also wear a head sensor attached to a lightweight cap, as well as fingerless gloves and shoe attachments with hand and foot sensors. The total weight of the suit is 1.5 kg.

**Gait and Speech Measurements:**

The GAITRite carpet will be used for gait measurements. It consists of a roll-up carpet with sensor pads used to measure functional ambulatory status. You will be required to walk on the walkway, so that the system can capture your walking patterns in various ways. Your speech will be recorded using a head-mounted microphone and a digital recording device.

**Video recording:**

The gait and posture tasks of this study are video recorded for data analysis purposes only. The recorded video will be coded and not linked to your personal information.

**Benefits, risks and inconveniences:**

You may not benefit directly from participation in this study. However, the results may contribute to assessment of DBS parameters. Improved outcomes and quality of life, reduced programming time, and even better battery life could be some of the direct benefits. The potential side effects of DBS surgery will have been explained to you by your doctors as part of your treatment.

The full body suit is a light weight and fully portable technology for collecting information about your mobility. There is a minimal risk associated with wearing such a suit as the system only uses simple sensors that are attached to the suit. Some study participants may experience discomfort such as itching and sweating in their body while wearing the suit.

Some study participants may experience minor emotional distress with completing the scales and questionnaires. Scales will be administered by an experienced researcher trained in administering items in a sensitive manner. You will be allowed rest periods as necessary during the scales and questionnaires to facilitate comfort.

Some study participants may be uncomfortable with being video taped. However, the research team is only recording from your neck down in an attempt to study your mobility and gait. The study is video recorded only for data analysis purposes and all recorded files will be de-identified and stored in a secure location.

Some study participants may experience fatigue with the laboratory walking and balance tasks. The walking tasks are simple walking and turning tasks that do not contain any obstacles or barriers. The tasks are not designed to evaluate falling. Therefore, the risk of falling will be equal to the risk of falling during routine walking and turning in everyday life. The data is collected wirelessly, so there are no intrusive wires in the walking path.

**Data collection and use of information**

Participation in this study is voluntary. Information and data obtained in the study will not be labeled with any of your personal information (name, initials, date of birth, medical record number, etc.).

The data from the study will be kept electronically and securely using the LHSC computer network. At all times, the data will be in the possession of one of the investigators of this study and will not be stored off-site. *The recorded videos will also be stored in a secure location until all the analysis is complete.*

For the purposes of contacting you to arrange the data collection sessions and linking your data from the multiple visits, we will keep a master list of all participants. This list will contain your first name, telephone number, address, the dates you completed your sessions, and a number that we will assign to you that will also appear on your data recordings. At the conclusion of this study, this master list will be destroyed.

Your signed consent, which will have your name on it, will not be stored with the data collected from the study and will not be connected to the data collected. The master list with your contact information on it will also be stored separately from the data collected to avoid linking your personal information to your data recordings. Consent forms and the master list will be stored in a secure location in the Movement Disorders Laboratory of Dr. Jog at University Hospital.

Any use of this information for publication in scientific journals or presentation at professional conferences, will not contain any of your personal information that could be linked back to you or to your health information. You will receive a copy of this information letter for your records.

#### **Withdrawal from the study by the investigator**

The investigator may decide to take you off the study if he feels your continued participation would impair your wellbeing or if the measuring devices are causing discomfort. The investigator may also decide to terminate your participation if compliance at follow-up is deemed insufficient.

#### **Monetary compensation**

You will not be paid for participation in this study. Parking fees will however be compensated.

#### **Confidentiality**

In order to preserve your confidentiality, only the investigators in this study will have access to your research information. No personal information will be collected or retained with your data. AT NO TIME, will your name be used in scientific presentations or publications. The recorded data will remain secure, accessible only to research personnel.

Representatives of the University of Western Ontario Health Sciences Research Ethics Board may contact you or may require access to your study related records to monitor the conduct of the research.

**Voluntary participation**

Participation in this study is voluntary. You may refuse to participate, refuse to answer any questions or withdraw from the study at any time with no effect on your future care.

You will be able to withdraw from the study at any point in time. However, to protect the integrity of the study the data collected up to the point of your withdrawal will remain a part of the study. You will not have the option of withdrawing your data once it has been collected even if you choose to withdraw from the study.

**Alternatives to study participation**

The alternative to study participation is to continue on your current course of medication and disease management under the direction of Dr. Mandar Jog.

## Appendix C: Unified Parkinson’s Disease Rating Scale

# Unified Parkinson’s Disease Data Form



THE WE MOVE CLINICIANS’ GUIDE  
TO PARKINSON’S DISEASE

Name \_\_\_\_\_ Unit Number \_\_\_\_\_

	Date																
DOPA mg/day	hrs DOPA lasts																
		ON	OFF														
1. Mentation																	
2. Thought Disorder																	
3. Depression																	
4. Motivation/Initiative																	
<b>Subtotal 1–4 (maximum = 16)</b>																	
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																	
<b>Subtotal 5 – 17 (maximum = 52)</b>																	
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



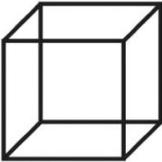
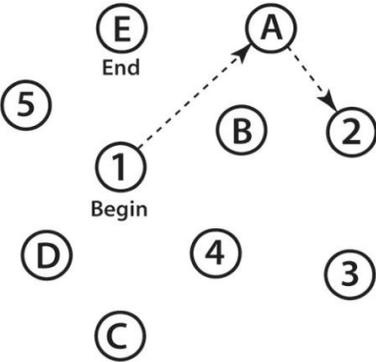
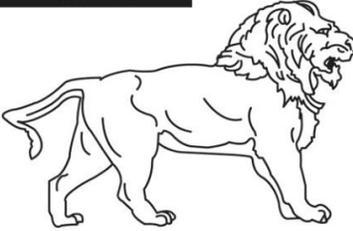
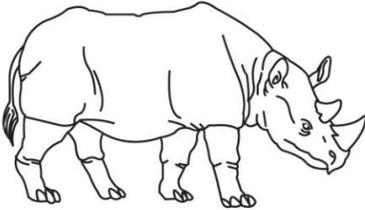
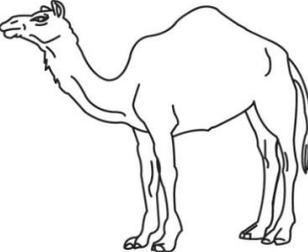
Date																
	ON	OFF														
23. Finger taps: right																
left																
24. Hand grips: right																
left																
25. Hand pronate/supinate: right																
left																
26. Leg agility: right																
left																
27. Arise from chair																
28. Posture																
29. Gait																
30. Postural stability																
31. Body bradykinesia																
<b>Sub-total:18-31 (maximum=108)</b>																
<b>Total points: 1-31 (max=176)</b>																
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																
<b>Name of Examiner</b>																
	BEST	WORST														
<b>Hoehn &amp; Yahr Stage</b>																
<b>% ADL Score (PD)</b>																
<b>% ADL (with dyskinesia)</b>																

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

## Appendix D: Montreal Cognitive Assessment Scale

**MONTREAL COGNITIVE ASSESSMENT (MOCA)**  
Version 7.1 Original Version

NAME : \_\_\_\_\_  
Education : \_\_\_\_\_ Date of birth : \_\_\_\_\_  
Sex : \_\_\_\_\_ DATE : \_\_\_\_\_

<b>VISUOSPATIAL / EXECUTIVE</b>			Copy cube  Draw CLOCK (Ten past eleven) (3 points)	<b>POINTS</b>  _____/5	
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>NAMING</b>					_____/3
<b>MEMORY</b>		Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.	FACE    VELVET    CHURCH    DAISY    RED	No points	
		1st trial	<input type="checkbox"/>	<input type="checkbox"/>	
		2nd trial	<input type="checkbox"/>	<input type="checkbox"/>	
<b>ATTENTION</b>		Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order	<input type="checkbox"/> 2 1 8 5 4	_____/2	
		Subject has to repeat them in the backward order	<input type="checkbox"/> 7 4 2		
		Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors	<input type="checkbox"/> FBACMNAAJKLBFAFAKDEAAAJAMOF AAB	_____/1	
		Serial 7 subtraction starting at 100	<input type="checkbox"/> 93 <input type="checkbox"/> 86 <input type="checkbox"/> 79 <input type="checkbox"/> 72 <input type="checkbox"/> 65	_____/3	
		4 or 5 correct subtractions: <b>3 pts</b> , 2 or 3 correct: <b>2 pts</b> , 1 correct: <b>1 pt</b> , 0 correct: <b>0 pt</b>			
<b>LANGUAGE</b>		Repeat : I only know that John is the one to help today. [ ] The cat always hid under the couch when dogs were in the room. [ ]		_____/2	
		Fluency / Name maximum number of words in one minute that begin with the letter F	<input type="checkbox"/> _____ (N ≥ 11 words)	_____/1	
<b>ABSTRACTION</b>		Similarity between e.g. banana - orange = fruit [ ] train - bicycle [ ] watch - ruler		_____/2	
<b>DELAYED RECALL</b>		Has to recall words <b>WITH NO CUE</b>	FACE    VELVET    CHURCH    DAISY    RED <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	_____/5	
<b>Optional</b>		Category cue Multiple choice cue	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	Points for UNCUED recall only	
<b>ORIENTATION</b>		[ ] Date    [ ] Month    [ ] Year    [ ] Day    [ ] Place    [ ] City		_____/6	
© Z.Nasreddine MD <a href="http://www.mocatest.org">www.mocatest.org</a> Normal ≥ 26 / 30		TOTAL _____/30 Add 1 point if ≤ 12 yr edu			

Administered by: \_\_\_\_\_

## Appendix E: The Activities-specific Balance Confidence (ABC) Scale

### Instructions to Participants:

For each of the following, please indicate your level of confidence in doing the activity without losing your balance or becoming unsteady from choosing one of the percentage points on the scale from 0% to 100%. If you do not currently do the activity in question, try and imagine how confident you would be if you had to do the activity. If you normally use a walking aid to do the activity or hold onto someone, rate your confidence as if you were using these supports. If you have any questions about answering any of these items, please ask the administrator. The Activities-specific Balance Confidence (ABC) Scale\* For each of the following activities, please indicate your level of self-confidence by choosing a corresponding number from the following rating scale:

0%    10 %    20%    30%    40%    50%    60%    70%    80%    90%    100%

no confidence

completely confident

“How confident are you that you will not lose your balance or become unsteady when you...

1. ...walk around the house? \_\_\_\_%
2. ...walk up or down stairs? \_\_\_\_%
3. ...bend over and pick up a slipper from the front of a closet floor \_\_\_\_%
4. ...reach for a small can off a shelf at eye level? \_\_\_\_%
5. ...stand on your tiptoes and reach for something above your head? \_\_\_\_%
6. ...stand on a chair and reach for something? \_\_\_\_%
7. ...sweep the floor? \_\_\_\_%
8. ...walk outside the house to a car parked in the driveway? \_\_\_\_%
9. ...get into or out of a car? \_\_\_\_%
10. ...walk across a parking lot to the mall? \_\_\_\_%
11. ...walk up or down a ramp? \_\_\_\_%
12. ...walk in a crowded mall where people rapidly walk past you? \_\_\_\_%
13. ...are bumped into by people as you walk through the mall? \_\_\_\_%
14. ...step onto or off an escalator while you are holding onto a railing? \_\_%
15. ... step onto or off an escalator while holding onto parcels such that you cannot hold onto the railing? \_\_\_\_%
16. ...walk outside on icy sidewalks? \_\_\_\_%

\*Powell, LE & Myers AM. The Activities-specific Balance Confidence (ABC) Scale. *J Gerontol Med Sci* 1995;

## Appendix F: Geriatric Depression 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? \_\_\_\_\_

## Appendix G: Freezing of Gait Questionnaire (FOGQ)

1. **During your worst state—Do you walk:** \_\_\_\_\_
  - 0 Normally
  - 1 Almost normally—somewhat slow
  - 2 Slow but fully independent
  - 3 Need assistance or walking aid
  - 4 Unable to walk
  
2. **Are your gait difficulties affecting your daily activities and independence?** \_\_\_\_\_
  - 0 Not at all
  - 1 Mildly
  - 2 Moderately
  - 3 Severely
  - 4 Unable to walk
  
3. **Do you feel that your feet get glued to the floor while walking, making a turn or when trying to initiate walking (freezing)?** \_\_\_\_\_
  - 0 Never
  - 1 Very rarely—about once a month
  - 2 Rarely—about once a week
  - 3 Often—about once a day
  - 4 Always—whenever walking
  
4. **How long is your longest freezing episode?** \_\_\_\_\_
  - 0 Never happened
  - 1 1–2 s
  - 2 3–10 s
  - 3 11–30 s
  - 4 Unable to walk for more than 30 s

**5. How long is your typical start hesitation episode (freezing when initiating the first step)? \_\_\_\_\_**

- 0 None
- 1 Takes longer than 1 s to start walking
- 2 Takes longer than 3 s to start walking
- 3 Takes longer than 10 s to start walking
- 4 4 Takes longer than 30 s to start walking

**6. How long is your typical turning hesitation: (freezing when turning) \_\_\_\_\_**

- 0 None
- 1 Resume turning in 1–2 s
- 2 Resume turning in 3–10 s
- 3 Resume turning in 11–30 s
- 4 Unable to resume turning for more than 30 s

## Appendix H: Curriculum Vitae

<b>Name:</b>	Greydon Gilmore
<b>Post-secondary Education and Degrees:</b>	<p>Carleton University Ottawa, Ontario, Canada 2010-2013 B.Sc. Neuroscience</p> <p>Algonquin College Ottawa, Ontario, Canada 2007-2010 Advance Diploma. Biotechnology</p>
<b>Honours and Awards:</b>	<p>Canadian Institute of Health Research 2014-2015</p> <p>Western Graduate Research Scholarship 2013-2015</p>
<b>Related Work Experience</b>	<p>Teaching Assistant The University of Western Ontario 2013-2015</p>