Quantitative Assessment of Gait and Balance Following Deep Brain Stimulation in Patients with Parkinson's Disease

By

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by tremor, rigidity, bradykinesia and postural instability. Deep Brain Stimulation (DBS) targeting either the subthalamic nucleus (STN) or globus pallidus interna (GPi) is highly effective for treating the cardinal motor symptoms of PD and motor complications of levodopa (L-DOPA) therapy, but its impact on gait and balance symptoms is not well established. In the advanced stages of PD, gait and balance impairments can limit patient mobility, increase the risk of falls and fall-related injuries, and reduce quality of life. The objective of our study was to investigate the precise impact of DBS on the mechanisms of gait (pace, rhythm, variability, asymmetry and postural control) using a quantitative gait analysis. Eight participants awaiting DBS (prospectively implanted participants) were recruited for our study, as well as five PD participants who had previously received DBS (already implanted participants). Prospectively implanted participants were evaluated pre-operatively and post-operatively at four weeks, three months and six months after the initial DBS programming session. Already implanted participants were evaluated after programming was optimized. All participants were tested in four standard treatment conditions: OFF-medication/OFF-DBS, OFF-medication/ON-DBS, ON-medication/OFF-DBS, and ON-medication/ON-DBS. Participants were instructed to walk on a computerized walkway (GaitRite), which was used to collect objective spatial and temporal parameters. To investigate changes in the five domains of gait, our study measured gait velocity (cm/s), step length (cm), stance time (ms), swing time (ms), stance time ratio (|L/R|), step length ratio (|L/R|), and step length variability (% coefficient of variation). Additional standard tests and clinical scales, including the Timed-Up and Go (TUG), Unified Parkinson's Disease Rating Scale-III (UPDRS-III), Montreal Cognitive Assessment (MoCA) and Freezing of Gait Questionnaire (FOG-Q),

were also analyzed. The ON-medication/ON-DBS condition, otherwise known as the best treatment condition (BTC), produced a significant improvement in UPDRS-III, TUG, gait velocity and step length at four weeks and three months post-programming relative to the OFF-medication/OFF-DBS condition ($P<0.05$). There was a trend towards further improvement in these parameters at six months post-programming in the BTC, but statistical significance was not achieved, likely due to smaller sample size at this time point. Step length variability was significantly reduced in the BTC at four weeks post-programming ($P=0.008$) and during the OFF-medication/ON-DBS condition at three months ($P=0.02$), once DBS programming approached optimization. Step length asymmetry improved in the BTC at three months post-programming ($P=0.004$). Swing time improved at four weeks during the OFF-medication/ON-DBS state ($P=0.002$) and at three months during the ON-medication/OFF-DBS state ($P<0.05$). Stance time, stance time ratio, and stride width did not significantly change for prospectively implanted participants. No statistically significant changes were observed in FOG-Q scores before and after DBS. For already implanted participants, performance during the TUG, along with gait velocity, step length and stride width were significantly improved in the BTC relative to OFF-medication/OFF-DBS ($P<0.05$). Gait velocity and TUG times were also significantly better in the BTC compared to the ON-medication/OFF-DBS condition ($P<0.05$). We also compared gait and balance outcomes between STN- and GPi-DBS. Our preliminary findings show GPi-DBS to have a slight advantage for improving pace, select gait asymmetry parameters, and balance-related parameters in the BTC.

Taken together, our study shows STN- and GPi-DBS does not seem to worsen axial gait and balance in PD patients without pre-existing FOG. However, further analyses with more participants should be conducted to verify our preliminary findings.

Preface

This thesis is an original work by Di Chang. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name "Quantitative Assessment of Gait and Balance Following Deep Brain Stimulation in Patients with Parkinson's Disease", REMO – pro 00078739.

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List of Abbreviations

APA	Anticipatory Postural Adjustments
APR	Autonomic Postural Reaction
ADL	Activities of Daily Living
BBS	Berg Balance Scale
BG	Basal Ganglia
BMT	Best Medical Therapy
BTC	Best Treatment Condition
COM	Center of Mass
COP	Center of Pressure
CV	Coefficient of Variation
DBS	Deep Brain Stimulation
FOF	Fear of Falling
FOG	Freezing of Gait
FOG-Q	Freezing of Gait Questionnaire
GPi	Globus Pallidus Interna
HFS	High Frequency Stimulation
IPG	Implanted Pulse Generator
LBs	Lewy Bodies
L-DOPA	Levodopa
LED	L-DOPA Equivalent Dose
LEDD	L-DOPA Equivalent Daily Dose
LFS	Low Frequency Stimulation

MLR	Mesencephalic Locomotion Region
MAO-B	Monoamine Oxidase-B
MoCA	Montreal Cognitive Assessment
PD	Parkinson's Disease
PD+FOG	Parkinson's Participants With Freezing of Gait
PD-FOG	Parkinson's Participants Without Freezing of Fait
PPN	Pedunculopontine Nucleus
PIGD	Postural Instability and Gait Disability
QoL	Quality of Life
STN	Subthalamic Nucleus
SMA	Supplementary Motor Area
SNr	Substantia Nigra Pars Reticulata
TUG	Timed-Up and Go
UPDRS	Unified Parkinson's Disease Rating Scale

1. Introduction

1.1 Parkinson's disease and its pathophysiology

Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting 1.8% of the population over 65 years old (Tysnes and Storstein 2017). It is clinically characterized by resting tremor, bradykinesia, rigidity and postural instability. The pathological hallmark of PD is a significant loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) (Obeso et al. 2008). In turn, less dopamine is transmitted from the SNc to the striatum, the major afferent structure of the basal ganglia (BG). In the central nervous system, dopamine is highly concentrated in two subdivisions of the dorsal striatum: the caudate nucleus and the putamen (Bernheimer et al. 1973). Evidence shows that dopamine is a pivotal neuromodulator for movement regulation, and its absence can lead to disabling motor impairments (Kish, Shannak, and Hornykiewicz 1988). In PD, depleted levels of striatal dopamine are associated with dysregulated transmission to downstream structures in the BG system, including the subthalamic nucleus (STN) and globus pallidus interna (GPi). The STN is an important modulator of BG output and receives inhibitory input from the external segment of the external globus pallidus (GPe), which prevents STN-hyperactivity (DeLong 1990). However, in PD there is a lack of STN-inhibition, which leads an excess of STN transmission to the output nucleus of the BG, the GPi. In turn, this results in excess GPi-inhibitory signalling to the thalamus, which supresses outgoing excitation to the motor cortex and manifests as motor impairment (Fig. 1). Upon reaching significant striatal dopamine depletion, the cardinal PD motor signs—tremor, bradykinesia and rigidity—begin to manifest (Bernheimer et al. 1973). In the early stages of PD, dopaminergic receptors are upregulated and have an increased binding affinity (Kaasinen et al. 2000). As PD advances, there is a progressive loss of dopaminergic nerve terminals and post-

synaptic dopaminergic receptors, which leads to the development of motor complications, such as motor fluctuations and dyskinesias (Antonini et al. 1997). Eventually, this impairs the long-term efficacy of medical treatment in PD.

Another pathological characteristic of PD is the formation of alpha-synuclein aggregates called Lewy bodies (LBs) (Spillantini et al. 1997). Post-mortem examinations have identified clusters of these intracytoplasmic protein aggregates on surviving neurons in the BG and throughout the brain (Bernheimer et al. 1973; Braak et al. 1996; Gibb and Lees 1988). LBs on surviving neurons are thought to be implicated with mitochondrial dysfunction, synaptic loss, oxidative stress and further neuronal death (Goldberg and Lansbury Jr 2000; Hashimoto et al. 2003). Furthermore, the accumulation of LBs within the cingulate gyrus, entorhinal region, amygdala and other subcortical regions have been associated with cognitive deficits in PD patients (Braak et al. 1996; Emre 2003). At present, it is well established that LBs develop in the prodromal stage of PD and their accumulation, along with Lewy neurites, may propagate further PD progression (Bernheimer et al. 1973; Braak et al. 2005; Spillantini et al. 1998).
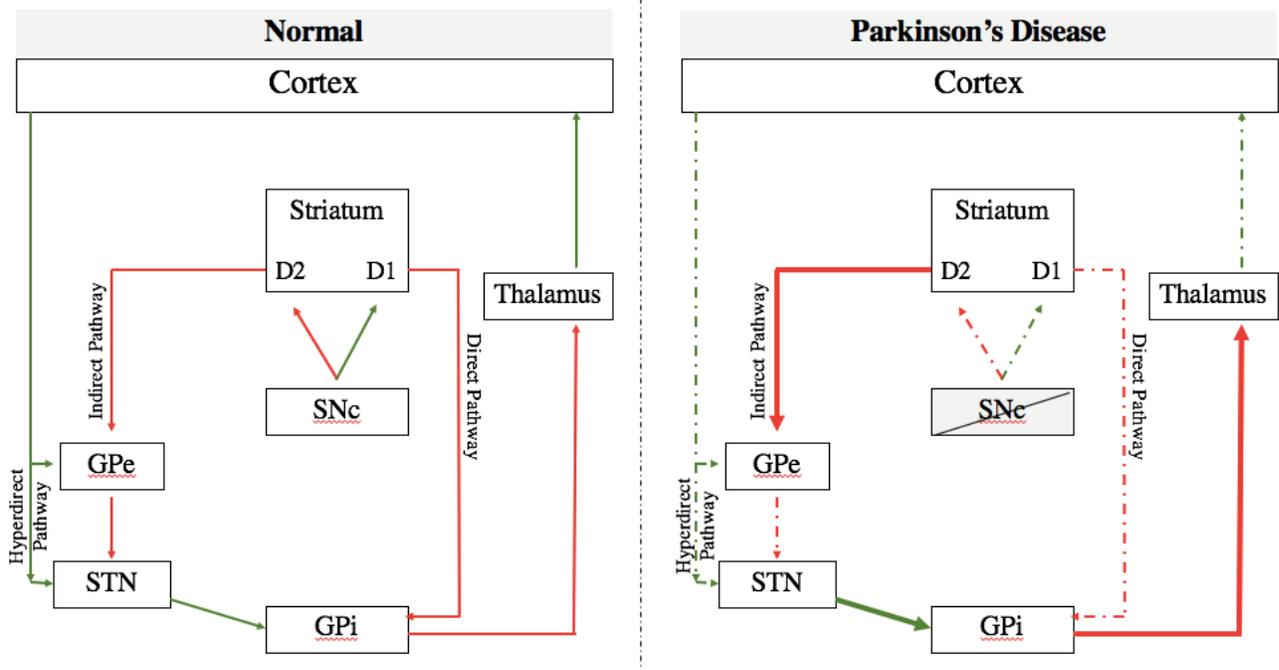
Figure 1. Modified diagram illustrating the rate model of Parkinson's disease. Schematic of the cortico-basal ganglia-thalamo-cortical loop and associated rate model of PD patholophysiology. Green arrows depict excitation, while red arrows depict inhibition. In PD, the loss of SNc dopaminergic neurons disrupt normal input to the striatum and leads to further dysfunction in the direct and indirect pathways downstream (DeLong 1990).

1.2 Diagnosis of idiopathic Parkinson's disease and motor subtypes

The diagnosis of probable idiopathic PD is based on an extensive clinical criteria (Postuma et al. 2015). Patients should be diagnosed with parkinsonism based on the presence of bradykinesia with either resting tremor, rigidity, or both (Postuma et al. 2015). Establishing PD as the primary cause of parkinsonism is based on: i) supportive criteria; ii) no 'red flags'; and iii) an absence of exclusion criteria (Postuma et al. 2015). An accurate diagnosis of PD is essential for improving patients' prognosis, providing the appropriate therapy, and improving patients' quality of life (QoL) (Tolosa, Wenning, and Poewe 2006).

PD patients can be classified into various phenotypes, that include Tremor Dominant, Postural Instability and Gait Difficulties (PIGD) Dominant, and indeterminate (Jankovic et al. 1990). Patients are categorized into motor subtypes using a clinical ratio of Unified Parkinson's Disease Rating Scale – III (UPDRS - III) items and a cut-off score. Patients are typically classified as Tremor Dominant if their average score of tremor-related items / average score of PIGD-related items is less than or equal to 1.5, while patients are classified as PIGD if their average score of tremor-related items / average score of PIGD-related items is greater or equal to 1.0 (Jankovic et al. 1990). Throughout the disease course, patients can also transition from one phenotype to another. Patients who are classified as PIGD typically display greater axial gait impairment and more functional disability with faster disease progression (Jankovic et al. 1990).

1.3 Appendicular motor signs

Tremor, bradykinesia and rigidity in the limbs are cardinal features of PD. Bradykinesia refers to the slowness of movement that can manifest during the initiation or execution of movement, and

is commonly associated with BG disorders (Berardelli et al. 2001). Bradykinesia can be observed during alternating or repeating movements (e.g., finger tapping, heel tapping, hand pronation and supination, etc.), as these movements become slower and decrease in amplitude (Hallett and Khoshbin 1980). Tremor refers to involuntary, rhythmic oscillations of agonist and antagonist muscle groups across a joint or axis. Various types of tremor exist in the realm of movement disorders but PD tremor predominantly occurs at rest (i.e., resting tremor) when the body is relaxed (Helmich et al. 2012). These tremors can also re-emerge with action or postural holding, and typically amplify with cognitive loading (Dovzhenok and Rubchinsky 2012; Helmich et al. 2012). Rigidity refers to increased muscle tone that presents through the whole range of motion during passive movement of the joints (Berardelli, Sabra, and Hallett 1983). As PD advances, most appendicular signs progressively worsen and eventually interfere with patients' daily functioning and QoL.

1.4 Axial motor signs

Axial motor signs refer to impairments in the face, neck and trunk of the body, that typically present in advanced PD (Morrish et al. 1998), though patients who are PIGD subtype experience axial impairment earlier on (Herman et al. 2014). Axial motor signs include dysarthria (inarticulation of speech), dysphagia (difficulty swallowing), gait impairments, postural instability, whole body bradykinesia, axial rigidity, among other impairments (Steiger, Thompson, and Marsden 1996). Among axial impairments, gait and balance dysfunction are usually the most disabling, given their association with fall risk and fall-related injuries (e.g., head trauma, fractures, etc.) (Gazibara et al. 2017; Pressley et al. 2003). Patients with gait impairments have greater difficulty with daily tasks, such as rising from a chair, getting out of

bed or walking independently (Bryant et al. 2016; Steiger, Thompson, and Marsden 1996). As such, addressing the gait and balance issues is relevant to improving patients' QoL and daily functioning.

1.4.1 Pathology of axial motor signs

Although levodopa (L-DOPA) —the mainstay of pharmacological treatment in PD (see 1.5 below)—can improve certain cardinal PD signs, such as bradykinesia and rigidity, axial symptoms, such as gait and balance impairments, respond less consistently to conventional anti-parkinsonian therapy. Axial motor signs are posited to manifest from the involvement of non-dopaminergic pathways (Bonnet et al. 1987; Magrinelli et al. 2016), in addition to nigro-striatal denervation. In particular, the mesencephalic locomotor region (MLR), which includes the pedunculopontine nucleus (PPN), has become of clinical interest for its role in gait initiation and locomotor control (Benarroch 2013; Pahapill and Lozano 2000; Plaha and Gill 2005). Multiple studies have demonstrated the relationship between the PPN and locomotion (Kojima et al. 1997; Garcia-Rill et al. 1987; Pahapill and Lozano 2000) and thereafter, incited multiple studies to target the PPN for patients who display severe axial gait impairment (Ferraye et al. 2010; Khan et al. 2011; Paolo Mazzone et al. 2005; Stefani et al. 2007). However, these studies have only shown moderate or inconsistent improvements for gait and balance with PPN DBS (Khan et al. 2011, 200; Ferraye et al. 2010; Moro et al. 2010; Stefani et al. 2007). Therefore, the clinical benefits associated with PPN-DBS are not yet conclusive.

1.4.2 Gait impairments in Parkinson's disease

Parkinsonian gait is hypokinetic in nature and characterized by shuffling steps and mobility impairments that impede "rhythmically alternating leg movements, leading to forward movement of the body" (Bloem et al. 2016). Previous studies have primarily focused on gait velocity, which is perceived as a clinical vital sign for predicting clinical outcomes (e.g., community walking, fall risk, etc.) (Studenski, Perera, and Patel 2011). As our knowledge advances, the concept of gait has expanded to incorporate other domains that are useful for understanding PD severity (Mirelman et al. 2019). Lord and colleagues (Lord, Galna, and Rochester 2013) highlighted five independent but interrelated domains of gait: pace, rhythm, variability, asymmetry and postural instability (Fig. 2). According to this model, the pace domain, which includes gait velocity, contributes 20.9 % to overall gait variance. Other domains, such as rhythm, variability, asymmetry, and postural instability, contribute 63.7% (Lord, Galna, and Rochester 2013). The remaining 15.4% of gait variance may be attributed to cognitive deficits (e.g., attention processes) or motor impairment (e.g., axial rigidity) that influence axial mobility (Lord et al. 2010). Studying these domains together may establish a clearer understanding of the relationship between specific gait parameters and clinical outcomes. For example, gait variability is a measure of stride-to-stride fluctuations, automaticity, and arrhythmicity (Hausdorff et al. 2003; Hausdorff 2009). PD patients with increased gait variability experience a higher risk of falls and are more likely to develop freezing of gait (FOG; discussed below) (Hausdorff et al. 2003). Gait asymmetry is another mobility impairment that is associated with a higher fall risk and FOG, but has not been studied in detail following medical or surgical intervention (Plotnik et al. 2005; Yogev et al. 2005). In summary, an objective analysis of the five domains of gait in PD, as well

as the effects of PD therapy on these various domains and their interactions with clinical

outcomes, may offer invaluable mechanistic and clinically-useful knowledge.

		Pace	Rhythm	Variability	Asymmetry	Postural control
Pace 20.9%	Mean step velocity (m.s⁻¹)	**-.904**	-.297	-.150	-.133	-.121
	Mean step length (m)	**-.942**	.120	-.141	-.102	-.110
	Swing time variability (ms)	**.594**	.464	.433	.173	.196
Rhythm 19.1%	Mean step time (ms)	.266	**.925**	.077	.147	.121
	Mean swing time (ms)	-.282	**.877**	.071	.086	-.229
	Mean stance time (ms)	.452	**.794**	.067	.147	.252
Variability 17.0%	Step velocity variability (m.s⁻¹)	-.043	-.014	**.952**	-.023	-.071
	Step length variability (m)	.323	.063	**.838**	.020	.144
	Step time variability (ms)	**.533**	.433	**.589**	.186	.160
	Stance time variability (ms)	**.556**	.418	**.619**	.163	.115
Asymmetry 17.9%	Swing time asymmetry (ms)	.078	.152	.088	**.855**	.110
	Step time asymmetry (ms)	.107	.096	.018	**.948**	.036
	Stance time asymmetry (ms)	.112	.098	.011	**.952**	.038
Postural Control 9.5%	Step length asymmetry (m)	.089	-.076	.186	.093	**.715**
	Mean step width (m)	.216	.111	-.149	.106	**.698**
	Step width variability (m)	-.383	.241	.287	-.387	**.502**

Figure 2. Five domains of gait. This figure illustrates the five independent domains of gait: pace, rhythm, variability, asymmetry and postural control (Lord, Galna, and Rochester 2013).

1.4.3 Freezing of gait

FOG consists of brief, episodic disturbances to forward walking that are common while turning, initiating gait (start hesitation) or moving in confined spaces. These paroxysmal episodes develop in 40 – 60% of PD patients and mainly manifest during the advanced stages of PD (Perez-Lloret et al. 2014). Studies report that PD patients with FOG (PD+FOG) exhibit more gait abnormalities than non-freezers (PD-FOG) (Nanhoe-Mahabier et al. 2011). More specifically, PD+FOG patients walk with greater axial rigidity, more arrhythmicity and more gait asymmetry (Hausdorff 2009). PD+FOG patients also have more asymmetric balance control, which makes the appropriate weight shift from one leg to another more difficult. This leads to improper interlimb coordination, and when combined with short step lengths and gait asymmetry, can increase the risk of freezing (Chee et al. 2009). These abnormal gait impairments may become exacerbated with stressful triggers (e.g., cognitive loading, anxiety, etc.) and lead to an injurious fall (Plotnik and Hausdorff 2008; Spildooren et al. 2010).

The UPDRS - II, Activities of Daily Living (ADL) Item #14 and the Freezing of Gait Questionnaire (FOG-Q) are valid clinical tools for assessing FOG severity and occurrence (Giladi et al. 2009; Niu et al. 2012; Vercruysse et al. 2014). Evaluating the frequency and duration of FOG is typically achieved with patient reports using the FOG-Q (Amboni et al. 2015). However, the FOG-Q only addresses freezing while patients are initiating gait or making a turn. FOG in other contexts, such as forward walking, moving in confined spaces, or dual-tasking, are not directly addressed and therefore may not be accounted for with the FOG-Q (Snijders et al. 2008). Furthermore, evaluating FOG is largely based on patient reports, which may introduce a degree of recall bias. Measuring the frequency and duration of FOG in a clinical

or laboratory setting can be difficult since freezing does not reliably appear with conventional triggers (e.g., motor repetition, gait initiation, turning, etc.) (Snijders et al. 2008). This makes the management of FOG difficult, since clinical evaluations may not completely demonstrate the true severity or prevalence of freezing in patients' daily lives (Snijders et al. 2008). Patients are typically classified as PD+FOG based on: 1) a medical history; 2) a clinical evaluation of FOG episodes during the OFF-medication and ON-medication conditions; 3) the UPDRS-II Item #14; and 4) the FOG-Q (Snijders et al. 2008).

1.4.4 Postural instability

Postural instability is a debilitating phenomenon that, unlike other cardinal signs, typically present in the advanced stages of PD. However, postural instability can develop early in PIGD patients. Postural instability was first described as the inability to maintain upright posture while walking, sitting or standing (Parkinson 1817). This has evolved over time to our modern definition of postural instability: the inability to maintain one's center of mass (COM) over one's base of support in static or dynamic conditions (Bloem 1992). Posture is primarily controlled through two mechanisms: anticipatory postural adjustments (APAs) and automatic postural reactions (APRs). APAs involves a series of muscle activations just prior to an external perturbation, which works to minimize COM displacement (Aruin, Forrest, and Latash 1998). By contrast, APRs react to postural disturbances that are signaled through the visual, vestibular and sensorimotor system (Bloem et al. 1996). PD patients with postural instability typically have reduced or absent APAs and APRs compared to healthy controls (Mak and Pang 2009). The lack or absence of these postural adjustment mechanisms compromise the balance equilibrium of PD patients, who subsequently walk with greater instability and longer hesitations between each

stride (Park, Kang, and Horak 2015). Considering PD patients with postural instability are unable counteract perturbations to their balance, the risk of experiencing a fall-related injury is much higher (Plotnik et al. 2011).

1.4.5 Falling in Parkinson's disease

Falls are a major concern in PD. Reportedly, 68% of PD patients fall at least once annually, while 51% of patients experience recurrent falls (Grimbergen, Munneke, and Bloem 2004; Wood et al. 2002). PD patients lack the compensatory mechanisms to counteract or protect themselves from hard-impact falls, making them more prone to injury. Direct consequences of these falls include fractures, head trauma, and other fall-related injuries that may require hospitalization (Gazibara et al. 2014; Rudzińska et al. 2013). Patients who fall may also develop a fear of falling (FOF), which hinders their involvement in daily activities and leads to a loss of independence (Adkin, Frank, and Jog 2003; Jonasson et al. 2018). Several risk factors have been linked to future falls (e.g., disease severity, dementia, etc.) (Kerr et al. 2010; Wood et al. 2002), though there is no gold-standard for predicting their occurrence. The best known predictor of future falls is whether a fall occurred in the previous twelve months (Wood et al. 2002). Though the relationship between gait impairments and falls is not entirely clear, gait abnormalities seem to exacerbate fall risk (Hausdorff et al. 1997; Maki 1997). In particular, increased gait variability, which reflects more stride-to-stride fluctuations and unsteadiness, may be useful for predicting future falls (Hausdorff et al. 1997; Maki 1997; Nakamura, Meguro, and Sasaki 1996).

1.5. Initial medication therapy and motor complications

Cotzias and colleagues first demonstrated the benefits of dopaminergic replacement therapy for improving tremor, rigidity and bradykinesia in PD patients (Cotzias, Van Woert, and Schiffer 1967). Dopaminergic replacement therapy, in particular L-DOPA, is highly effective for treating most appendicular motor signs, though it tends to be less effective against tremor. However, axial motor signs are not consistently responsive to dopaminergic medication (Fabbri et al. 2016; Fasano et al. 2010). Medical therapy for PD can enhance depleted dopamine levels through various mechanisms in the brain. For instance, monoamine oxidase-B (MAO-B) inhibitors bind to MAO-B and block the metabolism of dopamine (Tong et al. 2017). Other therapies, such as dopamine agonists, mimic dopamine by binding directly to dopaminergic D_2-receptors (Brooks 2000). Among these therapies, the gold-standard and most efficacious is L-DOPA, a non-polar molecule that converts into dopamine upon crossing the blood-brain barrier. In the best medically 'on' state, L-DOPA can produce a significant improvement on the UPDRS-III (Bejjani et al. 2000). L-DOPA is best for improving bradykinesia, rigidity, and sometimes tremor. To enable continuous L-DOPA delivery to the brain, catechol-*O*-methyltransferase (COMT) inhibitors can be administered in adjunct with L-DOPA to inhibit peripheral L-DOPA metabolism (Müller 2015). Despite the relative effectiveness of dopaminergic therapy against motor symptoms in PD, the management of axial motor signs with conventional dopaminergic medication has been a clinical challenge.

Typically 5 – 10 years after starting dopaminergic replacement therapy, as many as 60 – 90% of PD patients experience some form of L-DOPA-induced motor complications (Gershanik 2010; Warren Olanow et al. 2013). These complications result from a progressive loss of dopaminergic

neurons and post-synaptic dopaminergic receptors throughout the disease course. A common motor complication experienced by 50% of PD patients is the 'wearing off' phenomenon (Caillava-Santos, Margis, and de Mello Rieder 2015). This refers to the gradual decline of L-DOPA in the plasma and the premature re-emergence of motor signs. Some patients can also develop abnormal, uncontrolled, and involuntary movements, called dyskinesias. The most common form is peak-dose dyskinesia, which results from an excess of dopamine in the plasma (Thanvi, Lo, and Robinson 2007). Lastly, patients can also develop motor fluctuations, which refer to cyclic periods of optimal symptomatic control (Weiner 2006). For some patients, the development of these motor complications can become disabling and intolerable. If so, an alternative treatment may be required in order to effectively control PD motor signs and motor complications.

1.6 Deep Brain Stimulation

DBS is a neurosurgical procedure first pioneered by Benabid and colleagues (Benabid et al. 1987). Though DBS was initially used to treat parkinsonian tremor, it is now used to manage PD cardinal motor features and motor complications in carefully selected candidates. DBS involves surgically implanting small stimulating electrodes into precise regions of the brain. The DBS targets for PD include the STN, the GPi, or the ventral intermediate nucleus of the thalamus. The electrodes are connected to an implanted pulse generator (IPG) embedded in the patient's chest wall, that can be programmed using an external programmer to deliver constant, direct, often high frequency electrical stimulation (HFS) (>130Hz) to the target site (Garcia et al. 2005). DBS, provided in conjunction with best medical therapy (BMT), significantly approves appendicular

PD motor signs, as well as motor fluctuations and dyskinesias (Deuschl 2006; Weaver et al. 2009; Williams et al. 2010).

Despite its clinical benefits, the underlying mechanisms of DBS are still not completely understood. Initially, DBS was thought to work in a similar manner as ablative procedures (thalamotomy and pallidotomy), in that DBS reversibly "lesions" the target structure and reduces neuronal firing (Benazzouz et al. 1995; Limousin et al. 1995; Wu et al. 2001). Multiple theories outline the potential influences of electrical stimulation on target structures. Among other possible mechanisms, HFS may: i) generate or inhibit action potentials, depending on the stimulated region of the neuron; and ii) induce neurochemical changes around the target site. First, HFS can depolarize or hyperpolarize neurons depending on the position and distance of the neuron relative to the electrode. Axons possess a lower stimulation threshold compared to cell bodies and are typically the site of depolarization (Nowak and Bullier 1998). The generation of local action potentials can then excite adjacent neurons through synaptic connections, and modulate output to downstream BG structures. However, HFS can also induce a depolarization blockade (i.e., hyperpolarize neurons) by supressing sodium and calcium voltage-gated currents, that block the spontaneous activity of STN neurons (Beurrier et al. 2001). Together, DBS likely generates a complex pattern of firing that is dependent on the activated component of the neuron and distance from the electrode (Vitek 2002; Beurrier et al. 2001). HFS has also been shown to induce neurochemical changes. Electrical stimulation can facilitate the release of intracellular calcium from neighboring astrocytes (Tawfik et al. 2010; Vedam-Mai et al. 2012), which initiates the release of local excitatory and inhibitory neurotransmitters (i.e., glutamate and adenosine) (Tawfik et al. 2010; Windels et al. 2003). Whether DBS induces excitatory or

inhibitory effects is partially dependent on the neurotransmitter implicated in the afferent fibre pathway of the target site (Vitek 2002). For instance, HFS to afferent inhibitory structures may release GABAergic projections to the GPi and suppress mean discharge firing rates (Boraud et al. 1996). In contrast, microdialysis of the GPi has shown high concentrations of glutamate, which implies an increase in excitatory projections from the STN (Windels et al. 2003). Together, each mechanism of action likely contributes to some degree to the efficacy of DBS in treating PD.

After patients undergo the surgical procedure, a neurologist will program the IPG at an initial programming session (on average four weeks after implantation) and conduct monthly follow-up programming adjustments. The objective is to optimize stimulation for motor control, while minimizing current spread to adjacent surrounding regions that causes adverse effects. The IPG is programmed to adjust the pulse width, frequency, and voltage until all parameters are 'optimized', which is typically achieved by six months after the initial programming session. At present, there is well-established evidence from randomized controlled trials that, in appropriately selected patients, DBS in conjunction with BMT, is superior to BMT alone, for improving motor function and QoL in PD (Deuschl 2006; Weaver et al. 2009; Williams et al. 2010).

1.7 Deep Brain Stimulation and axial motor signs

1.7.1 Deep Brain Stimulation and gait impairment

The effect of DBS on gait impairment—assessed using quantitative approaches—is inconsistent. While some studies speculate on the development of post-operative worsening (St George et al. 2012; Fasano et al. 2010) or else no change (Brandmeir et al. 2018) for gait and balance, other

studies report post-operative improvement if these symptoms initially improved with dopaminergic medication (Allert et al. 2001; Roper et al. 2016; P. Weiss et al. 2015). Studies that report axial improvement often focus on gait velocity and stride length, which do consistently increase after DBS (Faist 2001; Scholten et al. 2017). In these studies, PD patients have been shown to have a slower velocity of 34 – 98 cm/s while off-medication, prior to surgery. After DBS, velocity increased to 70 - 119 cm/s, demonstrating a marked improvement up to 184% (Faist 2001; Piper, Abrams, and Marks 2005; Roper et al. 2016; Stolze et al. 2001). However, an increase in gait velocity is not always paralleled by an improvement in other gait parameters. Cadence, the number of steps per minute, along with stance time and swing time, often do not change with DBS, though to date, stance and swing time have only been examined in the setting of DBS for essential tremor, rather than PD (Earhart et al. 2009; Faist 2001; McNeely and Earhart 2013). One parameter that has been linked to adverse events, but has rarely been studied after DBS, is gait variability (Hausdorff et al. 1997; Maki 1997). Gait variability is measured as a coefficient of variation (CV), which reflects the degree of instability during locomotion (Hausdorff 2009). The CV of certain parameters, such as step time, is shown to improve after DBS, even though step time itself may not change (Vallabhajosula et al. 2015). Taken together, these issues suggest that gait velocity may not be a comprehensive tool for evaluating overall gait changes following DBS, and should be studied with other domains (Duncan and Earhart 2012).

1.7.2 Deep Brain Stimulation and freezing of gait

Studying the clinical benefits of DBS on FOG has been a challenge due to the complexity of FOG and the heterogenous methods used in previous studies. First, the impact of DBS on

patients' FOG status can be difficult to evaluate, since classifying patients as 'probable' or 'definite' freezers depend on patient-reports (Heremans, Nieuwboer, and Vercruysse 2013). Furthermore, some patients do not fully understand what FOG is and therefore, do not report these incidences before or after DBS (Tan et al. 2011). Second, the lack of objective and quantitative data may also contribute to the ambiguity of post-operative FOG changes. The current 'gold-standard' for evaluating FOG is videotaping patients walk, and having an independent rater count the number of FOG episodes that occur (T. Morris et al. 2012). Morris and colleagues (2012) reported this 'gold-standard' to have a moderate reliability and low intra-rater-reliability. Instead, utilizing more quantitative and objective measures, while considering FOG risk factors, may provide a clearer understanding of FOG before and after DBS (T. Morris et al. 2012). Third, certain studies that report a post-operative FOG improvement often use programming parameters that have limited symptomatic control on other appendicular motor signs. Multiple studies have shown low-frequency stimulation (LFS) to be superior to HFS for attenuating FOG and other gait abnormalities (Moreau et al. 2008; Xie, Kang, and Warnke 2012). However, LFS does not effectively control rigidity, tremor and bradykinesia, which leaves patients with an unpleasant trade-off. The effect of DBS on FOG remains unclear as some studies report a post-operative improvement following STN-DBS (Davis, Lyons, and Pahwa 2006; Niu et al. 2012; Vercruysse et al. 2014), while others report post-operative worsening (Fleury et al. 2016; Kim et al. 2017; Tommasi et al. 2007). With this, studying the specific gait-related abnormalities associated with FOG (e.g., higher gait variability, asymmetry, shorter step lengths, etc.) may clarify the mechanisms that contribute to this gait impairment.

1.7.3 Deep Brain Simulation and postural impairments

The impact of DBS on postural instability is typically measured with clinical tools, such as the Berg Balance Scale (BBS), the Timed-Up and Go (TUG) for functional mobility, and balance items on the UPDRS-III (e.g., Item 27 and 30) (Nilsson et al. 2009; Visser et al. 2008). STN-DBS has been shown to improve BBS scores, UPDRS-III balance items, and the TUG (McNeely and Earhart 2013; Umemura et al. 2010). However, some suggest that the BBS may only be sensitive to moderate changes in balance, while smaller changes go undetected (Downs, Marquez, and Chiarelli 2013). Recent studies have moved towards using objective evaluations, such as measuring center of pressure (COP) or COM changes after DBS. So far, some of these studies report improvements in postural instability (McNeely and Earhart 2013; Shivitz et al. 2006), while others report post-operative worsening (Fasano et al. 2010; St George et al. 2012; Visser et al. 2008), and some suggest there is no post-operative change (Brandmeir et al. 2018). Furthermore, Visser and colleagues (2008) noted that patients who were L-DOPA-resistant experienced more postural impairment after surgery (Visser et al. 2008), which confirms that pre-operative screening is critical for preventing axial deterioration after DBS.

1.7.4 Deep Brain Stimulation and falling

Falls are a common source of injury and disability for select PD patients, that can lead to FOF and restrict patients' daily functioning (Jonasson et al. 2018). Studies report that DBS can induce a higher risk of falling compared to BMT (Weaver et al. 2012; D. Weiss et al. 2013), and STN-DBS in particular can exacerbate this risk (Follett et al. 2010). However, other studies report DBS to be associated with an improved fall risk and found similar improvements in gait and balance (Follett et al. 2010; Lilleeng et al. 2015; Moro et al. 2010; Nilsson et al. 2009). Together,

these studies suggest that post-operative changes in fall risk are related to post-operative changes in gait and balance. As such, studying the precise changes in gait, balance (more specifically gait variability, asymmetry and arrhythmicity) and fall risk may provide a clearer understanding of this relationship.

1.8 STN- vs GPi-DBS on gait impairments

Both STN- and GPi-DBS are equally effective for improving the cardinal motor signs of PD (Odekerken et al. 2016). Selecting the appropriate target depends on the patient profile. For example, GPi-DBS provides direct anti-dyskinetic benefits and appears to be safer for patients with cognitive decline (Weaver et al. 2012). Meanwhile, STN-DBS produces better outcomes for rigidity and bradykinesia and allows select patients to reduce their medication dosage (Okun et al. 2009; Weaver et al. 2012). However, few studies have investigated differences in gait and balance outcomes between STN- and GPi-DBS (Follett et al. 2010; Rocchi et al. 2012; St George et al. 2012). This may be because DBS is primarily used to treat cardinal motor signs and motor complications, rather than axial features. However, understanding the target-specific changes in PD gait and balance may advance our clinical understanding of these impairments. Existing studies show that GPi-DBS provides an advantage for functional mobility (e.g., Stand-Walk-Sit), which persists long-term (Follett et al. 2010), whereas, STN-DBS seems to worsen postural reactions against external perturbations (St George et al. 2012). This may also explain why patients who undergo STN-DBS report more falls (Follett et al. 2010). Lastly, a meta-regression on the long-term effects of STN and GPi-DBS showed a gradual decline in PIGD scores (measure of axial impairment) after two years in the STN-DBS group, but not in the GPi-DBS group (St George et al. 2010, 20).

1.9 Limitations of previous studies and project rationale

The lack of consensus over the effect of DBS on gait and balance impairments has stimulated a growing number of investigations into this topic, though the results are still inconsistent. As mentioned above, though clinical scales (e.g., UPDRS-III) are widely used and highly reliable, there is a limited selection of items that evaluate gait and balance. The use of objective measures has helped to evaluate precise changes in gait parameters after DBS, though only select features (e.g., gait velocity and stride length) have been consistently studied (Faist 2001; Hausdorff et al. 2009, 20; Johnsen et al. 2009; McNeely and Earhart 2013; Roper et al. 2016). Other domains, such as variability and asymmetry, have rarely been investigated after DBS in PD patients, despite their reported associations with falling and FOG (Hausdorff et al. 2003; Hausdorff 2009). Tracking future falls and FOG, while closely investigating changes in variability, asymmetry, pace, rhythm, and postural instability, may provide further insight into these associations. As such, the primary objective of our study was to use objective and quantitative measures to investigate changes in the five domains of gait that occur following STN and GPi-DBS in PD patients. Our secondary aim was to evaluate post-operative changes in secondary, gait-related measures, including the FOG-Q, TUG, and prospective fall diaries. We hypothesized that: i) overall motor function, as scored by the UPDRS-III, should improve following DBS (as reported extensively in the DBS literature); ii) gait parameters associated with pace (i.e., gait velocity, step length and the TUG) should improve following DBS relative to the pre-operative OFF-medication condition; iii) parameters associated with balance (i.e., stance time, swing time and stride width) should not change following DBS relative to the pre-operative OFF-medication condition; iv) the ON-medication/ON-DBS condition should not produce a significant change for

gait parameters relative to the pre-operative ON-medication condition; and v) FOG-Q scores and prospective falls should not change following DBS.

By helping to better characterize gait-related changes after STN- and GPi-DBS, this study may lead to further insights into the underlying mechanisms behind these axial impairments in PD.

2. Methods

2.1 Participants

PD participants were recruited from the Comprehensive Parkinson and Movement Disorders Program at the University of Alberta and Kaye Edmonton Clinic. Inclusion criteria for recruitment of PD participants included: 1) diagnosis of idiopathic PD by a movement disorders neurologist; 2) ability to walk independently while OFF-DBS and/or OFF-medication; and 3) had previously undergone DBS implantation surgery, and were actively being treated with DBS; or 4) were deemed eligible for DBS and awaiting surgery. Enrolled participants had either received or were scheduled to receive unilateral, bilateral or staged STN- and GPi-DBS. Five participants implanted with a DBS system prior to the commencement of this study were evaluated post-operatively after programming was optimized. Given these "already implanted" participants were only evaluated at one time-point, they were evaluated via cross-sectional analysis. Eleven participants awaiting DBS were evaluated pre-operatively to obtain a baseline assessment, followed by post-operative evaluations at four weeks, three months and six months after their initial programming session. The initial DBS programming session was scheduled typically four to six weeks after DBS implantation. All participants enrolled voluntarily and

provided written consent for their participation. A power calculation was not calculated given the exploratory nature of this study. A Human Study proposal was submitted and approved by Research Ethics and Management Online at University of Alberta (REMO – pro 00078739).

2.2 Deep Brain Stimulation implantation procedure and programming

All participants underwent DBS implantation by the same neurosurgeon and within the same treatment center. DBS eligibility was assessed pre-operatively by an interdisciplinary team of clinical experts, based on a number of indications and contraindications. Indications for surgery were: 1) clear diagnosis of idiopathic PD; 2) disabling and intolerable motor complications or refractory tremor; and 3) significant motor improvement with above-threshold doses of L-DOPA equivalent dose (LED) (25% higher than the regular LED), as scored by the UPDRS-III. Some contraindications for DBS included: a) predominant refractory axial motor signs (i.e., bulbar, gait, or balance impairments); b) significant cognitive decline or clinically diagnosed dementia; and c) uncontrolled psychiatric or behavioral disorders. The optimal DBS target (i.e., STN or GPi), and unilateral, bilateral, or staged placement of electrodes, were determined by an interdisciplinary team of experts based on the participant's profile.

DBS implantation was performed using a standard, awake DBS-implantation protocol (see below). Briefly, a stereotactic headframe was fixed onto participants' heads on the morning of surgery using local anesthetic, to provide a three-dimensional coordinate system of the target site (Brown 1979). Pre-operative MRI scans were taken in the frame and used to select the DBS-target and plan the point of entry and trajectory to the target site. Electrophysiological recordings with microelectrodes were used to determine the optimal track for DBS lead implantation that

would provide the best symptomatic relief and fewest side effects. Improvement of bradykinesia, rigidity, and tremor were evaluated intraoperatively by asking participants to perform motor tasks, while also evaluating potential side effects. Following the successful implantation of the lead(s), participants were placed under general anesthesia and the lead(s) were connected to subcutaneous lead extensions, which were in turn connected to an IPG inserted into the subclavian area in the chest wall.

Four weeks after surgery, the IPG was turned on and programmed by the same Movement Disorders neurologist for all participants. Adjustments were made in voltage, pulse width, frequency, and contact configuration (e.g., monopolar, bipolar, etc.). Programming aimed to produce the best symptomatic relief, while avoiding potential stimulation-induced side effects due to current spreading. Different group settings were provided for each participant and adjusted monthly for the first six months until DBS programming was optimized. All gait evaluations were conducted after the monthly programming session to ensure the participants' motor performance reflected the most recent programming adjustments.

2.3 Gait assessment and clinical conditions

For pre-operative evaluations, participants were instructed to arrive at 9 am in their OFF-medication state (withholding their anti-parkinsonian medication for over twelve hours). Participants were first examined OFF-medication, followed by the ON-medication condition with an above-threshold dose of L-DOPA. We defined the ON-medication condition as beginning when participants self-reported as being 'optimally ON', which typically occurred 30 – 60 minutes after taking the above-threshold dose of L-DOPA (Nutt et al. 1984).

For post-operative evaluations, participants were instructed to enter the laboratory in the OFF-medication / ON-DBS state. Upon arrival, participants' IPGs were turned off for one hour in order to washout the effects of stimulation. All participants were tested in the following clinical conditions: 1) OFF-medication / OFF-DBS; 2) OFF-medication / ON-DBS; 3) ON-medication / OFF-DBS; and 4) ON-medication / ON-DBS. All four conditions were tested on the same day. The conditions were not randomized given the twelve hour washout period that is required for the defined OFF-medication condition (Hausdorff et al. 2009; Rocchi, Chiari, and Horak 2002; Ryu et al. 2017). Objective gait and balance parameters were collected using the GaitRite mat, a reliable and validated objective tool for gait assessment (Lynall et al. 2017; Morrison et al. 2016). Upon hearing 'Go', participants walked from the start line to the finish line (both measured one meter from the mat to minimize acceleration and deceleration effects), turned around and walked back to the start line, which constituted as two passes. This was conducted for two trials, which provided at least fifteen steps per participant, that was considered to be sufficient for data analyses (Hollman, McDade, and Petersen 2011).

2.4 Clinical scales and gait parameters

The UPDRS-III was used to examine participants' motor performance in each clinical condition (Goetz et al. 2008). The UPDRS-III is administered by an expert examiner, with scores ranging from 0 to 108; higher scores indicate worse motor function. Cognitive function was assessed by an examiner using the Montreal Cognitive Assessment (MoCA), a widely used cognitive screening test that evaluates memory, language, attention and executive and visuospatial function. Scores on the MoCA ranges from 0 – 30, with lower scores indicating more cognitive

dysfunction. Other standard clinical tools for measuring gait performance and functional mobility, including the FOG-Q, prospective fall diaries and the TUG, were also collected (Delbaere et al. 2010; Giladi et al. 2009; Hannan et al. 2010; Sebastião et al. 2016). The FOG-Q is a self-reported questionnaire that ranges from 0 – 24. Participants are asked to rate (from 0 – 4) their gait difficulties and the frequency and duration of any FOG episodes during their daily ambulation. Higher FOG-Q scores reflect worse gait difficulties that may be accompanied by more frequent and/or longer FOG episodes. There is no clear FOG-Q cut-off score for distinguishing PD+FOG and PD-FOG. Instead, the FOG-Q was used in combination with other clinical tools (see section 1.4.3) to distinguish PD+FOG and PD-FOG. For prospective fall diaries, all participants were asked to self-report any falls that occurred either at the time of the fall or immediately after. Participants answered standardized questions that detailed the location of the fall, the events preceding the fall, what may have caused the fall, and any injuries that resulted from the fall. Lastly, the TUG was used to evaluate functional mobility by assessing: 1) participants' balance as they transitioned from the sit-to-stand position; and 2) the time required to walk a designated distance. For the TUG, participants began while sitting in a chair. Upon hearing 'Go', participants were asked to rise out of the chair, walk at their self-preferred pace for ten feet, turn around, walk back towards the chair and sit down. The TUG was administered twice by an examiner for each clinical condition.

Analysis of GaitRite footfalls were done using the ProtoKinetics Movement Analysis Software (PKMAS). Based on the major domains of gait (Lord, Galna, and Rochester 2013), we investigated pace, rhythm, variability, asymmetry and postural control, to evaluate how these components changed after DBS. From these domains, gait velocity (cm/s), step length (cm),

stance time (ms), swing time (ms), stride width (cm), step length ratio (|L/R|), stance time ratio (|L/R|), and step length variability (%CV) were measured (see Table 1). The asymmetry of gait was calculated as an absolute ratio of the left/right footfalls (Patterson et al. 2010). Variability of gait was automatically calculated as %CV by the PKMAS software (Beauchet et al. 2009; Thorpe, Dusing, and Moore 2005).

Table 1. Operational Definition of Gait Parameters

Gait Parameter	Operational Definition
Gait velocity (cm/s)	Distance divided by ambulation time
Step length (cm)	Anterior-posterior distance between two contralateral footfalls in a single step
Stride width (cm)	Lateral distance between two contralateral footfalls in a single step
Stance time (ms)	Constitutes 60% of gait cycle; begins with heel strike and ends with toe off from same foot
Swing time (ms)	Constitutes 40% of gait cycle; begins with toe off and ends with initial heel strike from same foot
Step length ratio (|L/R|)	Absolute ratio of left/right step length
Stance time ratio (|L/R|)	Absolute ratio of left/right stance time
Step length variability (%CV)	Coefficient of variation = (standard deviation / mean) * 100

2.5 Statistical analysis

Between-group statistical differences were compared for participants who were already implanted and participants awaiting surgery. Statistical differences in age and disease duration were analyzed using the Mann-Whitney test, while differences in gender, target location (STN or GPi) and unilateral or bilateral placement were analyzed using the Fisher's Exact test. Pre-operative differences between the ON- and OFF-medication state were analyzed using a non-parametric paired t-test (Wilcoxon signed-rank test). Within-subject differences across clinical conditions and time-points were analyzed using non-parametric repeated measures ANOVA (Friedman's test). Dunn's multiple comparison's test was used post-hoc. GraphPad Prism 8 was used for all statistical analyses. Despite the high number of statistical analyses, a Bonferroni correction was not conducted, given the exploratory nature of our study and the potential risk of inflating the type I error.

3. Results

3.1 Participant demographics

Our combined study groups consisted of thirteen males and no female participants, despite PD typically occurring in a male: female ratio of 1.5:1. However, PD patients within our treatment center that have received DBS are predominantly male (forty-eight males and twelve females), which may contribute to the lack of female participants in the present study. One female participant was recruited into the study but then later excluded (see below).

Participants who were already implanted with DBS (i.e., already implanted participants) were on average 53 ± 9.8 years old and had an average disease duration of 13.2 ± 7.7 years (see Table 2). Already implanted participants had a median L-DOPA equivalent daily dose (LEDD) (Tomlinson et al. 2010) of 1650 ± 769.4 mg and a MoCA score of 28 ± 1.3 (see Table 3). Out of the five already implanted participants, three received STN-DBS and two received GPi-DBS. Four participants had electrodes implanted bilaterally and one participant had a unilateral placement.

Participants awaiting DBS (i.e., prospectively implanted participants) were on average 60.8 ± 10.3 years old and had an average disease duration of 10.9 ± 3.7 years (see Table 2). Prospectively implanted participants had a median pre-operative and post-operative LEDD of 1560 ± 536.0 mg and 1200 ± 469.8 mg, respectively, which were not significantly different. Pre-operative and post-operative MoCA scores were 29 ± 2.3 and 26 ± 1.6, respectively (see Table 4), and were also not significantly different. One female participant was excluded from the study because she was unable to walk independently and experienced intolerable FOG episodes while OFF-medication. A second participant was excluded because they ultimately did not receive the DBS procedure. A third participant withdrew because they were hesitant to turn off the DBS for one hour (i.e., the washout period). From the remaining eight prospectively implanted participants, four participants received STN-DBS and four participants received GPi-DBS. All participants had electrodes implanted bilaterally, though one participant underwent a staged bilateral procedure, with a delay of six months between each side. No statistical differences were found between the 'already implanted' and 'prospectively implanted' participants in terms of age, disease duration, target placement, and unilateral or bilateral implantation (see Table 2).

Table 2. Participant demographics

Clinical Characters \\ Groups	Already Implanted Participants (N=5)	Prospectively Implanted Participants (N=8)	P
Age (years)	53±9.8	60.8±10.3	0.08
Disease Duration (years)	13.2±7.7	10.9±3.7	0.60
Gender (M:F)	5:0	8:0	>0.99
Bilateral : Unilateral	4:1	8:0 (1 Staged bilateral)	0.29
STN : GPi	3:2	4:4	>0.99
Time After Surgery (months)	12±7.4	-	-

Participant demographics for already implanted (N=5) and prospectively implanted (N=8) participants. No statistical differences were found between the two participant groups in terms of age, disease duration, gender, bilateral or unilateral placement, or the DBS target site.

Table 3. L-DOPA Equivalent Daily Dose (LEDD) and Montreal Cognitive Assessment (MoCA) for already implanted participants (N=5).

Patient ID	LEDD (mg)	MoCA
P1	1650	26
P2	2000	29
P3	800	28
P4	1000	28
P5	2700	26
Median ± standard deviation	**1650±769.4**	**28±1.3**

Table 4. L-DOPA Equivalent Daily Dose (LEDD) and Montreal Cognitive Assessment (MoCA) for prospectively implanted participants (N=8).

Patient ID	Pre-DBS LEDD (mg)	Post-DBS LEDD (mg)	Pre-DBS MoCA	Post-DBS MoCA
P1	450	350	29	26
P2	600	1000	29	30
P3	1000	750	30	26
P4	1800	NA	30	26
P5	1560	1200	28	27
P6	1750	1750	23	28
P7	1060	1300	29	26
P8	1700	1500	29	25
Median ± standard deviation	**1310±536.0**	**1200±469.8**	**29±2.2**	**26±1.6**

Neither the pre-DBS LEDD and post-DBS LEDD comparisons nor pre-DBS MoCA and post-DBS MoCA were significantly different.

3.2 Clinical changes assessed by standard scales

3.2.1 Unified Parkinson's Disease Rating Scale – III

As expected, stimulation and medication combined, otherwise known as the best treatment condition (BTC) produced a significant improvement on the UPDRS-III relative to OFF-medication/OFF-DBS for already implanted participants (Fig. 3. N=5; P=0.006).

Prospectively implanted participants showed significant improvement on the UPDRS-III in the ON-medication condition compared to OFF-medication before surgery (N=8; P=0.008). At four weeks post-programming, UPDRS-III scores were significantly lower (i.e., improved) in the OFF-medication/ON-DBS state compared to pre-operative OFF-medication (Fig. 4B. N=8; P=0.04). UPDRS-III scores were also significantly lower in the BTC compared to pre-operative OFF-medication and OFF-medication/OFF-DBS (Fig. 4B. N=8; P=0.0002 and 0.0004, respectively). At three months post-programming, UPDRS-III scores were significantly lower in the OFF-medication/ON-DBS condition relative to pre-operative OFF-medication (Fig. 4C. N=8; P=0.02). UPDRS-III scores in the BTC were significantly lower than pre-operative OFF-medication and OFF-medication/OFF-DBS (N=8; P<0.0001 and 0.0004, respectively). At six months post-programming, UPDRS-III scores in the BTC were significantly lower than the pre-operative OFF-medication and OFF-medication/OFF-DBS states (Fig. 4D. N=5; P=0.004 and 0.008, respectively). UPDRS-III scores did not change in the BTC overtime up to six months post-programming (Fig. 4A).
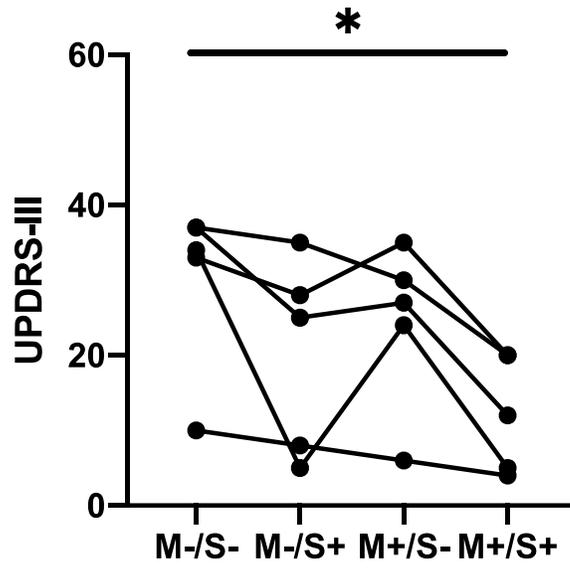
Figure 3. UPDRS-III scores for already implanted participants (N=5). 'M' denotes medication state while 'S' denotes stimulation state.
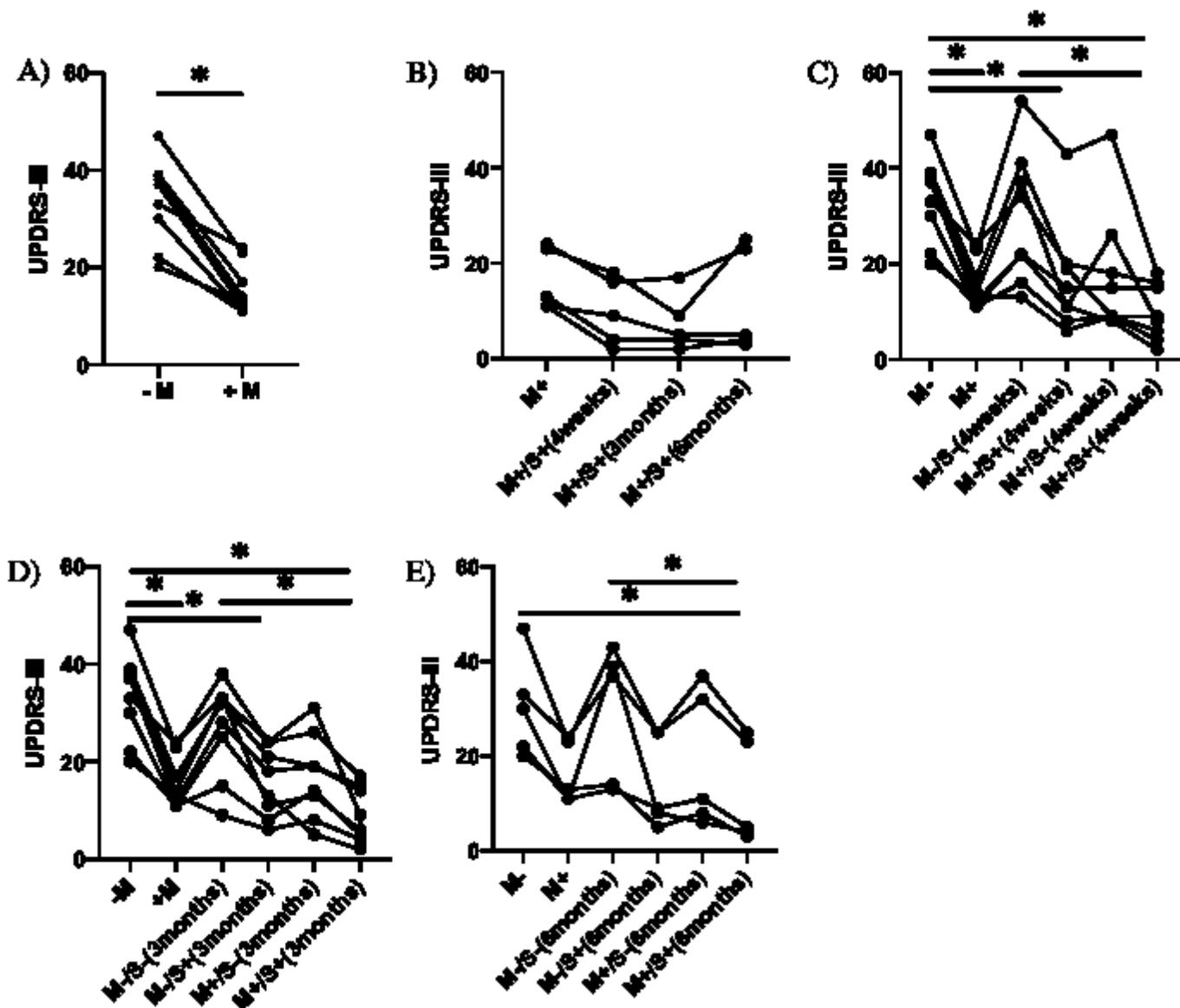
Figure 4. UPDRS-III motor scores for prospectively implanted participants (N=8). A) Pre-operative UPDRS-III scores in the OFF- and ON-medication states (N=8). B) UPDRS-III scores in the BTC at four weeks, three months, and six months post-programming for prospectively implanted participants. UPDRS-III scores across treatment conditions for prospectively implanted participants at C) four weeks post-programming (N=8), D) three months post-programming (N=8), and E) six months post-programming (N=5). 'M' denotes medication state while 'S' denotes stimulation state.

3.2.2 Freezing of Gait Questionnaire and prospective fall diaries

The frequency and duration of FOG episodes were evaluated in prospectively implanted participants using the FOG-Q. Participants were administered the FOG-Q in a retrospective manner to document FOG episodes before DBS. The FOG-Q was also administered after DBS at three months post-programming (Fig. 5B). Three-month FOG-Q scores were used for analysis because FOG-Q scores at six months were limited due to the small sample size. Meanwhile, FOG-Q scores from four weeks post-programming would not reflect the clinical benefits from DBS programming. Therefore, only pre-operative and three-month post-operative comparisons were used for analysis (Fig. 5B).

The average FOG-Q score was 3.9 before DBS and increased to 6 after DBS (i.e., worsened), though this was not statistically significant. One participant with pre-existing FOG prior to DBS experienced post-operative worsening, which was shown by a 6-point increase on the FOG-Q and eight reported falls. One participant developed FOG after DBS ($FOG-Q_{before\ DBS} = 1$ vs. $FOG-Q_{after\ DBS} = 12$), which progressively worsened. This participant displayed severe axial impairment following DBS and reported two injurious fall that required medical attention. Prospective fall diaries were also kept by participants following DBS. PD+FOG participants (N=3. See section 1.4.3 above for classifying PD+FOG and PD-FOG participants) experienced a median of 4 falls following DBS, while PD-FOG participants (N=5) experienced 1 fall (Fig 5A. P=0.04).
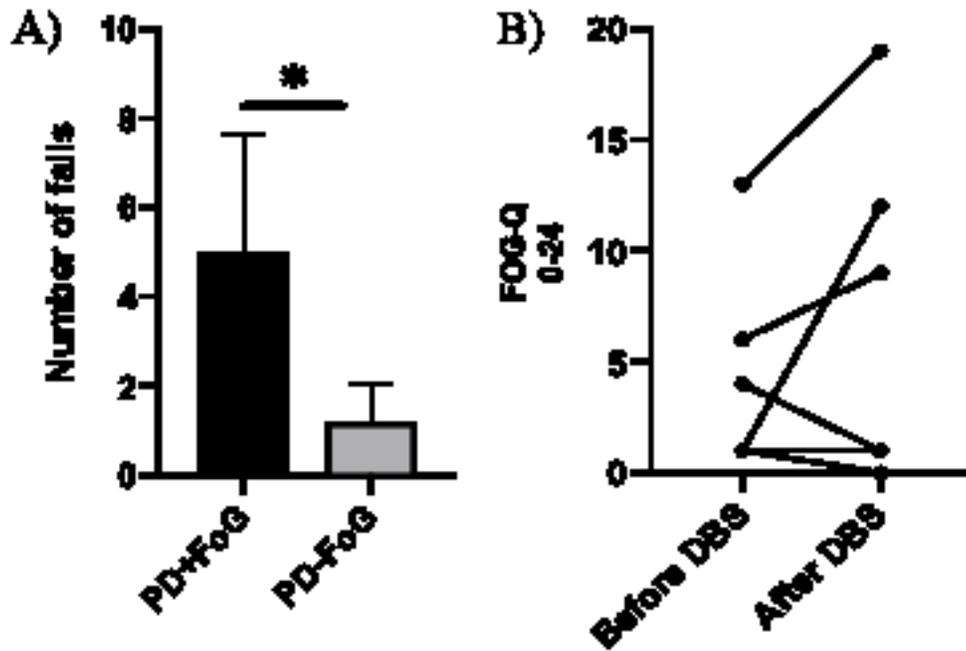
Figure 5. Freezing of Gait Questionnaire and prospective falls over the course of three months post-programming. A) The number of falls were significantly higher for PD+FOG participants (N=3) compared to PD-FOG participants (N=5). B) Frequency and duration of FOG was evaluated for prospectively implanted participants (N=7). No significant differences in FOG-Q scores were detected before or after DBS.

3.3 Gait and balance

3.3.1 Timed-Up and Go

For the TUG, already implanted participants performed significantly better (i.e., shorter TUG times) in the BTC relative to OFF-medication/OFF-DBS (Fig. 6. N=5; P=0.0002) and ON-medication/OFF-DBS (Fig. 6. N=5; P=0.003).

Prospectively implanted participants had significantly shorter TUG times while ON-medication than OFF-medication (N=8; P=0.002). At four weeks post-programming, TUG time in the ON-medication state was significantly shorter than during the OFF-medication/OFF-DBS condition (Fig. 7B. N=8; P=0.0006). TUG times were also significantly shorter in the BTC relative to pre-operative OFF-medication and OFF-medication/OFF-DBS (Fig. 7B. N=8; P=0.005 and 0.006, respectively). At three months post-programming, TUG time in the BTC was significantly shorter than pre-operative OFF-medication and OFF-medication/OFF-DBS (Fig. 7C. N=8; P=0.001 and P=0.01, respectively). TUG during the ON-medication state was also significantly shorter than the OFF-medication/OFF-DBS state (Fig. 7C. N=8; P=0.007). At six months post-programming, participants had shorter TUG times while ON-medication relative to OFF-medication/OFF-DBS (Fig. 7D. N=5; P=0.04). TUG performance in the BTC did not change up to six months post-programming (Fig. 7A).
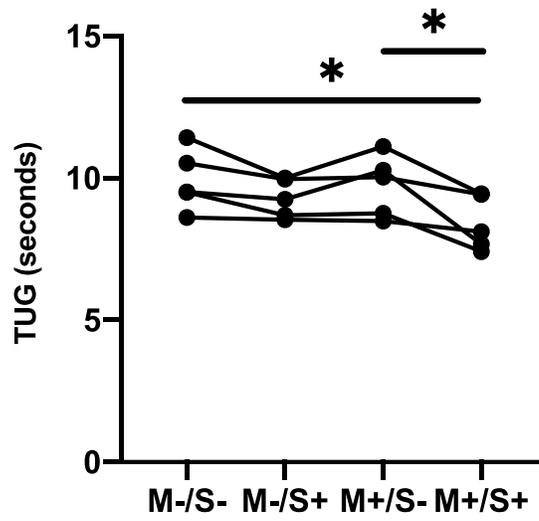
Figure 6. Timed-Up and Go performance for already implanted participants (N=5). 'M' denotes medication state while 'S' denotes stimulation state.
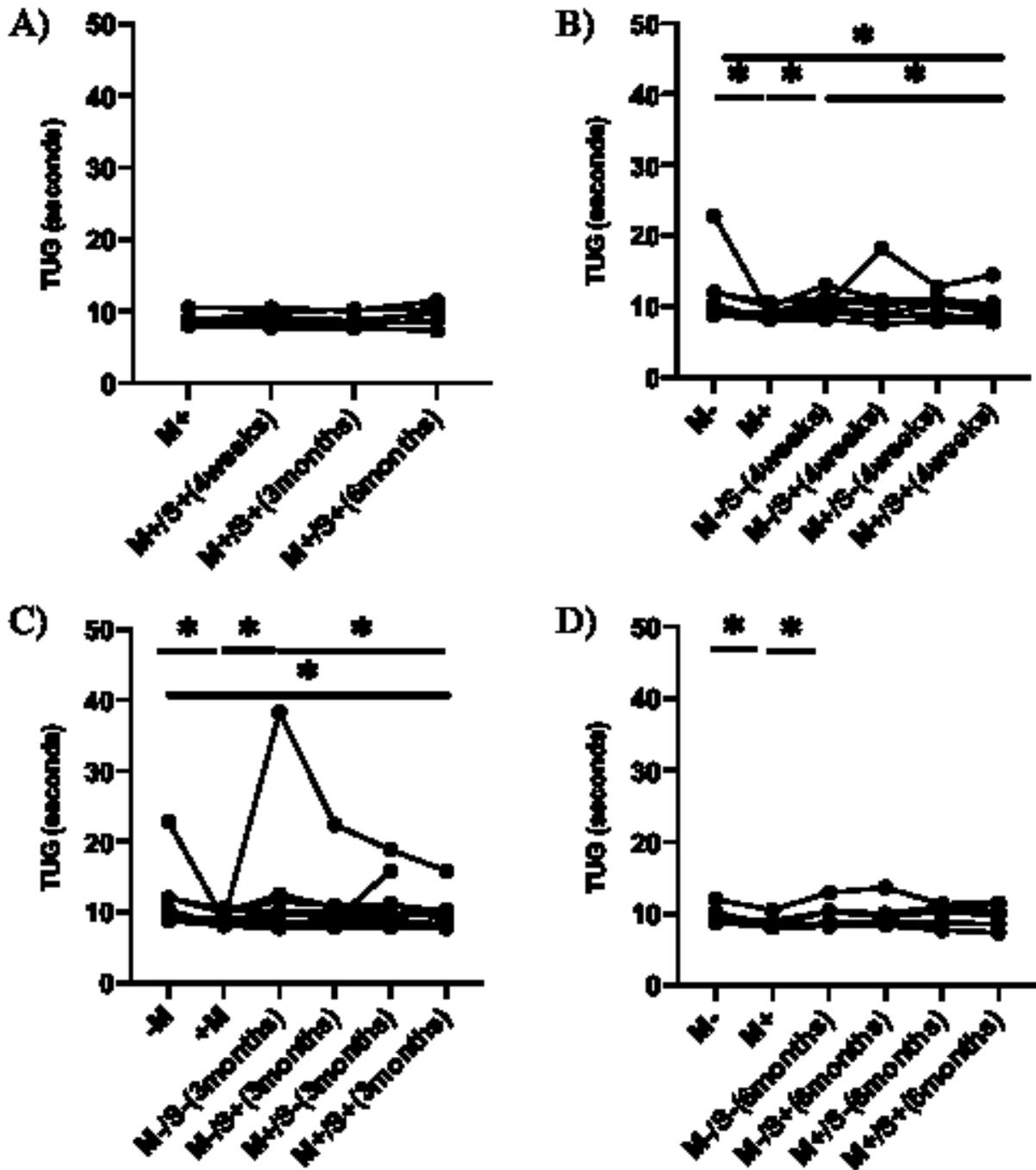
Figure 7. Timed-Up and Go for prospectively implanted participants. A) TUG performance in the BTC at four weeks, three months, and six months post-programming for prospectively implanted participants. TUG performance across treatment conditions for prospectively implanted participants at B) four weeks post-programming (N=8), C) three months post-programming (N=8), and D) six months post-programming (N=5). 'M' denotes medication state while 'S' denotes stimulation state.

3.3.2 Pace domain

We evaluated gait velocity (Fig. 8 & 9) and step length (Fig. 10 & 11) for all participants to evaluate changes in the pace domain following DBS. Already implanted participants had significantly faster gait velocity in the BTC relative to the OFF-medication/OFF-DBS (Fig. 8. N=5; P<0.0001), OFF-medication/ON-DBS (N=5; P=0.02) and ON-medication/OFF-DBS conditions (N=5; P=0.02). Step length was also significantly longer in the BTC compared to OFF-medication/OFF-DBS (Fig. 10. N=5; P=0.0004).

Prospectively implanted participants had significantly higher velocity while ON-medication compared to OFF-medication/OFF-DBS (Fig. 9B. N=8; P=0.005) at four weeks post-programming. Participants also walked significantly faster in the BTC relative to pre-operative OFF-medication and OFF-medication/OFF-DBS (Fig. 9B. N=8; P=0.0006 and P=0.003, respectively). At three months post-programming, the improvements in gait velocity were sustained as participants walked significantly faster in the BTC compared to the pre-operative OFF-medication and OFF-medication/OFF-DBS states (Fig. 9C. N=8; P=0.002 and P=0.03, respectively). There was also a significant improvement in gait velocity in the ON-medication/OFF-DBS state compared to the pre-operative OFF-medication and OFF-medication/OFF-DBS state (Fig. 9C. N=8; P=0.001 and P=0.02, respectively). At six months post-programming, participants walked significantly faster in the ON-medication state compared to OFF-medication/OFF-DBS (Fig. 9D. N=5; P=0.0004), though no other significant differences were found at this time; importantly, the addition of stimulation, or the BTC, did not produce significant improvements in gait velocity compared to OFF-medication/OFF-DBS. Gait velocity

and step length during the BTC did not significantly change up to six months post-programming (Fig 9A and 11A).

Figure 8. Gait velocity for already implanted participants (N=5). 'M' denotes medication state while 'S' denotes stimulation state.
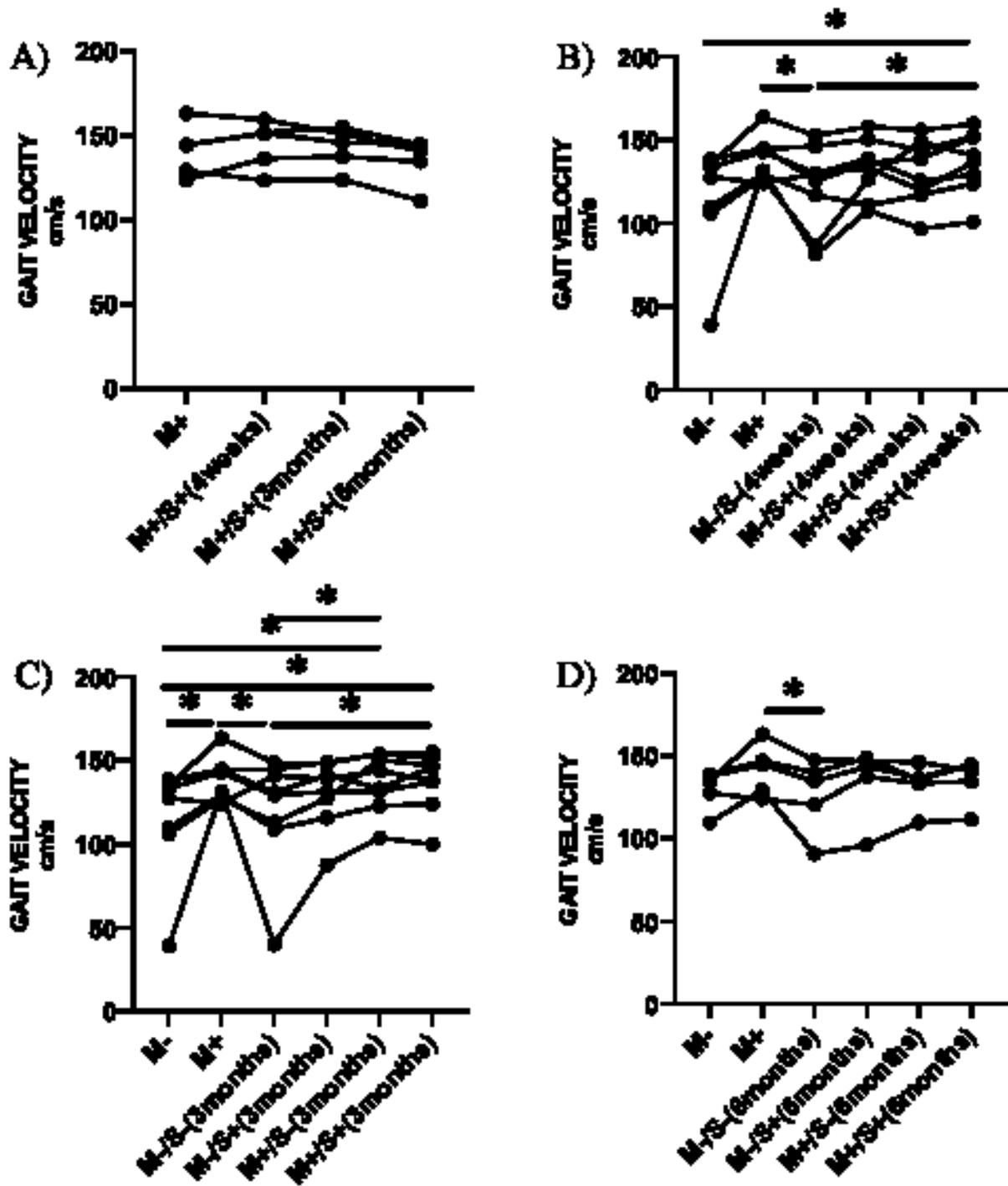
Figure 9. Gait velocity for prospectively implanted participants. A) Gait velocity in the BTC at four weeks, three months, and six months post-programming for prospectively implanted participants. Gait velocity across treatment conditions for prospectively implanted participants at B) four weeks post-programming (N=8), C) three months post-programming (N=8), and D) six months post-programming (N=5). 'M' denotes medication state while 'S' denotes stimulation state.

Prospectively implanted participants walked with significantly longer step lengths while ON-medication compared to OFF-medication (N=8; P=0.002). At four weeks post-programming, step length was significantly longer in the ON-medication condition and BTC compared to OFF-medication/OFF-DBS (Fig. 11B. N=8; P=0.0004 and P=0.01, respectively). At three months post-programming, step length was significantly longer in the ON-medication state compared to OFF-medication/OFF-DBS (Fig. 11C. N=8; P=0.004). Step length in the BTC was also significantly longer than the pre-operative OFF-medication and OFF-medication/OFF-DBS states (Fig. 11C. N=8; P=0.02 and P=0.01, respectively). At six months post-programming, participants walked with significantly longer step lengths in the ON-medication condition compared to the OFF-medication/OFF-DBS state (Fig. 11D. N=5; P= 0.04), but as was observed for gait velocity, there was no improvement in step length at six months in the BTC. Step length in the BTC also did not change up to six months post-programming (Fig. 11A).

Figure 10. Step length for already implanted participants (N=5). 'M' denotes medication state while 'S' denotes stimulation state.
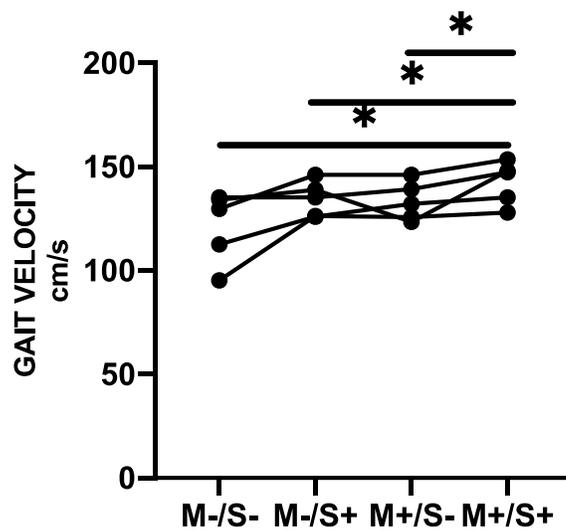
Figure 11. Step length for prospectively implanted participants. A) Step length in the BTC at four weeks, three months, and six months post-programming for prospectively implanted participants. Step length across treatment conditions for prospectively implanted participants at B) four weeks post-programming (N=8), C) three months post-programming (N=8), and D) six months post-programming (N=5). 'M' denotes medication state while 'S' denotes stimulation state.

3.3.3 Asymmetry of gait

Step length ratio and stance time ratio were measured to evaluate changes in gait asymmetry following DBS. Participants who were already implanted with DBS did not have significant changes in step length ratio (Fig. 12) or stance time ratio (Fig. 14) between the clinical conditions.

Pre-operatively, prospectively implanted participants did not have any significant changes in stance time ratio or step length ratio between the ON- and OFF-medication state. At four weeks post-programming, there were no significant changes in step length ratio (Fig. 13B) or stance time ratio (Fig. 15B). At three months post-programming, the BTC significantly reduced (i.e., improved) step length ratio relative to the pre-operative OFF-medication state (N=8; P=0.004), though there was no significant change in stance time ratio. At six months post-programming, there were no statistical differences for step length or stance time ratio in any of the clinical conditions compared to OFF-medication/OFF-DBS. Step length ratio and stance time ratio in the BTC did not significantly change up to six months post-programming (Fig. 13A and 14A).

Figure 12. Step length ratio for already implanted participants (N=5). 'M' denotes medication state while 'S' denotes stimulation state.
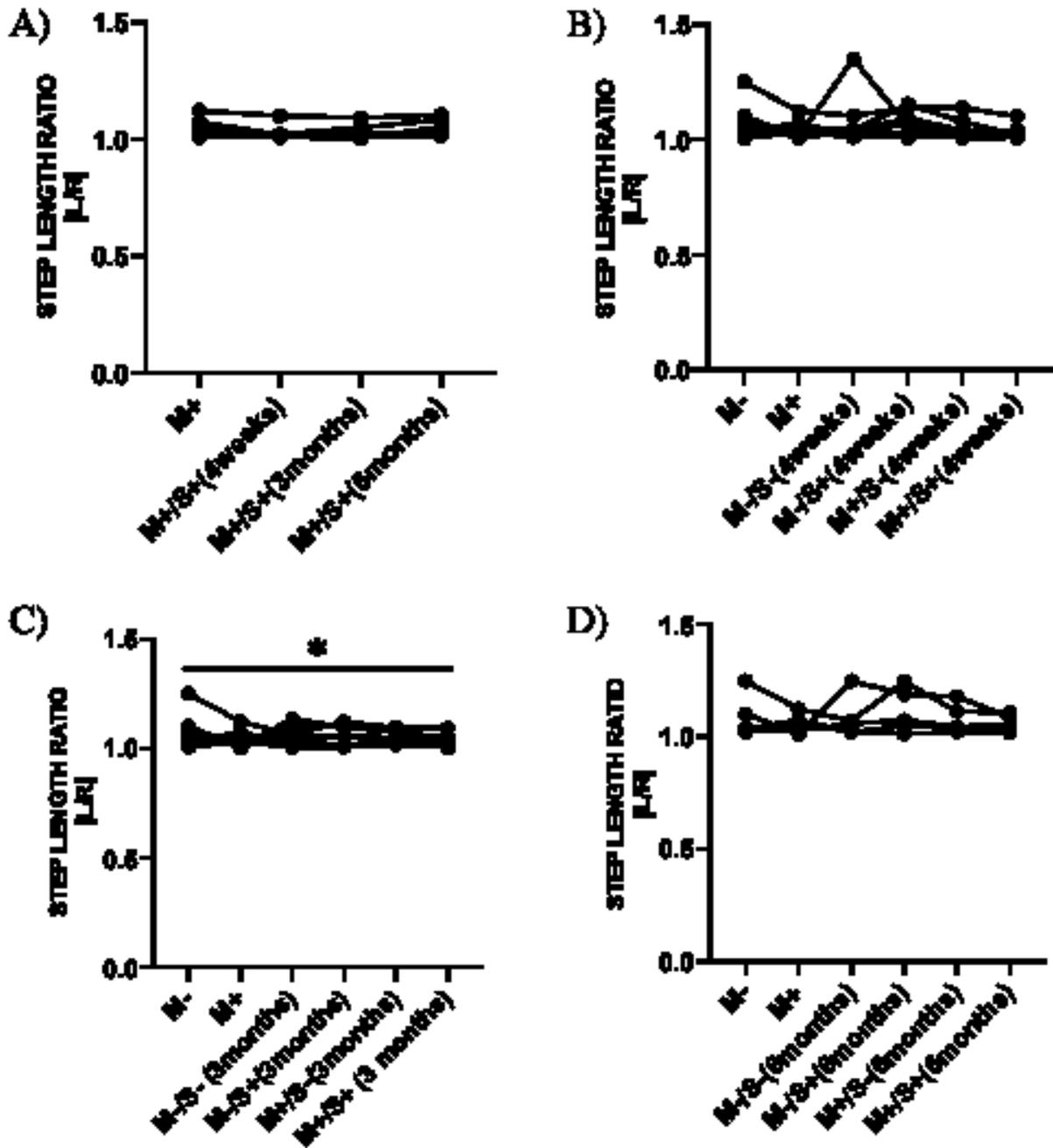
Figure 13. Step length ratio for prospectively implanted participants. A) Step length ratio in the BTC at four weeks, three months, and six months post-programming for prospectively implanted participants. Step length ratio across treatment conditions for prospectively implanted participants at B) four weeks post-programming (N=8), C) three months post-programming (N=8), and D) six months post-programming (N=5). 'M' denotes medication state while 'S' denotes stimulation state.
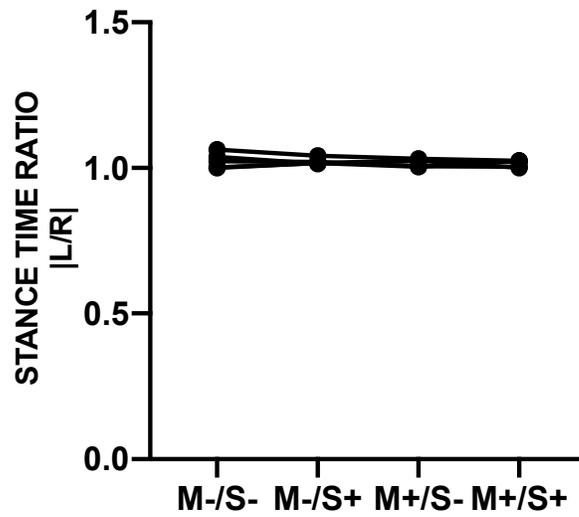
Figure 14. Stance time ratio for already implanted participants (N=5). 'M' denotes medication state while 'S' denotes stimulation state.

Figure 15. **Stance time ratio for prospectively implanted participants.** A) Stance time ratio in the BTC at four weeks, three months, and six months post-programming for prospectively implanted participants. Stance time ratio across treatment conditions for prospectively implanted participants at B) four weeks post-programming (N=8), C) three months post-programming (N=8), and D) six months post-programming (N=5). 'M' denotes medication state while 'S' denotes stimulation state.

3.3.4 Postural instability

Stride width was assessed to evaluate balance control following DBS. For already implanted participants, there was a significant difference in stride width between the BTC and the OFF-medication/OFF-DBS condition (Fig. 16. N=5; P=0.03). Prospectively implanted participants did not have any significant changes in stride width at four weeks, three months or six months post-programming (Fig. 17B-D). Stride width in the BTC also did not change up to six months post-programming (Fig. 17A).
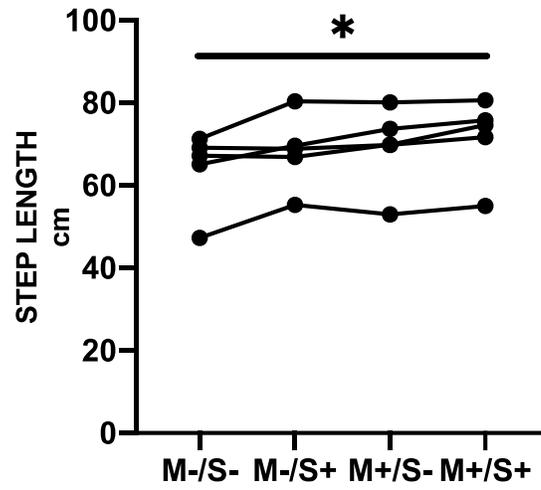
Figure 16. Stride width for already implanted participants (N=5). 'M' denotes medication state while 'S' denotes stimulation state.
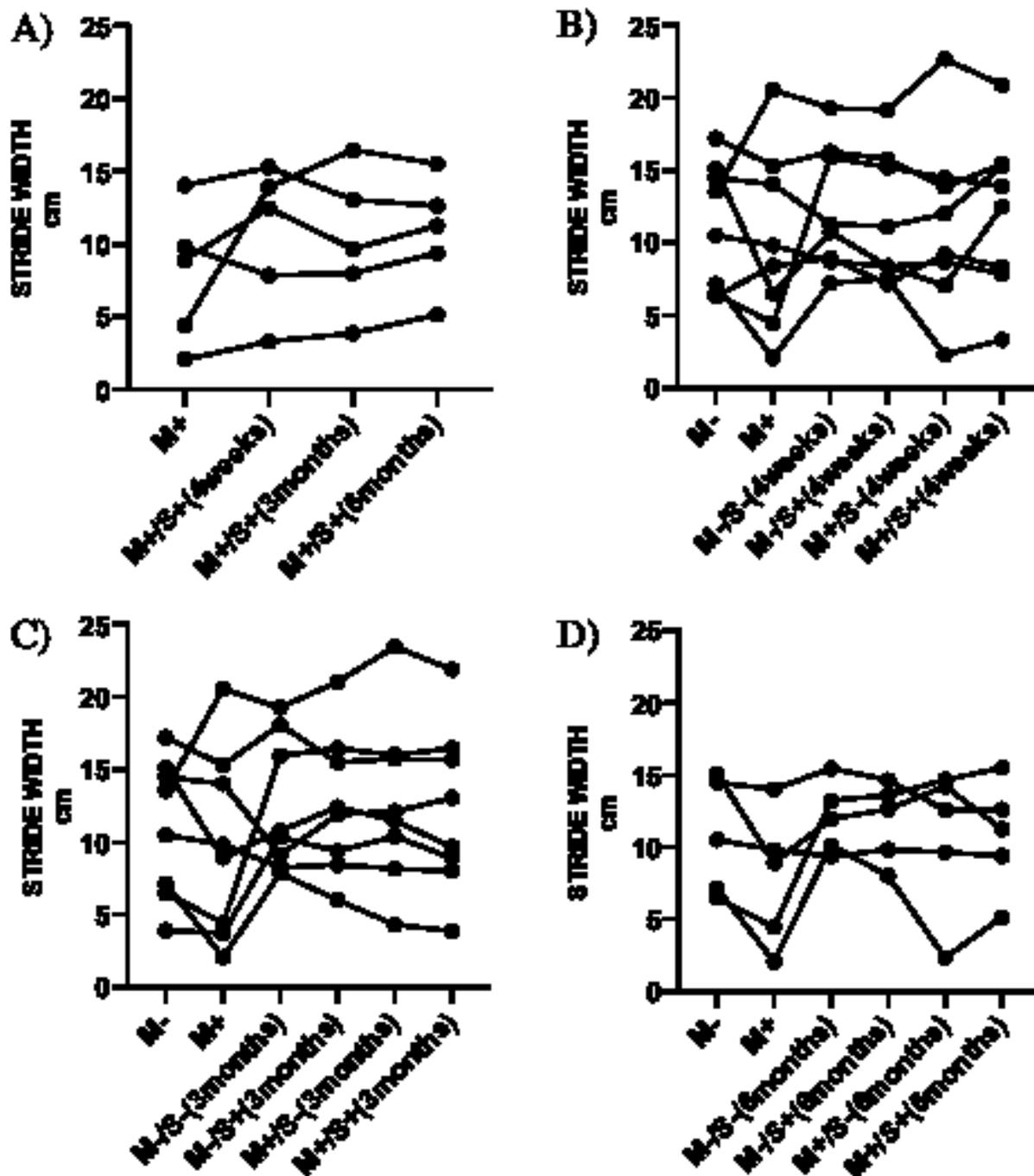
Figure 17. Stride width for prospectively implanted participants. A) Stride width in the BTC at four weeks, three months, and six months post-programming for prospectively implanted participants. Stride width across treatment conditions for prospectively implanted participants at B) four weeks post-programming (N=8), C) three months post-programming (N=8), and D) six months post-programming (N=5). 'M' denotes medication state while 'S' denotes stimulation state.

3.3.5 Variability of gait

Step length %CV was measured to evaluate gait variability following DBS. There were no statistical differences in step length %CV between the four clinical conditions in already implanted participants (Fig. 18).

Prospectively implanted participants had a significant reduction in step length %CV in the ON-mediation state compared to the OFF-medication state (N=8; P=0.001). At four weeks post-programming, step length %CV was significantly reduced in the ON-medication/OFF-DBS condition and BTC relative to pre-operative OFF-medication (Fig. 19B. N=8; P= 0.04 and P= 0.008, respectively). At three months post-programming, step length %CV was significantly reduced in the OFF-medication/ON-DBS state compared to the pre-operative OFF-medication condition (Fig. 19C. N=8; P= 0.02). At six months post-programming, there were no statistical changes in step length %CV. Step length %CV in the BTC did not significantly change up to six months post-programming (Fig. 19A).
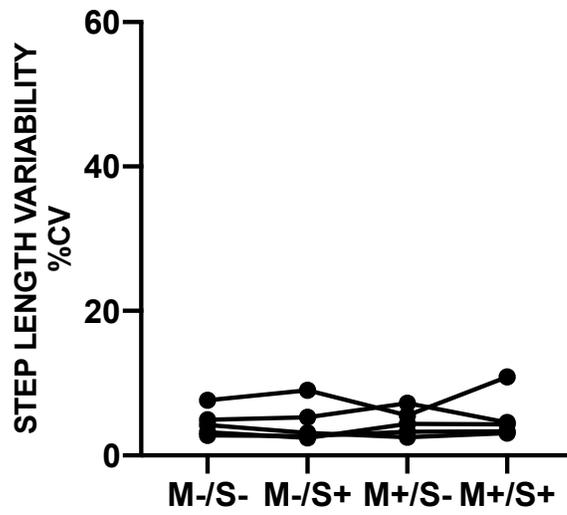
Figure 18. Step length variability for already implanted participants (N=5). 'M' denotes medication state while 'S' denotes stimulation state.
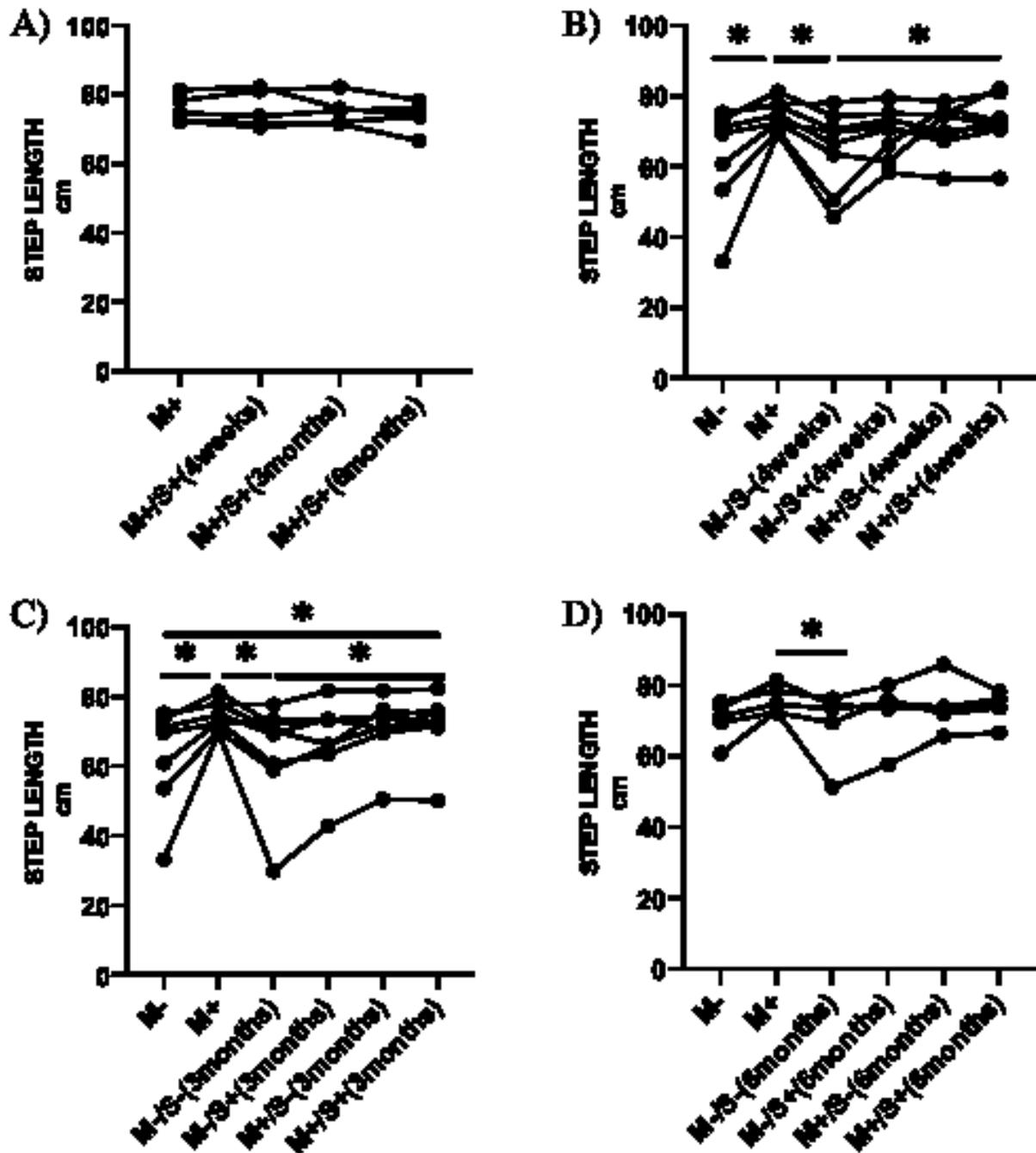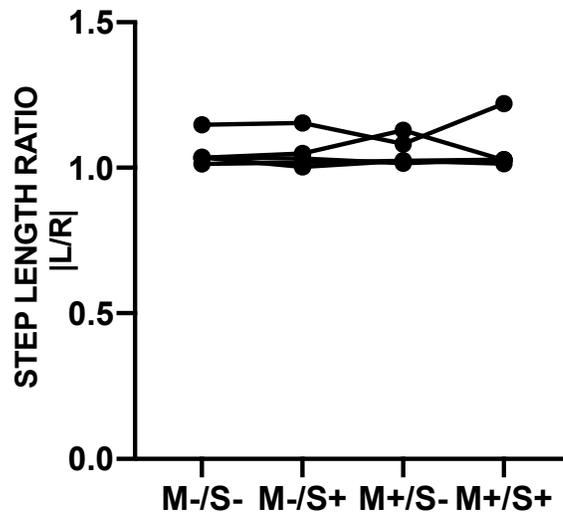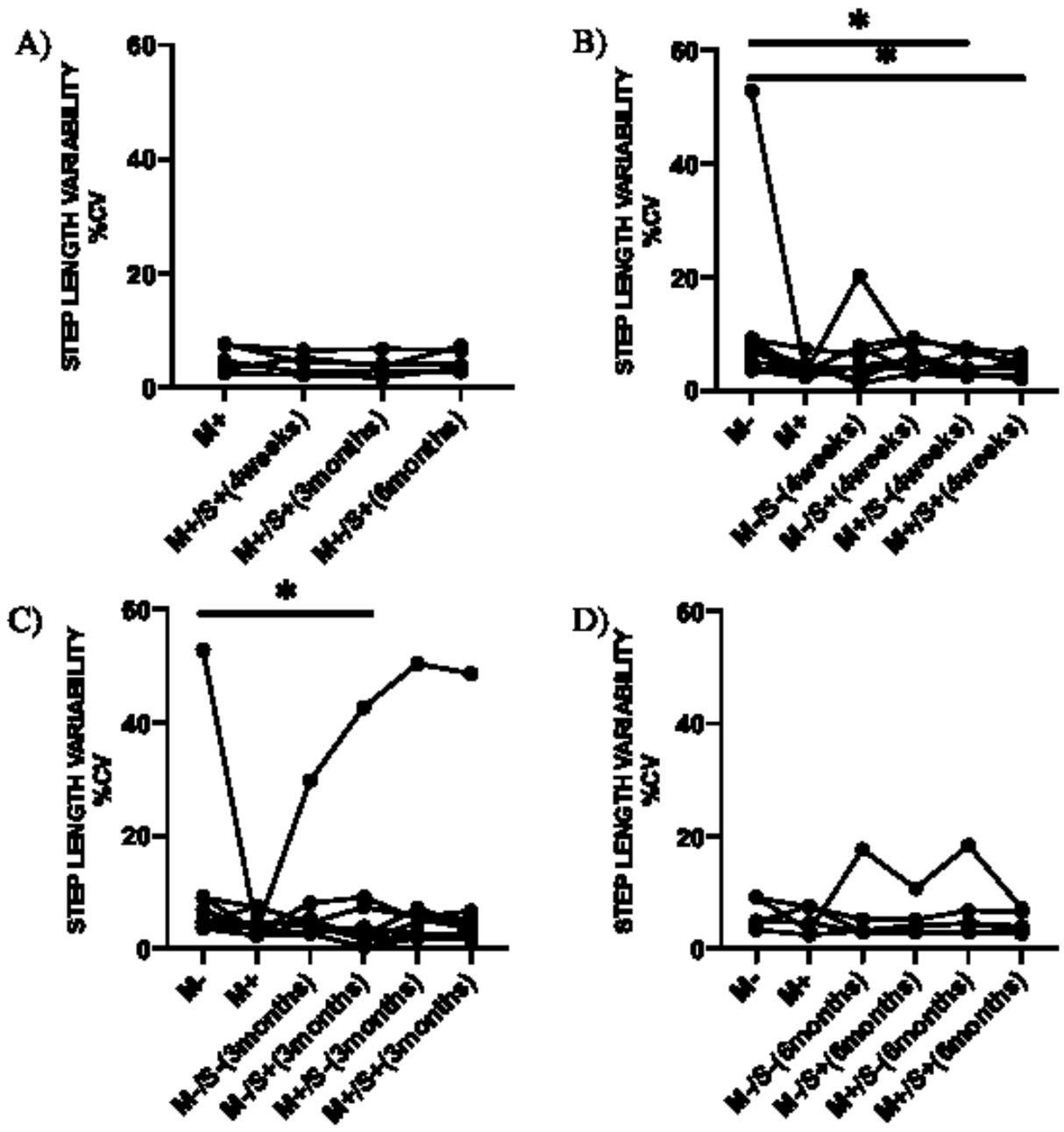
Figure 19. Step length variability for prospectively implanted participants. A) Step length variability in the BTC at four weeks, three months, and six months post-programming for prospectively implanted participants. Step length variability across treatment conditions for prospectively implanted participants at B) four weeks post-programming (N=8), C) three months post-programming (N=8), and D) six months post-programming (N=5). 'M' denotes medication state while 'S' denotes stimulation state.

3.3.6. Rhythm

Stance time and swing time were measured to evaluate changes in rhythm following DBS. Already implanted participants had significantly shorter stance times in the BTC relative to OFF-medication/OFF-DBS (Fig. 20. N=5; P=0.0002). However, there were no significant changes in swing time between the four clinical conditions (Fig. 22).

Prospectively implanted participants did not show any significant differences in stance time or swing time between the ON- and OFF-medication condition. For prospectively implanted participants, there were no significant changes in stance time at four weeks, three months or six months post-programming (Fig. 21B-D). At four weeks post-programming, there was a significant difference in swing time between the OFF-medication/ON-DBS and ON-medication conditions (Fig. 23B. N=8; P=0.02 and P=0.02). At three months post-programming, swing time in the OFF-medication/OFF-DBS state was significantly shorter than the ON-medication state (Fig. 23D. N=8; P=0.0004). There was also a significant difference in swing time between the ON-medication/OFF-DBS condition compared to the ON-medication state (Fig. 23C. N=8; P=0.002). At six months post-programming, there were no significant changes in swing time. Stance time and swing time in the BTC did not significantly change up to six months post-programming (Fig. 21A and 23A).
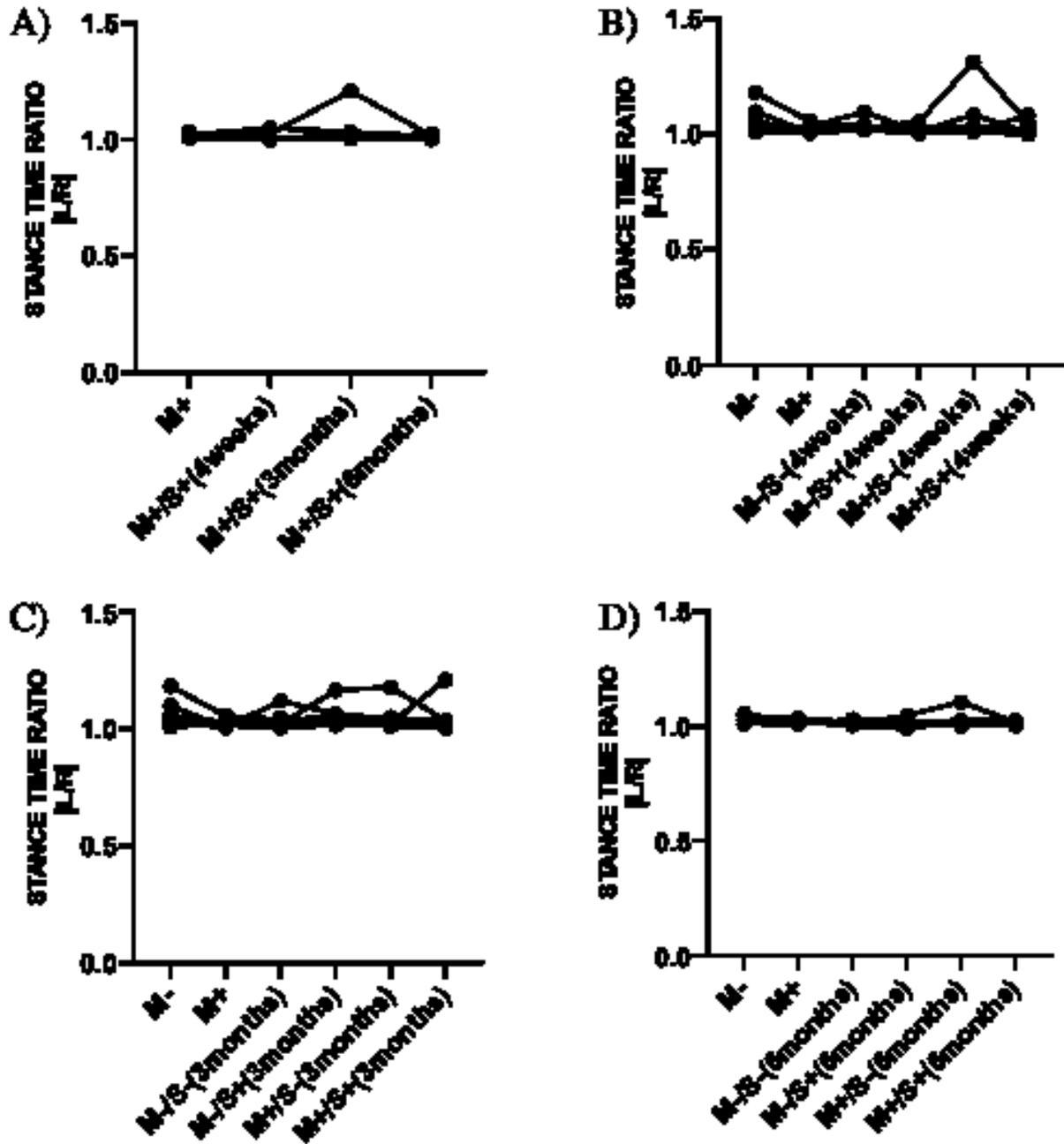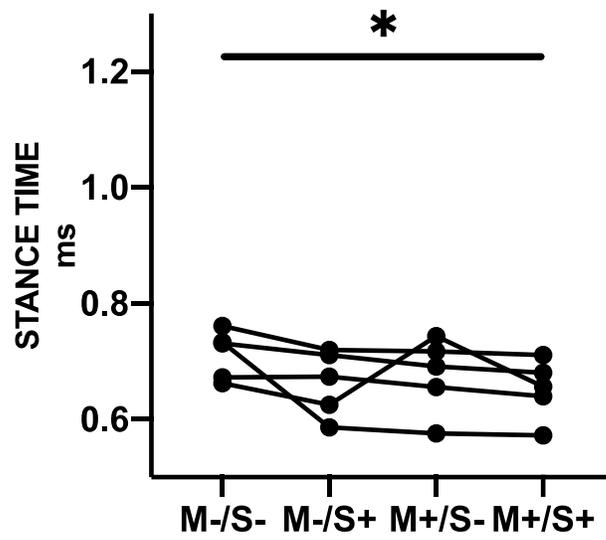
Figure 20. Stance time for already implanted participants (N=5). 'M' denotes medication state while 'S' denotes stimulation state.
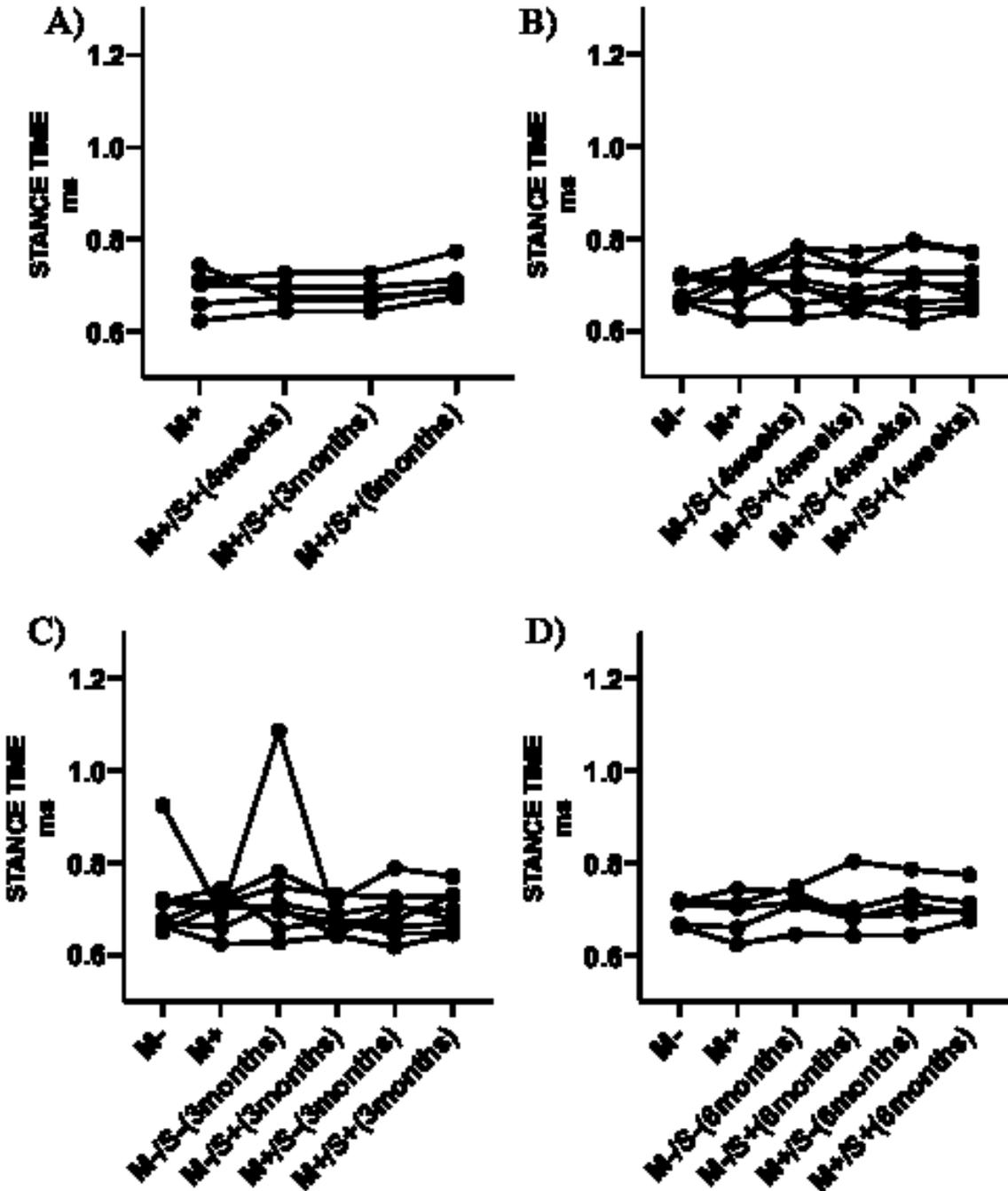
Figure 21. Stance time for prospectively implanted participants. A) Stance time in the BTCat four weeks, three months, and six months post-programming for prospectively implanted participants. Stance time across treatment conditions for prospectively implanted participants at B) four weeks post-programming (N=8), C) three months post-programming (N=8), and D) six months post-programming (N=5). 'M' denotes medication state while 'S' denotes stimulation state.
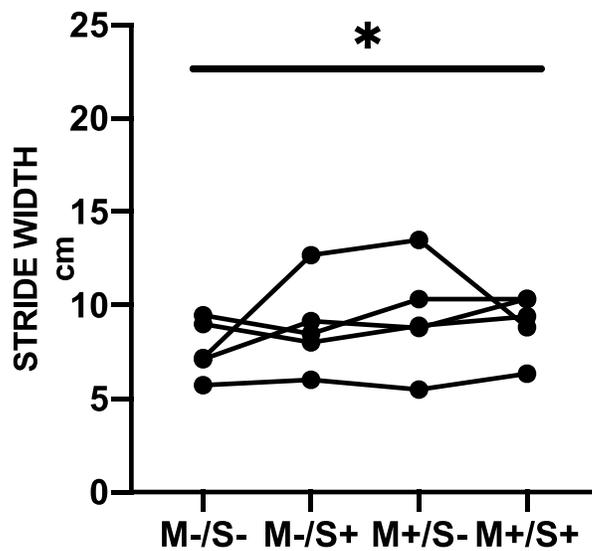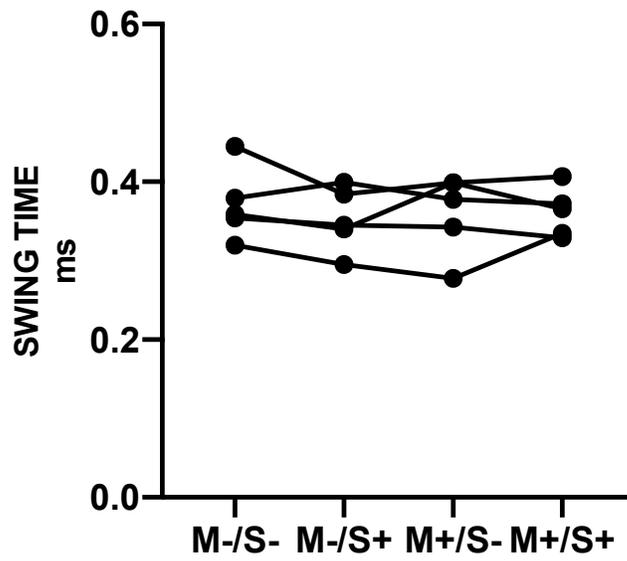
Figure 22. Swing time for already implanted participants (N=5). 'M' denotes medication state while 'S' denotes stimulation state.
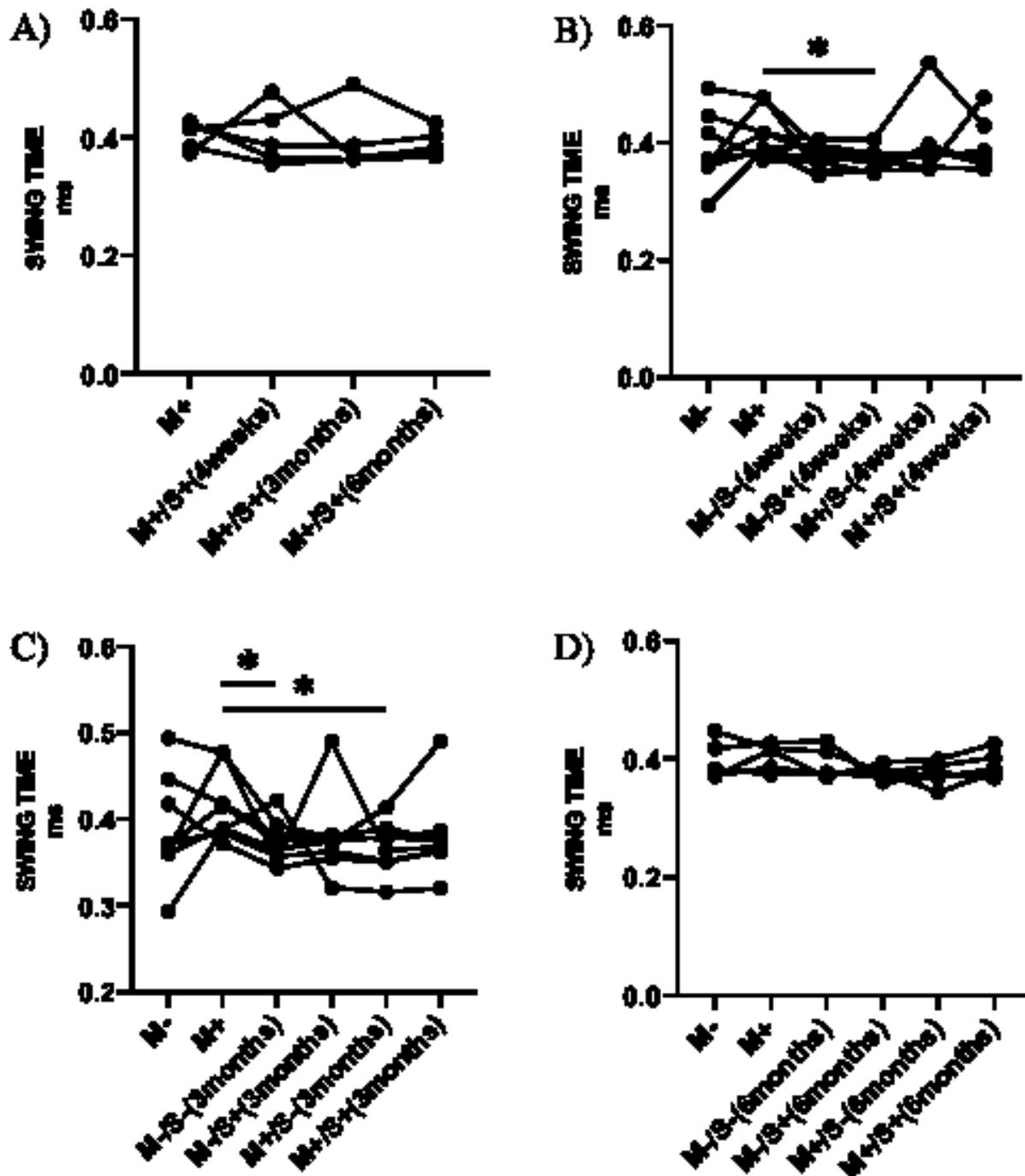
Figure 23. Swing time for prospectively implanted participants. A) Swing time in the BTC at four weeks, three months, and six months post-programming for prospectively implanted participants. Swing time across treatment conditions for prospectively implanted participants at B) four weeks post-programming (N=8), C) three months post-programming (N=8), and D) six months post-programming (N=5). 'M' denotes medication state while 'S' denotes stimulation state.

3.3.7 Gait and balance outcomes between STN- and GPi-DBS

Differences in gait and balance parameters between STN-DBS and GPi-DBS prospectively

implanted participants are depicted in Figure 24. Already implanted participants were not

included in the analysis in an attempt to reduce heterogeneity. Particular attention was paid to

differences in the ON-medication condition prior to surgery versus the BTC after surgery. Within

our cohort, four participants received STN-DBS and four participants received GPi-DBS,

making these small sample comparisons more preliminary than other data presented in this

thesis. STN- and GPi-DBS comparisons were conducted at three months post-programming,

because all participants have gone through three-month programming, whereas only five

participants have received six month programming at this time.

Compared to the ON-medication state before surgery, TUG times were 7.6% longer for STN-

DBS participants at three months post-programming, while GPi-DBS participants took 10.1%

longer to complete the TUG. For gait velocity, STN-DBS participants had a 0.4% improvement

following DBS, while GPi-DBS participants had a 8.7% improvement. In terms of step length,

STN-DBS experienced a post-operative worsening of 5.2%, while GPi-DBS participants

experienced a 3% improvement. For step length asymmetry, most STN- and GPi-DBS

participants displayed reduced asymmetry following the procedure; STN-DBS participants

showed a 1.3% improvement for step length ratio and GPi-DBS participants showed a 2.3%

improvement. Both groups showed a minimal change for stance time ratio before and after DBS

(STN-DBS: 0.65% vs GPi-DBS: 0.31%). STN-DBS participants had 19.7% wider (i.e., more

unstable) stride width, while GPi-DBS had 6.2% wider stride width. In STN-DBS participants,

stance time was prolonged by 0.6%, while GPi-DBS participants had a 4.1% reduction in stance

time. STN-DBS participants had a 16.7% reduction in swing time, while GPi-DBS had a 5.7%

reduction in swing time. STN-DBS participants had a 5.2% improvement in step length %CV,

while GPi-DBS had a 2% improvement in step length %CV. All GPi-DBS participants showed a

trend towards improved step length %CV, with the exception of one participant who experienced

severe FOG prior to DBS and presented as an outlier. No significant differences were found for

any gait parameters between participants who received STN- and GPi-DBS.
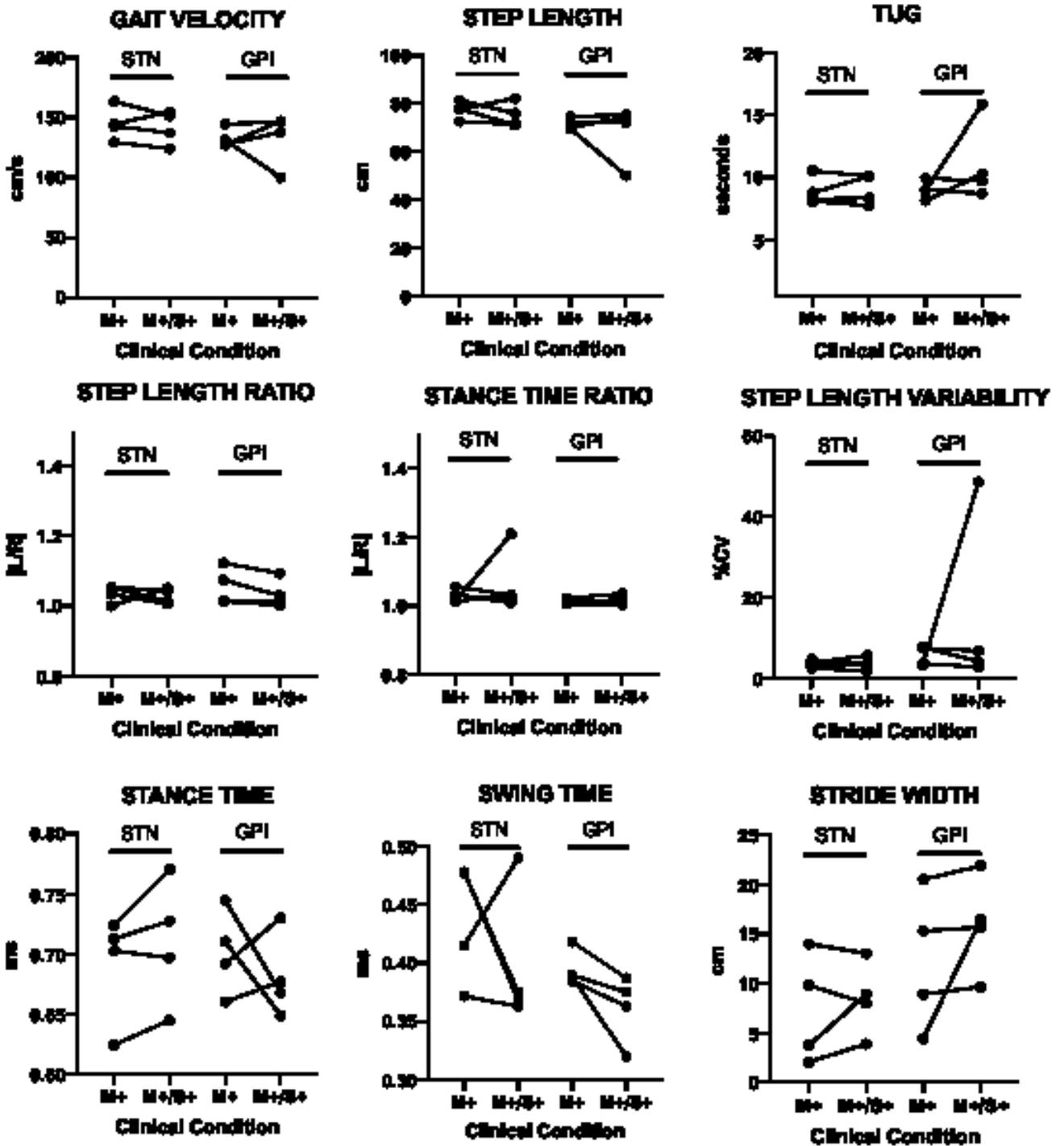
Figure 24. STN vs GPi-DBS gait impairments. This figure illustrates the change in gait parameters during the BTC before surgery (i.e., ON-medication) and after surgery (i.e., ON-medication/ON-DBS). Changes were assessed before and after STN- and GPi-DBS ($N_{STN-DBS}$ = 4 and $N_{GPi-DBS}$ = 4) at three months post-programming.

4.0 Discussion

The present study aims to understand the spatiotemporal changes in gait and balance after STN-
and GPi-DBS. Our study collected objective and quantitative gait parameters using the
ProtoKinetic GaitRite mat, as well as self-reported outcomes via prospective fall diaries and the
FOG-Q. To our knowledge, this is the first study to investigate the mechanism of gait by
examining the five gait domains following STN- and GPi-DBS in PD participants using
objective and quantitative data.

4.1 Unified Parkinson's Disease Rating Scale – III scores improve following Deep Brain Stimulation

All participants in the study were L-DOPA responsive prior to surgery: in the prospectively
implanted group, there was a 61.4% improvement on the UPDRS-III between the ON- and OFF-
medication state prior to DBS. As per the literature, we therefore expected all participants to
receive a significant motor benefit from DBS (Lang et al. 2006; Morishita et al. 2011). Indeed,
we found that all prospectively implanted participants experienced a significant improvement on
the UPDRS-III in the BTC relative to the pre-operative OFF-medication and post-operative OFF-
medication/OFF-DBS conditions. As also expected, already implanted participants showed
significantly lower UPDRS-III scores with the BTC compared to the OFF-medication/OFF-DBS
condition (64.7% lower). In short, DBS across all participants achieved its desired clinical
benefit.

In the prospectively implanted group at four weeks, three months and six months post-
programming, the BTC induced a 75.7%, 78.6% and 83.3% improvement (see Table 1 – 4 in

Appendix), respectively, relative to pre-operative OFF-medication. At four weeks and three months post-programming, stimulation alone produced a significant motor improvement relative to pre-operative OFF-medication. Both groups of participants experienced the greatest motor improvement in the BTC (Rodriguez-Oroz et al. 2005; Simuni et al. 2002).

4.2 Gait and balance

4.2.1 Timed-Up and Go improves with medication and stimulation combined

For already implanted participants, TUG was significantly longer during the ON-medication/OFF-DBS and OFF-medication/OFF-DBS state compared to the BTC, which is consistent with previous findings (McNeely and Earhart 2013; Seri-Fainshtat et al. 2013). The OFF-medication/ON-DBS state also improved TUG performance for all already implanted participants but the BTC provided the best mobility for the TUG (McNeely and Earhart 2013).

At four weeks and three months post-programming, prospectively implanted participants had shorter TUG times in the BTC relative to the pre-operative OFF-medication and OFF-medication/OFF-DBS conditions. However, the BTC was not significantly better than any other condition at six months post-programming. This may be due to the exclusion of select participants who demonstrated more severe axial impairment but were not yet analyzed at six months post-programming. The outlier shown in Fig.7B and C may also have skewed some results for the TUG at four weeks and three months post-programming. Nocera and colleagues (2013) noted a cut-off score of 11.5 seconds to distinguish PD fallers from non-fallers (Nocera et al. 2013). In our study, two participants required >11.5 seconds to complete the TUG during the pre-operative OFF-medication and OFF-medication/OFF-DBS conditions. These participants

reported a higher rate of falls, near-falls and FOG frequency, than other participants who completed the TUG below this threshold.

4.2.2 Pace domain improves with medication and stimulation

Our already implanted patients showed that the combination of DBS and medication (i.e., the BTC) resulted in a faster gait velocity compared to all other conditions. At three months post-programming for prospectively implanted participants, the pre-operative ON-medication condition produced a significantly faster gait velocity than the pre-operative OFF-medication and post-operative OFF-medication/OFF-DBS conditions. The OFF-medication/ON-DBS condition did not show a significant improvement (5.4% increase at four weeks and 3.4% at three months post-programming) compared to the OFF-medication/OFF-DBS condition. These DBS-related changes are considerably smaller than reported in previous studies (Allert et al. 2001; Faist 2001; Stolze et al. 2001), which presented a 34 -184% change with STN- and GPi-DBS. However, participants from these previous studies had severe gait impairment (average gait velocity at baseline ranged from 10 – 40 cm/s). In contrast, participants in our cohort walked with a median velocity of 130.5 cm/s during the pre-operative OFF-medication condition, which approximates the velocity of healthy age- and sex-matched controls. DBS provided a marginal increase in gait velocity to 134.7 cm/s at four weeks post-programming (see Table 1 in Appendix), which matches the average velocity of healthy age- and sex-matched controls (133.0 cm/s) (Bohannon, Andrews, and Thomas 1996). At six months post-programming, the increased the median velocity to 143.6 cm/s. Accordingly, in prospectively implanted participants with medication and DBS combined, our results are in line with the previously reported synergistic effect of both therapies on gait velocity, though statistically significant differences were not detected.

In our study, the BTC improved step length for already implanted and prospectively implanted

participants relative to the OFF-medication/OFF-DBS condition. Previous studies report faster

gait velocity to be a function of longer step lengths (Allert et al. 2001; Faist 2001; Stolze et al.

2001). In our study, we report that participants were able to increase step length by 2.6%, 4.1%

and 3.5% at four weeks, three months and six months post-programming in the OFF-

medication/ON-DBS state, which parallels the percent change found with gait velocity. Unlike

other domains of gait, step length and gait velocity are parameters that improve more robustly

with stimulation or medication. This may be because: i) parameters associated with pace are

often the most impaired gait features (Ferrandez and Blin 1991); or ii) stimulation and

medication primarily target the BG, which is thought to have a central role in regulating step

length and gait velocity (see below).

It has previously been shown that step length and gait velocity can be explained using a linear

model and change in relation to each other (Ferrandez and Blin 1991; Stern et al. 1983), under

the influence of the BG. There are two primary roles through which the BG controls locomotion.

First, the BG sends phasic output to the supplementary motor area (SMA), which enables the

release of sub-movements by the motor cortex (Brotchie, Iansek, and Horne 1991). These

internal cues from the BG allow the SMA to string together sub-movements necessary for gait in

the correct sequence. Second, the BG contributes to a 'cortical motor set', which maintains the

readiness and execution of whole movement sequences. As the BG becomes dysregulated in PD,

step execution is under-scaled, which results in shorter step lengths (M. Morris et al. 1996). Both

the dysregulation of internal cues and disordered motor set have been postulated to mediate

shorter steps (M. Morris et al. 1996; 1994). However, Morris and colleagues (1996) propose that an inadequate motor set is more likely to underlie gait hypokinesia. This is because cadence is properly maintained in PD, which implies the internal cueing system is less affected. If stride length dysregulation is primarily governed by BG dysfunction, this may explain why stride length consistently improves upon DBS-stimulation targeting BG-related structures. In turn, longer stride lengths may generate faster gait velocity in PD participants.

4.2.3 Step length asymmetry improves with medication and stimulation combined

Gait asymmetry is becoming a more commonly reported parameter, and one that is frequently associated with unstable balance and adverse clinical events (Patterson et al. 2008). The asymmetry ratio of step length and stance time are most often reported and, therefore, were the parameters measured in our study (Baltadjieva et al. 2006; Johnsen et al. 2009). Patterson and colleagues (2010) evaluated the asymmetry ratio for various spatiotemporal parameters and reported that a step length ratio or stance time ratio above 1.08 and 1.05, respectively, were significantly different from healthy controls (Patterson et al. 2010). In both groups of participants, the median stance time ratio at four weeks, three months and six months post-programming did not exceed 1.05 (see Tables 1 – 4 in Appendix) as these participants did not exhibit significant gait asymmetry prior to surgery. This likely explains the lack of change for step length ratio between clinical conditions.

At four weeks post-programming, prospectively implanted participants had the highest step length ratio (1.07) during the OFF-medication/ON-DBS state (see Table 1 in Appendix). This may imply that step length asymmetry can worsen slightly with stimulation during the early

stages of DBS programming. However, at three months post-programming, step length asymmetry improved as participants received more programming adjustments for symptomatic control. Only at three months did we find a significant improvement in step length asymmetry during the BTC compared to the pre-operative OFF-medication state. Furthermore, we observed that prospectively implanted patients with more asymmetric step length displayed a greater propensity for FOG episodes and a higher fall risk. However, this was only an observed trend and no correlational analysis was conducted to confirm this association. Three participants exhibited step length ratios above 1.08 and experienced FOG, whereas other participants below the 1.08 threshold did not. One participant experienced severe FOG and reported a higher incidence of falls and near-falls. Another participant developed FOG that worsened in frequency and duration from four weeks to six months post-programming. These preliminary data support the notion that as asymmetrical gait exceeds a clinical threshold, gait eventually becomes akinetic and hinders forward locomotion (Plotnik et al. 2005). Our results may also further support previous findings suggesting that asymmetric and uncoordinated bilateral movement is characteristic of FOG (Plotnik et al. 2005; Rocchi, Chiari, and Horak 2002).

4.2.4 Stride width does not change following Deep Brain Stimulation

Stride width is a measure of balance control (Hollman, McDade, and Petersen 2011). Typically, participants who walk with more instability require a wider stance to compensate (Hollman, McDade, and Petersen 2011). For prospectively implanted participants, there was no change in stride width in response to medication, stimulation and both treatments combined. Though PD participants walk with longer stride widths, this has not been reported to be significantly

different from healthy controls (Stolze et al. 2001; Yang et al. 2008). This may explain the lack of change observed in our study following DBS.

4.2.5 DBS but not medication improves gait variability with near-optimized programming

Higher gait variability is a marker of arrhythmicity and instability during locomotion (Hausdorff 2009). Gait variability can even present during the early stages of PD and gradually worsen with PD progression (Hausdorff 2009). Multiple studies have linked gait variability to falls, FOG and unstable balance (Frenkel-Toledo et al. 2005; Hausdorff et al. 2009; Schaafsma et al. 2003), making it of great clinical interest. At four weeks post-programming, the OFF-medication/ON-DBS state induced a slightly higher degree of step length variability than any other clinical condition, though this was not significant. At three months post-programming, participants had undergone several programming sessions and many experienced clinical benefits as programming approached optimization. At this time, the OFF-medication/ON-DBS condition provided a significant improvement for step length variability relative to the pre-operative OFF-medication state. Once stimulation was removed during the ON-medication/OFF-DBS state, step length variability worsened and matched the %CV observed during the OFF-medication/OFF-DBS state. Once medication and stimulation were combined during the BTC, the %CV was reduced and matched that of OFF-medication/ON-DBS. Together, this may suggest that stimulation is a key contributor to the improvement of gait variability, as programming approaches optimization. However, this can only be confirmed if participants who undergo six month post-programming receive further improvement or at least no worsening of gait variability. These results were supported by Hausdorff (2009), who reported that stimulation is

likely the largest contributor to %CV improvement, and combining medication and DBS did not generate any additional improvements (Hausdorff et al. 2009).

4.2.6 Swing time is reduced following Deep Brain Stimulation while stance time does not change

Stance time is a temporal parameter that indicates the amount of time a foot is in contact with the ground during locomotion, while swing time indicates the amount of time a foot is in the air. In a healthy individual, the stance phase makes up 60% of the gait cycle, whereas the swing phase makes up 40% (Umberger 2010). Previous studies report that elderly fallers walked with a longer stance time than elderly non-fallers (Hausdorff et al. 1997). As some PD participants have trouble initiating gait or executing successive steps, we expected PD participants to walk with a longer stance phase and a shorter swing phase. While one would predict an abnormal ratio of stance: swing duration in PD participants, few studies have found this to be significantly different from healthy controls (Curtze et al. 2015; Nelson et al. 2002; Yang et al. 2008). Stance time did not change for prospectively implanted participants at any follow-up evaluation. We did not find a significant change with stance time between the OFF- and ON-medication state. Previous studies have shown stance time to improve with L-DOPA (Blin et al. 1991; Stolze et al. 2001). However, in these studies, multiple participants had FOG and severe gait impairment compared to our cohort of participants. In our study, the median stance time for prospectively implanted participants was 0.68 ms during the OFF-medication condition, which closely resembles the average stance time of elderly non-fallers (0.69 ms) in a previous study (Hausdorff et al. 1997); this relative lack of stance time impairment in our participant group may well explain the lack of change with medication and stimulation. Considering stance time is

prolonged during unstable gait in PD participants, swing time would be expected to decrease in proportion (Frenkel-Toledo et al. 2005; Stolze et al. 2001).

4.2.7 Summary of Deep Brain Stimulation and medication on gait parameters

L-DOPA is a well-established treatment for improving appendicular motor function, and to a lesser degree, aspects of gait performance. However, axial changes from DBS are still incompletely characterized and were thus the central focus of our study. While the individual effects of DBS and medication on axial motor function are difficult to isolate based on our preliminary findings, it is worth noting that DBS was not inferior to medication for the majority of gait parameters (see Tables 1 – 4 in Appendix), and we actually found that gait %CV was superior with DBS, suggesting that DBS may actually improve gait variability during ambulation. However, participants who displayed pre-existing FOG prior to surgery, were most likely to experience post-operative axial gait worsening. Taken together our findings suggest that: 1) DBS likely does not worsen the majority of axial gait parameters; and 2) patients who display FOG or axial worsening prior to DBS should continue to be screened for DBS eligibility with caution, given the potential for further post-operative axial deterioration.

4.3 Slight advantage of GPi-DBS on gait and balance function

We evaluated changes in gait and balance for STN- and GPi-DBS participants at three months post-programming. Similar to previous literature (Rocchi et al. 2012; St George et al. 2012), we aimed to compare axial differences between STN- and GPi-DBS in the BTC before and after DBS (i.e., ON-medication vs ON-medication/ON-DBS). Follett and colleagues (2010) evaluated STN- and GPi-DBS participants during the Stand-Walk-Sit test, and reported a slight advantage

for GPi-DBS, though this difference was not significant. In our study, GPi-DBS participants performed slightly worse on the TUG. However, GPi-DBS participants performed slightly better in terms of gait velocity, step length asymmetry, stride width, stance time and swing time. In our cohort, GPi-DBS participants seemed to have a slight improvement for balance-related measures (e.g., stance time, swing time and stride width). Similarly, St. George et al., (2012) found GPi-DBS participants to have better APR stability compared to STN-DBS participants. Overall, our results support previous literature (Follett et al. 2010; Rocchi et al. 2012; St George et al. 2012) that suggest GPi-DBS participants might have a slight advantage for select gait and balance parameters. However, given our small sample size ($N_{STN-DBS} = 4$; $N_{GPi-DBS} = 4$), our results are only preliminary at this time.

4.4 Limitations

The present study has several limitations. Our study had a small sample size with eight prospectively implanted participants and five already implanted participants. Within our cohort, one participant displayed severe FOG and gait impairments, and presented as an outlier during the analyses of select gait parameters. Our study lacked healthy age- and sex-matched controls so we were unable to identify the gait parameters that significantly differed from age and sex-matched non-PD participants. However, the objective of our study was to investigate gait and balance changes before and after DBS within subjects. Thus, healthy controls were not a crucial component to our study. We were also not able to randomize the order of our clinical conditions. Given the requirements for the defined OFF-medication state (withdrawing from anti-parkinsonian medication for at least twelve hours), we conducted OFF-medication state experiments (i.e., OFF-medication/OFF-DBS and OFF-medication/ON-DBS) as the first two

conditions in the morning, to limit the total amount of time participants were required to be OFF-medication state. Furthermore, neither the examiner nor the participants were blinded to the clinical condition, which may have introduced a degree of bias during examinations. To rectify this issue, we propose having an additional blinded examiner to review video recordings of each session in order to confirm our results. Our DBS washout period was also limited to one hour, despite previous studies suggesting an optimal washout period of over three hours (Temperli et al. 2003). Similarly, our washout period was limited due to safety reasons, as we expect many participants would have become fatigued from a prolonged data collection process. In our prospectively implanted cohort, only three participants experienced FOG. Therefore, our observations of FOG-related changes following DBS were limited (though this is a well-known challenge in the field). Lastly, we were not able to collect six-month follow-up data for all prospectively implanted participants. Therefore, our preliminary findings are limited for participants who have received optimized DBS programming (assuming optimization is indeed achieved by six months).

4.5 Novel findings and future directions

Despite our limitations, the current study offers several new insights into gait-related changes following STN- and GPi-DBS. First, we found that near-optimized DBS can improve select gait asymmetry and variability parameters. Despite these improvements, three participants continued to experience FOG and festinations that were maintained or worsened with disease progression (though immediate FOG development after DBS may imply DBS to a direct cause). This lends support to the notion that the clinical benefits of DBS may be limited for advanced PD participants who have already developed FOG prior to surgery. In support of previous literature,

step length and gait velocity showed a robust improvement with both DBS and medication at each follow up evaluation; indeed, improvements within the pace domain presented as early as four weeks post-programming. However, other gait parameters, such as stance time, stance time ratio and stride width did not change following DBS. Meanwhile, other gait parameters (e.g., step length variability and step length asymmetry) exhibited a delayed benefit, with improvement occurring after several programming sessions.

In the future, studying the five gait domains in a larger sample of PD+FOG participants would be useful to understand which parameters change as FOG improves or worsens following DBS. Furthermore, the timeline of our study was limited to six months post-programming. Studying gait-related changes in a longitudinal manner over a longer follow-up period may demonstrate the trajectory of gait parameters throughout the disease course, though disease progression could introduce an important confound. Finally, we did not evaluate the effects of unilateral stimulation on gait asymmetry. One possible approach would be to turn off DBS stimulation on one side and evaluate the degree of asymmetry for gait and balance. For our study, this would have extended the duration of our protocol and likely fatigued the participants. However, investigating the relationship between unilateral stimulation and gait asymmetry should be considered for future studies.

5. Conclusion

The present study investigates the five domains of gait following STN- and GPi-DBS in PD participants. Pace (i.e., step length and gait velocity) showed the largest and most consistent improvement immediately following DBS. Other select domains showed either delayed or no

benefit in the BTC after several programming sessions. Considering participants with FOG did not experience significant gait improvement, individuals who are PIGD Dominant, PD+FOG, or display severe gait worsening, should continue to be evaluated for DBS eligibility with caution. Our study also demonstrated that DBS stimulation does not worsen axial gait and balance for participants who did not have pre-existing FOG prior to DBS. The results of our study demonstrate the complex and interconnected nature of gait. Conducting similar and larger-scale quantitative studies may offer further insight into the gait-related changes following STN- and GPi-DBS in PD.

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Appendix

Table 1. Clinical and gait parameters at four weeks post-initial programming for prospectively implanted participants (N=8).

	M-	M+	M-/S-	M-/S+	M+/S-	M+/S+
UPDRS-III	35.0±9.0	13.5±5.2	28.0±14	13.0±11.7	12.0±13.4	8.5±5.9
Timed-Up and Go (s)	9.9±4.6	8.8±0.9	10.5±1.5	10.3±3.3	10.6±1.5	9.6±2.1
Gait Velocity (cm/s)	130.5±33.5	137.2±13.0	127.5±25.6	134.7±17.5	132.0±19.6	138.6±19.0
Step Length (cm)	70.4±14.6	73.7±14.6	68.3±11.3	71.0±7.1	72.3±6.9	72.3±7.8
Step Length Ratio (|L/R|)	1.05±0.08	1.04±0.04	1.03±0.11	1.07±0.05	1.03±0.04	1.03±0.03
Stance Time Ratio (|L/R|)	1.04±0.06	1.02±0.02	1.03±0.02	1.02±0.02	1.03±0.10	1.01±0.03
Stride Width (cm)	12.0±4.3	9.1±6.1	11.0±4.3	9.8±4.5	10.6±6.1	13.2±5.5
Step Length Variability (%CV)	7.2±16.5	3.6±1.5	5.3±6.0	5.9±2.3	3.8±2.0	4.2±1.4
Stance Time (ms)	0.69±0.03	0.71±0.04	0.71±0.06	0.68±0.05	0.71±0.06	0.69±0.05
Swing Time (ms)	0.37±0.06	0.4±0.04	0.38±0.02	0.37±0.02	0.39±0.06	0.38±0.04

'M' denotes medication state while 'S' denotes stimulation state. Entries are median ± standard deviation.

Table 2. Clinical and gait parameters at three months post-initial programming for prospectively implanted participants (N=8).

	M-	M+	M-/S-	M-/S+	M+/S-	M+/S+
UPDRS-III	35.0±9.0	13.5±5.2	30.0±9.9	15.5±7.1	16.5±8.7	7.5±5.7
Timed-Up and Go (s)	9.9±4.6	8.9±0.9	9.8±10.1	9.9±4.6	10.5±3.4	9.9±2.5
Gait Velocity (cm/s)	130.5±33.5	137.2±13.0	130.1±35.2	135.3±20.5	138.6±17.5	141.9±17.9
Step Length (cm)	70.4±14.6	73.7±4.2	69.7±15.2	69.7±11.6	72.8±9.1	73.4±9.4
Step Length Ratio (|L/R|)	1.05±0.08	1.04±0.04	1.05±0.05	1.03±0.05	1.05±0.03	1.02±0.03
Stance Time Ratio (|L/R|)	1.04±0.06	1.02±0.02	1.02±0.04	1.04±0.05	1.03±0.05	1.02±0.07
Stride Width (cm)	12.0±4.8	9.4±6.4	10.6±4.6	12.2±4.9	11.8±5.8	11.4±5.7
Step Length Variability (%CV)	5.9±16.7	3.6±2.0	4.6±9.1	3.2±14.1	5.0±16.4	3.8±15.9
Stance Time (ms)	0.69±0.09	0.71±0.04	0.71±0.14	0.67±0.03	0.69±0.05	0.69±0.04
Swing Time (ms)	0.37±0.06	0.4±0.04	0.37±0.03	0.37±0.05	0.37±0.03	0.37±0.05

'M' denotes medication state while 'S' denotes stimulation state. Entries are median ± standard deviation.

Table 3. Clinical and gait parameters at six months post-initial programming for prospectively implanted participants (N=5).

	M-	M+	M-/S-	M-/S+	M+/S-	M+/S+
UPDRS-III	35.0±9.0	13.5±5.2	37.0±14.5	9.0±9.8	11.0±14.5	5.0±11.0
Timed-Up and Go (s)	9.9±4.6	8.9±0.9	10.3±1.8	9.6±2.1	10.3±1.5	9.8±1.6
Gait Velocity (cm/s)	130.5±33.5	137.2±13.0	134.7±22.4	143.6±21.9	135.5±13.5	141.0±13.9
Step Length (cm)	70.4±14.6	73.7±4.2	73.3±10.2	74.9±8.6	73.5±7.3	73.8±4.4
Step Length Ratio (|L/R|)	1.05±0.08	1.04±0.04	1.06±0.09	1.07±0.1	1.04±0.07	1.06±0.04
Stance Time Ratio (|L/R|)	1.04±0.06	1.02±0.02	1.02±0.01	1.02±0.02	1.02±0.04	1.02±0.01
Stride Width (cm)	12.0±4.8	9.4±6.4	12.0±2.4	12.6±2.8	12.6±5.1	11.3±3.9
Step Length Variability (%CV)	5.9±16.7	3.6±2.0	3.2±6.4	4.1±3.1	4.5±6.2	3.9±2.0
Stance Time (ms)	0.69±0.09	0.71±0.04	0.72±0.04	0.68±0.06	0.71±0.05	0.7±0.04
Swing Time (ms)	0.37±0.06	0.4±0.04	0.37±0.05	0.38±0.02	0.38±0.02	0.38±0.02

'M' denotes medication state while 'S' denotes stimulation state. Entries are median ± standard deviation.

Table 4. Clinical and gait parameters for already implanted participants (N=5).

	M-/S-	M-/S+	M+/S-	M+/S+
UPDRS-III	34.0±11.4	25.0±13.1	27.0±11.1	12.0±7.8
Timed-Up and Go (s)	9.5±1.1	9.3±0.7	10.0±1.1	8.1±1.0
Gait Velocity (cm/s)	129.8±17.2	135.2±8.6	132.0±9.4	147.4±10.5
Step Length (cm)	67.2±9.6	68.9±8.9	69.8±10.1	74.7±9.8
Step Length Ratio (|L/R|)	1.04±0.05	1.03±0.06	1.03±0.05	1.03±0.09
Stance Time Ratio (|L/R|)	1.02±0.03	1.02±0.01	1.02±0.01	1.02±0.01
Stride Width (cm)	7.2±1.5	8.5±2.4	8.9±2.9	9.4±1.6
Step Length Variability (%CV)	4.2±1.9	3.1±2.8	4.4±1.9	4.3±3.2
Stance Time (ms)	0.73±0.04	0.67±0.06	0.69±0.07	0.66±0.05
Swing Time (ms)	0.36±0.05	0.35±0.04	0.38±0.05	0.37±0.03

'M' denotes medication state while 'S' denotes stimulation state. Entries are median ± standard deviation.