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Exploring the effects of spinal cord stimulation for freezing of gait in parkinsonian patients

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A thesis submitted in partial fulfillment of the requirements for the Doctor of Philosophy degree in Physiology and Pharmacology

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Abstract

Dopaminergic replacement therapies (e.g. levodopa) provide limited to no response for axial motor symptoms including gait dysfunction and freezing of gait (FOG) in Parkinson's disease (PD) and Richardson's syndrome progressive supranuclear palsy (PSP-RS) patients. Dopaminergic-resistant FOG may be a sensorimotor processing issue that does not involve basal ganglia (nigrostriatal) impairment. Recent studies suggest that spinal cord stimulation (SCS) has positive yet variable effects for dopaminergic-resistant gait and FOG in parkinsonian patients. Further studies investigating the mechanism of SCS, optimal stimulation parameters, and longevity of effects for alleviating FOG are warranted. The hypothesis of the research described in this thesis is that mid-thoracic, dorsal SCS effectively reduces FOG by modulating the sensory processing system in gait and may have a dopaminergic effect in individuals with FOG. The primary objective was to understand the relationship between FOG reduction, improvements in upper limb visual-motor performance, modulation of cortical activity and striatal dopaminergic innervation in 7 PD participants. FOG reduction was associated with changes in upper limb reaction time, speed and accuracy measured using robotic target reaching choice tasks. Modulation of resting-state, sensorimotor cortical activity, recorded using electroencephalography, was significantly associated with FOG reduction while participants were OFF-levodopa. Thus, SCS may alleviate FOG by modulating cortical activity associated with motor planning and sensory perception. Changes to striatal dopaminergic innervation, measured using a dopamine transporter marker, were associated with visual-motor performance improvements. Axial and appendicular motor features may be mediated by non-dopaminergic and dopaminergic pathways, respectively. The secondary objective was to demonstrate the short- and long-term effects of SCS for alleviating dopaminergic-resistant FOG and gait dysfunction in 5 PD and 3 PSP-RS participants without back/leg pain. SCS programming was individualized based on which setting best improved gait and/or FOG responses per participant using objective gait analysis. Significant improvements in stride velocity, step length and reduced FOG frequency were observed in all PD participants with up to 3-years of SCS. Similar gait and FOG improvements were observed in all PSP-RS participants up to 6-months. SCS is

a promising therapeutic option for parkinsonian patients with FOG by possibly influencing cortical and subcortical structures involved in locomotion physiology.

Keywords

Parkinson's disease, freezing of gait, gait dysfunction, spinal cord stimulation, neuromodulation, gait analysis, visuomotor, sensorimotor, DaTSCAN, electroencephalography

List of Abbreviations

ABC	Activities-Balance Confidence scale
AP	Atypical parkinsonism
BG	Basal ganglia
CWT	Clockwise turning
CCWT	Counterclockwise turning
COP	Centre of pressure
COMe	Centre of mass estimated
DAT	Dopamine transporter
DaTSCAN	Dopamine transporter imaging scan
DBS	Deep brain stimulation
DLPFC	Dorsolateral prefrontal cortex
EEG	Electroencephalography
FOG	Freezing of gait
FOG-Q	Freezing of Gait Questionnaire
GPe	Globus pallidus externa

GPi	Globus pallidus interna
M1	Motor cortex
MDS-UPDRS-III	Movement Disorders Society – Unified Parkinson's Disease Rating Scale Motor Items
MLR	Mesencephalic locomotor region
MoCA	Montreal Cognitive Assessment
PD	Parkinson's disease
PKMAS	Protokinetics Movement Analysis Software
PIGD	Postural instability and gait disorder
PPN	Pedunculopontine nucleus
PSP-RS	Progressive supranuclear palsy – Richardson's syndrome
ROI	Region of interest
SBR	Specific binding ratio
SCS	Spinal cord stimulation
SLR	Subthalamic locomotor region
SNr	Substania nigra pars reticula
SNpc	Substania nigra pars compacta
SPECT	Single-photon emission computerized tomography
STN	Subthalamic nucleus
tDCS	Transcranial direct current stimulation
TMS	Transcranial magnetic stimulation
VPD	Vascular Parkinson's disease

Summary for Lay Audience

Shuffling, freezing in place and slowness can force people living with Parkinson's disease (PD) and Richardson's syndrome progressive supranuclear palsy (PSP-RS) to lose independence and become housebound. Treating these walking problems is very challenging as available treatment options, such as dopamine replacement therapies (the gold standard is levodopa) or deep brain stimulation (which is surgical), do not improve these symptoms and have left a large patient population untreated. A new approach to regain mobility and reduce freezing is spinal cord stimulation (SCS), an implantable battery that delivers electrical pulses to a patient's spinal cord and stimulates nerve fibers within the spinal cord. In this thesis, dramatic improvements in walking speed, longer strides and significant reduction in freezing were seen in 5 PD patients with up to 3-years of therapy and in 3 PSP-RS patients with up to 6-months of therapy. However, it is not fully understood how SCS works to relieve freezing in PD. The theory is that SCS improves the way the brain perceives the environment thereby altering movement. This sensory-motor processing is dysfunctional in PD freezers. Both freezing and hand-eye coordination, measured by targeting shapes on a screen using their hands to move a robotic device, were improved over 6-months with SCS therapy in PD patients. The reduction in freezing was related to changes in brain activity of areas associated with sensory processing and movement control, which was independent of levodopa use (without dopamine replacement therapy). Thus, SCS may reduce freezing episodes by improving how the brain perceives and processes sensory information and ultimately refines movement (e.g. walking). Additionally, improvements in hand-eye coordination skills were related to changes in the deep brain structure (striatum), which is otherwise altered in PD due to the loss of dopamine producing cells. This current thesis suggests that freezing may be associated to the activity of brain areas for motor planning and locomotion and that hand-eye coordination skills may be related to changes in the presence of dopamine producing cells. SCS is a promising therapeutic option for PD and PSP-RS patients with primarily freezing in place who are unresponsive to currently available therapies.

Co-Authorship Statement

This integrated thesis contains three peer-reviewed publications. **Chapter 3**, entitled: “Spinal cord stimulation therapy for gait dysfunction in progressive supranuclear palsy patients” was written by Olivia Samotus (OS), Andrew Parrent (AP), and Mandar Jog (MJ), and was published in the Journal of Neurology in 2021. OS was responsible for research ethics submission and approval, study coordination, participant recruitment, obtaining participant written consent, programming of the SCS device, data collection, interpretation of data, statistical analysis, the original draft of the entire manuscript. OS, AP, and MJ were involved in study concept and design. OS and MJ were involved in editing and reviewing of the manuscript. AP and MJ were responsible for funding and in-kind contributions of spinal cord stimulation devices. AP was responsible for the implantation of devices. I conducted an estimate of 90% of the work reported in this paper.

Two peer-reviewed publications are combined in **Chapter 4**, entitled: “Spinal cord stimulation therapy for gait dysfunction in advanced Parkinson's disease patients” was written by OS, AP and MJ and was published in the Movement Disorders journal in 2018, and “Long-term update of the effect of spinal cord stimulation in advanced Parkinson's disease patients” was written by OS, AP, and MJ, and was published in the Brain Stimulation journal in 2020. OS was responsible for research ethics submission and approval, study coordination, participant recruitment, obtaining participant written consent, programming of the SCS device, data collection, interpretation of data, statistical analysis, and the original draft of the entire manuscript. OS, AP, and MJ were involved in study concept and design. OS and MJ were involved in editing and reviewing of the manuscript. AP and MJ were responsible for funding and in-kind contributions of SCS devices. AP was responsible for the implantation of devices. I conducted an estimate of 90% of the work reported in the 2018 paper and an estimate of 95% of the work reported in the 2020 paper.

Acknowledgments

First and foremost, I would like to acknowledge the dedication and time provided by the participants for believing in me and the research process. They have shown me kindness and patience and I am grateful to them for being able to make a positive impact in their lives and to contribute to the advancement of Parkinson's research.

I owe a deep sense of gratitude to my mentor, Dr. Mandar Jog, for his inspirations, enthusiasm, immeasurable guidance, and trusting me at every stage of my research. I would like to thank Dr. Jog for the knowledge he has passed on to me. I am truly grateful for his support and for providing me with countless opportunities to grow into the inquisitive scientist that I have always aspired to be.

I would also like to extend my appreciation to Dr. Andrew Parrent as this research project would only be an idea without his contributions, time, and support. Furthermore, I would like to thank Chloë Nicholson-Smith for helping me in the design of the tasks for the robotic device, and additionally Bosi Ding, Yokhesh KrishnasamyTamilselvam and Caroline Aitken for their time and effort in helping me collect data.

I would like to acknowledge the time and effort provided by my advisory committee members, Dr. Paul Gribble and Dr. Brian Corneil, for their valuable input and critiques.

Table of Contents

List of Tables

List of Figures

List of Appendices

Preface

Parkinson's disease (PD) is an extremely debilitating and fast-growing neurodegenerative disease with the number of PD cases expected to double to about 13 million by 2040.[1,2] Mobility deficits including freezing of gait (FOG), gait and balance impairments, and falls, negatively impact independence and quality of life for people suffering from PD. These gait symptoms develop early in Richardson's syndrome progressive supranuclear palsy (PSP-RS), which is the most common form of atypical parkinsonism (AP) characterized by its rapid progression of clinical features.[3] In PD, dopaminergic replacement pharmacotherapy (e.g. levodopa) and deep brain stimulation interventions have limited mobility benefits and can worsen postural stability, FOG and falls.[4] PSP-RS patients also experience limited to no response to levodopa therapy.[3] Dopaminergic-resistant FOG seen in parkinsonian individuals may not be related to basal ganglia dysfunction but may be a sensorimotor processing issue due to factors that trigger (e.g. narrow spaces, dual-tasking) and alleviate (e.g. sensory cueing) FOG. Spinal cord stimulation (SCS) is a minimally invasive, programmable, out-patient treatment that may act on sensorimotor processing pathways to improve locomotion, especially FOG, and other PD motor symptoms, as reported in several pilot PD studies[5] and in a limited number of AP clinical cases.[6-8] The studies described in this thesis investigated the relationship between improvements in FOG and upper limb visual-motor performance with changes in cortical activity and striatal dopaminergic innervation following SCS therapy in PD patients. Furthermore, the therapeutic effects of SCS to treat significant gait dysfunction and FOG symptoms resistant to dopaminergic pharmacotherapy in PD and PSP-RS patients were reported.

Chapter 1 outlines the current literature regarding the motor symptoms of PD and PSP-RS, the neural mechanisms and therapies relating to PD motor symptoms, parkinsonian gait dysfunction and FOG and the research tools utilized for assessing gait deficits.

Chapters 2 to 4 presents research completed as part of my thesis. **Chapter 2** describes the neurophysiological effects of SCS associated with improvements in visual-motor performance and FOG. **Chapter 3** is a peer-reviewed publication reporting the benefits of

SCS for FOG and gait symptoms in PSP-RS patients. **Chapter 4** includes two peer-reviewed publications reporting the therapeutic effects of SCS in advanced PD patients with significant freezing while ON dopaminergic medication up to 6-months and a long-term update at 3-years of stimulation therapy.

Chapter 5 states the key findings presented in **Chapters 2, 3 and 4** and the concluding statements regarding the impact of advancing gait therapies and future directions.

Chapter 1

1 Introduction

PD is the fastest growing and the most common neurodegenerative movement disorder affecting 1% of the population aged 60 years and older, and 3% of people older than 80 years. Age is the single most important risk factor for PD with 60 years being the median age of disease onset.[9] PD is characterized by the cardinal clinical features including rest tremor, bradykinesia, rigidity, and postural instability, along with a variety of other motor and non-motor features. The motor symptoms of PD arise largely from the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the accumulation of misfolded α-synuclein called Lewy bodies. The nigrostriatal pathway influences the thalamus and cerebral cortex via excitatory and inhibitory circuits in the basal ganglia leading to the cardinal appendicular motor symptoms. The most disabling and challenging to treat symptom of PD is FOG affecting 50% of patients in the moderate stage of the disease and up to 80% of patients in the advanced stage.[10] FOG is an axial symptom that can be triggered and alleviated by sensory input and generally does not respond well to available interventions. While the pathophysiology is poorly understood, dopaminergic-resistant gait impairment and FOG in PD is possibly connected to a sensorimotor processing issue and may not be related to nigrostriatal dysfunction. Unveiling the pathophysiology of FOG and the development of a novel, effective therapeutic for this symptom is a significant unmet need.

1.1 Parkinson's disease: symptoms and pathophysiology

1.1.1 Overview of motor symptoms and subtypes in Parkinson's disease

The expression of motor and non-motor features ranges between patients and consequently, PD subtypes have been proposed to categorize patients according to predominant motor symptoms, such as tremor-dominant, akinetic rigid, postural instability gait disorder (PIGD) or indeterminate/mixed. PIGD is characterized as the more severe disease manifestation with faster progression, a higher incidence of

developing motor fluctuations and dyskinesias, and a worse prognosis regarding survival when compared to the tremor-dominant subtype.[1,11] Motor features can be separated into two categories: appendicular and axial, where appendicular features involve symptoms presenting in the body limbs, and axial features are impairments of complex biomechanical patterns involving muscles that support the head, spine, ribs, sternum, and pelvis. Axial features include gait disturbances (see section 1.2) such as FOG (see section 1.2.1), balance impairments including postural instability and changes in postural alignment, dysphagia, and speech disorders especially dysarthria and stuttering. These symptoms dominate in the more advanced stages of disease and contribute to most of the disability experienced by PD patients such as reduced mobility and quality of life, loss of independence, recurrent falls leading to more injuries, and reduced survival.[4]

The presence of appendicular versus axial features hints to the underlying pathophysiology and their different control systems. In the early stages of PD with the predominance of appendicular features, it is thought that the pathophysiology is mainly within the dopaminergic striatal systems which are part of the basal ganglia (BG)-thalamocortical loop (see section 1.1.2).[12] However, as the disease progresses and axial symptoms such as gait impairments dominate, alterations to non-dopaminergic pathways involving cholinergic, serotonergic, and noradrenergic systems within the mesencephalic locomotor region (MLR), pedunculopontine nucleus (PPN), cerebellum (cerebellar locomotor region (CLR)), subthalamic locomotor region (SLR), frontal cortex and their inter-connections and connections with the BG may be affected (see section 1.1.3).[13-15]

1.1.2 Dopaminergic neural circuitry associated with appendicular features

Appendicular features, such as bradykinesia and rigidity that affect the limbs of the body, are attributed to the loss of dopaminergic neurons in the nigrostriatal-pallidal pathway of the BG[12,16] and respond well to dopaminergic replacement interventions (see section 1.4). The striatum, divided into the caudate and putamen in primates, is the primary afferent structure of the BG and receives glutamatergic input from the cerebral cortex, and dopaminergic innervation mainly from the neuronal dense zone of the dorsal part of the substantia nigra pars compacta (SNpc) and from the sparsely packed neuronal ventral

zone of the substantia nigra pars reticulata (SNr). In addition to about 76% of dopaminergic neurons originating from the SNpc in non-human primates, approximately 10% originate from the retrorubral area within the mesencephalic area and 14% from the ventral tegmental area (VTA).[17] Dopaminergic input from the SNpc and VTA modulates cortico-striatal transmission by having dual effects on the striatal projection neurons.[18] Activity of striatal neurons depends on the modulatory action of dopamine on dopaminergic D1 (substance-P and dynorphin, "direct" pathway) receptors and D2 (encephalin, "indirect" pathway) receptors, which are co-expressed. Typically, the dopamine effect excites D1 receptors and inhibits D2 receptors, thereby causing differing effects on the output nuclei. Striatal medium spiny projection neurons convey information to the output nuclei via monosynaptic GABAergic projections ("direct" pathway) and polysynaptic GABAergic projections ("indirect" pathway) involving the globus pallidus externa (GPe) and the subthalamic nucleus (STN) (see Figure 1-1). The globus pallidus interna (GPi) and SNr are the primary efferent nuclei of the BG that target their GABA (γ-aminobutyric acid)-ergic neurons to the thalamus and brainstem. The thalamus and brainstem are under tonic inhibitory control, which are paused by phasic inhibitory signals from the "direct" pathway, releasing thalamocortical and brainstem structures from inhibition allowing movement to proceed. The overall effect of dopamine promotes movement. In the parkinsonian state, there is a loss of dopaminergic input to the striatum. The activity in the "direct" excitatory pathway is reduced and "indirect" inhibitory pathway is increased. This causes increased inhibition from "indirect" striatal neurons to the GPe that disinhibits the STN and increases inhibitory output from the GPi and SNr. Ultimately, the GPi/SNr reduces excitatory activity from the thalamus and brainstem structures. Thus, dopamine depletion mediates cardinal parkinsonian features by suppressing movement, which are present at disease onset and over the course of the disease.

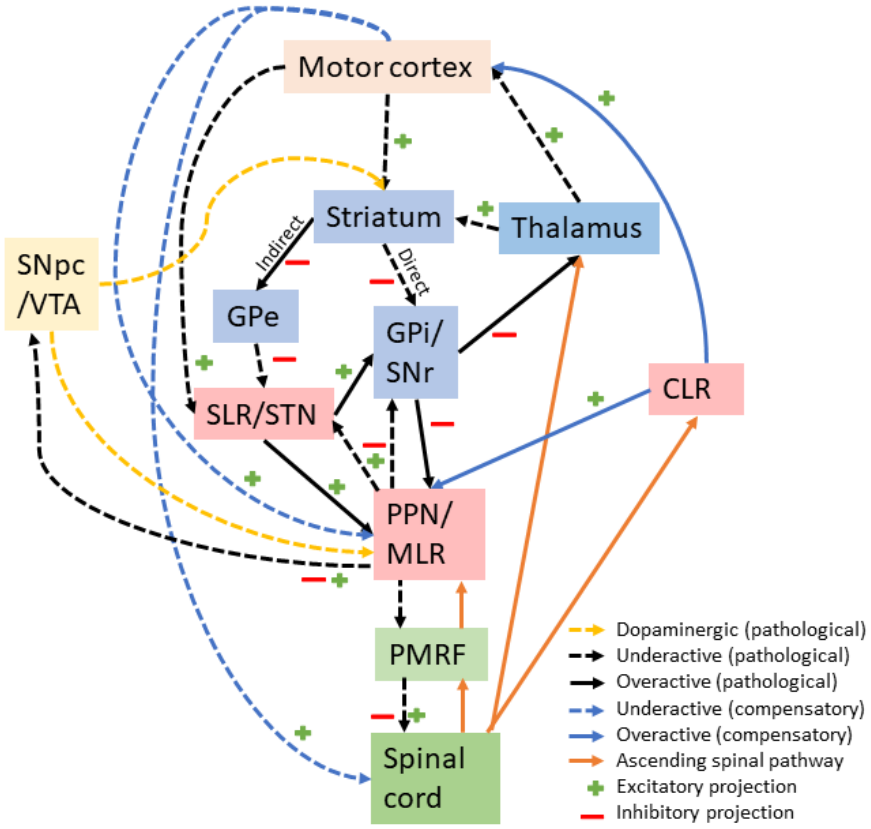

Figure 1-1: Schematic diagram of the suprasegmental areas involved in locomotion and freezing of gait. Pathological alterations due to the loss of dopaminergic neurons from the SNpc/VTA to the basal ganglia network causing excessive inhibitory (GABAergic) output to the thalamus (glutamatergic), motor cortex (glutamatergic), and PPN/MLR (glutamatergic and cholinergic) contribute to bradykinesia, gait slowness, increased postural instability, and freezing of gait (dopaminergic-responsive). Increased volitional control and compensatory activity of the cerebellum and motor cortex to the underactive PPN/MLR may contribute to freezing of gait (dopaminergic unresponsive) and gait variability and asymmetry. The MLR represents a crossroad of information coming from the basal ganglia and the cerebellum, which receives sensory feedback from ascending spinal pathways. CLR: cerebellar locomotor region; GPe: globus pallidus externa; GPi: globus pallidus interna; MLR: mesencephalic locomotor region; PMRF: pontomedullary reticular formation; PPN: pedunculopontine nucleus; SLR: subthalamic locomotor

region; SNpc: substantia nigra pars compacta; STN: subthalamic nucleus; VTA: ventral tegmental area.

More recent anatomical studies have shown the BG has a far greater complexity in the organization of synaptic connections, as there are feedback inputs from the GPe to the striatum, cortical inputs to the STN (denoted as the "hyperdirect" pathway), and STN afferents to the GPe, SNpc/VTA, and PPN. Thus, the STN is a major input structure and relays information from the striatum to the output BG nuclei and the brainstem locomotor region (MLR). Furthermore, spatial organization of the corticobasal ganglia-cortical loops is conserved, which may explain why preferential loss of dopamine in the sensorimotor areas causes deficits in habitual motor control and a shift to more goal-directed behavior in PD.[18] Post-mortem data shows the greatest loss of dopaminergic innervation is found in the posterior putamen that corresponds to dopaminergic cell loss in the ventrolateral SNpc.[18] The posterior putamen is engaged in sensorimotor functions whereas the caudate and anterior putamen nuclei are related to associative function and the ventral striatum relates to motivational and emotional functions.[18] Thus, PD patients have difficulty expressing automatic components of behaviour but can improve motor performance when guided by sensory or motivational cues.

Treating appendicular symptoms using dopaminergic replacement therapy, levodopa, is highly effective and can also improve axial symptoms predominantly related to appendicular symptoms (e.g. limb bradykinesia affecting quality of stepping).[4] Dopaminergic medication likely does interact with the underlying pathophysiology of FOG early in the disease course as studies suggest that the loss of dopaminergic input to the striatum at baseline contributes to FOG development (see section 1.4.1).[19] Furthermore, levodopa-induced side effects including dyskinesia that can impair gait and balance may be improved by modulating STN activity using deep brain stimulation (DBS) intervention (see section 1.4.2). Axial features that may be unrelated to dopaminergic loss continue to degrade and ultimately become predominant and are unresponsive to levodopa therapy (see section 1.1.3).

1.1.3 Non-dopaminergic neural circuitry associated with axial features

Axial features, such as gait, FOG, postural instability, speech, and other PD symptoms including cognition impairment and tremor do not respond well to dopaminergic replacement therapies and may not be correlated with basal ganglia (nigrostriatal) dysfunction. This is partly caused by the progression of non-dopaminergic brain lesions within the frontal lobe, adrenergic locus coeruleus, cerebellum and the cholinergic area of the PPN.[20,21] Such dopaminergic-resistant symptoms, in particular gait control, may be related to sensorimotor network dysfunction (see section 1.2.1.1 and 1.2.1.2). As the act of walking requires the complex integration of cortical, subcortical, brainstem, and spinal cord networks along with afferent feedback from sensory systems, gait impairments may be caused by pathology at multiple levels of these network integration systems.

The key areas involved in locomotion are the pontomedullary reticular formation (PMRF), mesencephalic locomotor region (MLR), BG, cerebellum (cerebellar locomotor region (CLR)), and the cerebral cortex (Figure 1-1).[22] BG, cerebellar and cortical neurons send outputs to the MLR, which is composed of the PPN and the cuneiform nucleus. In particular, the MLR is thought to be the site of gait initiation and regulation as it receives BG afferents that originate from the sensorimotor, associative, and limbic anatomo-functional territories.[23] The PPN is divided into two parts by the presence of cholinergic neurons: the pars compacta (PPNc) is dorsolaterally located containing the majority of cholinergic neurons and the pars dissipata (PPNd) is medially located containing more glutamatergic neurons than cholinergic neurons.[23] The PPN has ascending projections to the SNpc, STN, pallidum and thalamus and descending projections to the PMRF. The cuneiform nuclei projections are less known, but primate studies have shown descending projections.[23] The PMRF, understood to be the site of gait execution and where the reticulo-spinal pathway originates, receives MLR projections and modulates descending spinal cord circuitry for controlling posture and gait.[13]

Excessive GABAergic inhibitory output from the GPi/SNr can reduce MLR-activated step cycles, increase stance phase, and disrupt rhythmic locomotion patterns by reducing velocity and the amount of movement (bradykinesia).[13] Furthermore, the excessive

GABAergic output from the BG inhibits the PPN and may increase muscle tone and may contribute to axial rigidity features.[13] However, the over-activation of the GPi/SNr output nuclei inhibiting the PPN does not necessarily correlate with gait impairments,[24] as gait and falls in PD are correlated with cholinergic PPN dysfunction.[23,25] Non-human primate studies demonstrate the importance of cholinergic PPN neurons for the control of gait.[26] As well, a study with 22 early PD patients demonstrated cholinergic dysfunction, measured using paired-pulse transcranial magnetic stimulation (TMS), is significantly associated with slower gait speed and gait variability (speed, stride time, stride length and step width).[27] Cellular loss within the PPN has been correlated with disease progression and gait disturbances, which may act synergistically with nigrostriatal cell loss.[28] Post-mortem studies report cholinergic neuronal loss within the PPN is correlated with dopaminergic cell loss in PD patients.[29] Thus, the PPN is theorized to be a distinct entity from the SNpc that is also affected in PD leading to hypokinetic symptoms.[30]

The involvement of other structures such as the brainstem, cortex and cerebellum may contribute to gait dysfunction in PD. However, the relationship of noradrenergic and serotoninergic systems and gait is not fully understood. The excitatory, noradrenergic neurons of the locus coeruleus are known to degenerate in PD, which may contribute to gait impairments due to their widespread effects in the cortex, cerebellum, and spinal cord.[23] Coeruleus-cerebellar and coeruleus-spinal pathways are involved in autonomic regulation and postural reflexes, and the degradation of these pathways may explain postural instability in PD.[23] The raphe nuclei located in the brainstem utilizes serotonin and is important for rhythm and locomotion pattern modulation.[23] However, reduced serotonin levels in the cerebrospinal fluid have been related to severe gait and balance impairments in PD.[23] Furthermore, due to the shift to goal-directed motor control observed in PD, increased activation of the lateral premotor cortex is necessary to compensate for the impairment of the supplementary motor area function.[31] Another strategy to compensate BG dysfunction is the enhanced activation in the cerebellum, known for motor coordination and balance.[32] Thus, unraveling a specific cause for gait disturbances in parkinsonian syndromes is not possible due to the complex network involved in gait and motor control.

1.2 Parkinsonian gait impairments

In the early stages of PD, symptoms such as reduced gait speed and reduced arm swing on one side correspond to the asymmetry of BG neuropathology and ambulation becomes less automatic.[18] During the moderate stages of disease, movement is more bradykinetic with shuffling steps, increased double support time, bilateral reduced arm swing, stooped posture and higher cadence being commonly observed and contributing to the decline in gait kinematics.[33] Turning is defragmented (turning en bloc) and gait initiation problems such as FOG and festination can appear. At the advanced stage, significant gait impairments such as FOG can be frequent and are accompanied by reduced balance, postural control, and frequent falls. These gait symptoms can be exacerbated by motor fluctuations and dyskinesia resulting in the need for assistance or walking aids.[34]

PD gait characteristically has reduced self-paced walking speed, higher cadence, shorter step lengths, increased double support time gait phase, greater asymmetry and variability, stooped posture, reduced arm swing, and reduced hip, knee and ankle range of motion that contribute to these kinematic changes.[35] However, age, disease duration, Movement Disorders Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and Hoehn & Yahr ratings do not reflect gait biomechanics.[35] Slower walking speeds, which are related to stride length and cadence, may denote a compensatory strategy to avoid falling but are not disease specific.[33] Double support and swing time may be associated with gait instability as increased double support time is attributed to reduced ability to transfer weight in preparation for stepping adequately, as observed in FOG (see section 1.2.1). Non-motor symptoms such as anxiety, depression and cognitive impairment are common in PD and are associated with slow gait, greater gait variability, and the onset of FOG.[36] Accurate assessment of gait may inform physicians about early pathology, evaluate fall risk, and predict cognitive decline.[37] This can be done by categorizing gait features to better understand key gait parameters with respect to their role in pathology and may improve clinical interpretation of spatiotemporal gait parameters; these categories are pace, rhythm, variability, asymmetry, and postural control.[38]

Pace refers to step velocity and step length and is significantly reduced in patients regardless of dopaminergic medication state when compared to healthy age-matched

subjects.[35] Step time, swing time and stance time refer to gait rhythmicity and the timing of each phase of a gait cycle, which is important for safe walking. Increased temporal variability and asymmetry lead to gait instability and studies have suggested central pattern generators within the thoracic and lumbar regions of the spinal cord play a role in rhythm contractions of antagonistic flexor-extensor muscle groups.[39] Variability of gait measured by step length, velocity, and time refer to fluctuations from one step to the next. Such fluctuations tend to increase with disease progression and can be attributed to variability in muscle force production.[40] Temporal gait asymmetry (e.g. step time, and swing and stance gait phases between left and right footfalls) may be attributed to the neuropathological nature of PD, which often start on one side and advance on to the other side as the disease progresses. Another factor that can worsen gait asymmetry is the severity and asymmetry of symptoms such as rigidity or bradykinesia greatly affecting one limb rather than the other. Postural control typically is affected as PD patients have larger stride widths to maintain a stable centre of mass over the base of support. Other measures of postural control include step length asymmetry and step width variability.[38]

1.2.1 Freezing of gait

FOG is an episodic absence or marked reduction of forward progression of the feet despite the intention to walk.[41] When a FOG episode occurs, patients feel their feet are glued to the floor and may typically have their heels lifted further increasing postural instability and falls. FOG episodes can be brief (1-30 seconds) or can last from several minutes to hours until compensatory strategies, such as cueing, or assistance is required.

FOG can be triggered by gait initiation, turning while walking or on the spot, while performing dual tasks, and walking or navigating narrow or cluttered surroundings (e.g. doorways).[22] PD patients with FOG, denoted as PD freezers, may exhibit FOG at initiation and while turning though other patients may only exhibit freezing while turning and navigating corners. As there are differences in situations that trigger FOG, there are also clinical phenotypes of FOG such as knee trembling in place, shuffling forward or akinetic FOG, which further complicates our understanding of the underlying pathophysiology. Additionally, the relationship between FOG and dopaminergic replacement medication (levodopa) is complicated. The most common freezing is

relieved by levodopa (OFF-FOG). However, there are less recognized types of freezing such as “unresponsive FOG” (OFFON-FOG or “pseudo-on FOG”) that do not respond to levodopa and freezing that is induced by levodopa (ON-FOG).[42] Thus, understanding the characteristics and triggers of FOG and the response to pharmacotherapy and cueing approaches may improve FOG management or prevent fall injuries.

1.2.1.1 Somatosensory cueing and freezing of gait

Decreased walking speed through narrow doorways suggest impaired visual information processing in FOG patients.[43] Other proprioceptive deficits are apparent in PD as accuracy (under estimating movement targets) and speed are affected when patients cannot see their hand moving.[44] Freezers rely more on visual feedback to control balance and locomotion than non-freezers do.[45] This suggests that perceptual mechanisms are impaired and may disrupt planning of movement and contribute to FOG.[45] Thus, freezers have increased visual dependency, proprioceptive impairments, and inaccurate visuospatial perception.[46] These impairments disrupt freezers’ perception of motion required for the fine-tuning of gait and motor control. Sensory cueing, such as visual (e.g. stripes on the floor), auditory (e.g. footsteps on gravel/metronome), or haptic (e.g. muscle vibration), shifts motor control from habitual (predominantly relying on the posterior putamen) to a more goal-directed type (involving the anterior putamen) of motor control and can provide additional sensory feedback.[47] Cueing has been shown to reduce FOG severity, improve gait and upper limb movements after training.[47]

Visual cues can increase step length by providing spatial information to regulate scaling and amplitude generation during walking.[47] This supports the concept that sensory deficits influence FOG.[48] As a greater number of FOG episodes occur when patients rely on proprioception to walk through a doorway,[49] providing extra visual feedback before transitioning to a FOG event may be useful. However, the clinical evidence of using ambulatory visual cues such as the “laser-shoe” and augmented visual cues via Google glasses are limited due to compliance and the bulkiness of devices overshadowing the benefits of cueing.[47]

Auditory cues provide temporal information regarding the timing and coordination of limbs for a rhythmic gait cycle. Metronome based auditory cueing can improve gait kinematics but effectiveness for FOG is limited.[50] A recent study demonstrated action-relevant sounds (e.g. footsteps on gravel) that convey both temporal and spatial parameters to the relevant performance of an action, walking, reduced gait variability and increased step length.[50,51] However, stepping sounds that do not convey heel down and toe off were not as effective for improving gait.[50,51]

Vibration of the posterior lower limb or back muscles that creates an illusory forward displacement sensation (same direction of forward movement) has been shown to improve gait in PD.[52] However, vibration of the tibialis anterior that creates a backward displacement sensation reduces step length.[52] Furthermore, vibration of the less affected limb prior to FOG onset significantly reduces FOG.[53] Thus, improving gait by eliciting illusionary sensations that facilitates movement in the same (forward) direction by vibration may improve impaired proprioceptive feedback seen in freezers, which cannot be explained purely by cognitive and attentional mechanisms.[53]

As locomotion relies on internal generated cueing information that is defective in PD freezers, FOG may arise from impaired sensory processing primarily in the proprioceptive system.[48] However, benefits of sensory cueing in the long-term (after 6-weeks of training/use) appear to diminish and effectiveness may depend on disease profile and cueing type to avoid habituation.[47] Further research is needed to better understand which cue content, consolidation of learning and transfer towards untrained tasks, and dose of cues can be effective for improving gait for the needs of individual patients.[47]

1.2.1.2 Possible mechanisms underlying freezing of gait

As environmental situations trigger FOG and sensory cueing ameliorates FOG, these suggest deficits in the processing of sensory input and motor command outputs such as sensory-perceptual (proprioception) processing. Multiple interconnected networks are involved and play a significant role in this phenomenon. A series of parallel neuronal networks between the BG and regions of the cerebral cortex, thalamus and brainstem

need to function together for fine-tuning and execution of gait.[28] However, the mechanisms underlying FOG are not yet elucidated. At rest, PD freezers show reduced connectivity between cortical and subcortical structures and lead to impaired activation between the striatum and supplementary motor area (SMA), anterior cingulate cortex, dorsolateral prefrontal cortex (dlFPC), pre-motor cortex, orbitofrontal cortex, and cerebellum compared to non-freezers.[5,54] Furthermore, the fronto-striatal pathways and attentional networks are less efficient in PD freezers than in non-freezers.[54]

PD freezers have increased functional connectivity between frontal areas that process movement planning (especially the SMA) and emotion (amygdala) with subcortical areas that process gait rhythm and initiation (cerebellar locomotor region (CLR) and the MLR).[5] Decreased functional connectivity between the prefrontal cortex (SMA) and BG (STN that is involved in inhibitory control of competing motor commands) is also characteristically seen in PD freezers,[5] and reflects the observed loss of automatic motor control.[55] Diffusion tensor imaging in PD freezers has shown reduced connectivity between the PPN and the cerebellum,[56] which may be a possible target for future therapies. Thus, these studies highlight motor control in PD freezers is influenced by the activation of sensory and emotional information.

Freezing when turning, while dual-tasking, and when anxious may be related to reduced function of motor, cognitive and limbic networks, respectively.[57] Increased FOG severity may be related to increased coupling between the putamen and the cognitive and limbic networks whereas anti-coupling between these networks may be related to reduced FOG severity.[58] Thus, the coupling of emotional and sensory information with motor planning and gait initiation may contribute to predominant FOG triggers.

Ambulatory electroencephalography (EEG) studies have shown imbalance of oscillatory features (alpha, beta, gamma) during the transition phase from a repetitive motor task such as walking to a freezing episode.[58] Freezing during repetitive finger movements are correlated with increased alpha activity predominantly in the contralateral prefrontal and centro-parietal areas.[59] Increased cortical midline theta and beta activity have been reported in the transition phase.[60] However, interpretation of surface EEG during walking

is challenging as artifacts from head and body muscle movements, sweating, and breathing can be confounders.[58] Furthermore, artifacts inherent to PD itself such as altered muscle tone, tremor, dyskinesias and sleepiness can limit the applicability and interpretation of EEG activity.[61]

1.2.1.2.1 Models of freezing of gait

There are four models of FOG proposed to explain the episodic nature of FOG and the different situations that trigger FOG.[62] The threshold model suggested by Plotnik *et al* explains the transient occurrence of FOG where the accumulation of motor deficits reach a threshold and freezing occurs.[63] A coupled bilateral motor task such as walking deteriorates in freezers due to disturbances and susceptibility to breakdown between episodes.[62] Motor deficits in gait rhythmicity, step coordination and symmetry are greater in PD freezers.[46] These deficits lead to increased cadence and reduced step length that ultimately trigger FOG.[64] Thus, this model explains that deficiencies in gait rhythmicity, coordination and symmetry drive the motor system towards a FOG state.

The interference model (relating to dual task interference) of FOG proposed by Lewis and Barker is the competition for common central processing resources that ultimately induces breakdown and FOG.[28] Increasing the number and difficulty of concurrent tasks load the cognitive and motor systems resulting in a higher likelihood of FOG.[62] This has been confirmed by observing reduced neuronal connectivity between BG and oculomotor, sensorimotor, associative, and limbic networks and inducing inhibition of the PPN.[5] Overcoming FOG in this model would require focusing on goal-directed behaviour or an external cue.

The cognitive model proposed by Vandenbossche *et al* is the deterioration in processing conflict resolutions.[65] For example, situations that require a response selection and inhibition of unwanted responses involving automatic and consciously controlled mechanisms trigger FOG.[62,65] Fronto-striatal circuits involving the STN and right inferior frontal cortex, via the hyperdirect pathway, mediate action selection and response inhibition. Increasing the incongruency level, response time, and executive function load induce FOG by increasing GPi decision threshold.[66] Thus, deficits in executive function

by having stronger automatic activation of incorrect responses and less inhibition of unwanted responses may lead to FOG events.

The decoupling model proposed by Jacobs *et al* is the decoupling between pre-planned motor programs and motor responses that trigger FOG.[62,67] This is related to dysfunctional anticipatory postural adjustments (APAs), which is the preparatory phase of gait initiation involving a shift of the centre of mass to the stance limb and contributes to the trembling in place FOG subtype. Trembling in place FOG occurs when repetitive loading-unloading cycles are coupled by a delayed or failure to generate a stepping motion.[67] This is viewed as a dysfunctional pairing of APAs with a step caused by the decoupling of automatically triggered responses and is the reason why patients describe "their feet feeling glued to the floor".[67] A study demonstrated the possibility of the decoupling model of FOG using a startle-react paradigm.[68] FOG patients have delayed startle reflex responses to loud auditory stimuli and this lack of automatic movement response has been suggested to resemble FOG events.[68] By stimulating the PPN, these startle responses are restored and are associated with improved turning time and increased alpha oscillations recorded using implanted PPN electrodes.[68] These results elucidate the significant role of the PPN in the occurrence of FOG.

The four proposed models explain the heterogeneity of FOG. FOG during gait initiation may arise from both decoupling and cognitive models of FOG where deficits of a response decision, such as selecting a swing limb to use for initiating gait, interferes with motor coupling.[62] FOG triggered while walking or in complex situations may arise from conflict resolution problems when presented with environmental input, thus the interference model. Instability of motor control can drive the system towards the freezing threshold after which decoupling model impairs gait recommencement.[63] Hence, most types of FOG may be explained by decoupling and threshold models whereas interference and cognitive models may explain some aspects of FOG to a lesser extent.[62]

1.2.2 Assessment of gait impairments

Understanding gait using powerful tools to monitor disease progression and to measure the efficacy of interventions may be necessary for effective disease management and the

rehabilitation of PD patients whose independence is limited by fall risks and multi-system degradation. There are numerous measurement tools sensitive enough to detect subtle gait changes and to quantify the complex multidimensional nature of gait.[38] Thus, the continued use of clinical scales for rating the severity of gait should be discontinued for clinical and research purposes. However, the standardization of technology to measure spatiotemporal gait parameters such as using a gait carpet or inertial motion sensors has not been brought to the clinic due to their unsuitability for physicians. Scarcity of expertise to analyse gait, access to motion detection technology and analysis software, and understanding which biomechanical parameters are important for which stages of disease and under which phases of medication (e.g. wearing off, motor fluctuations) have limited the clinical feasibility of objective gait analysis but not for research purposes.[33,35] With the continued development of low-cost hardware and software that can accurately detect and extract relevant gait features, these tools have the potential to provide feedback on the effectiveness of therapeutic interventions and counteract subjectivity when assessing patients for clinical management decisions.

1.2.2.1 Clinical outcomes of gait

The MDS-UPDRS scale is the most used rating scale for PD symptoms but only has a few items relating to gait (0 – 4 scale) including the opportunity to ask the patient about the presence and severity of FOG while OFF-levodopa and ON-levodopa medication. FOG is assessed on a single scale and information regarding circumstances that trigger FOG and FOG durations are missed. Apart from the FOG items from the MDS-UPDRS, two validated FOG questionnaires exist: Freezing of Gait Questionnaire (FOG-Q) and the New FOG-Q (NFOG-Q), which rate FOG severity in terms of frequency and duration of FOG at initiation and while turning, and the impact of FOG on quality of life and activities of daily living.[69] The main drawback is that these subjective methods rely on a patient's ability to report on FOG. Examination of freezing in clinic typically includes 360-degree turning, small step walking, stopping on command, narrow walkways, or dual motor-tasking such as carrying a tray or with a cognitive load.[70] However, these commonly used clinical assessments do not provide the granularity or the capability of recording FOG frequency or duration. Due to the unpredictable nature of FOG, the best

method to examine FOG in the clinic or for research purposes is to provoke 360-degree on the spot turning in both clockwise and counterclockwise directions[50,71] or stepping in place[64] and should be repeated at separate visits.

Validated observational scales (e.g. Dynamic Gait Index) and performance-based tests (e.g. Timed up and Go Test) used in clinics assess gross motor characteristics such as slow walking speeds and shuffling steps but are not specific to PD.[33] Velocity, stride length, and initiation time may be an indication of bradykinesia and amplitude control, but it is unclear how these change with disease progression or medication status (e.g. OFF-levodopa, wearing off, ON-levodopa).[33] These test measures exhibit tester bias and are limited to measuring simple gait metrics (e.g. speed). Although clinical gait measures are easy to use, they do not provide information on the pattern or quality of movement.[33]

1.2.2.2 Objective measures of gait

Dedicated gait assessment laboratories with expensive technology such as fixed camera-based motion capture systems (e.g. VICON) permit researchers to collect a large number of spatiotemporal gait parameters, as mentioned in section 1.2. More affordable systems such as a gait carpet or sole inserts (e.g. Tekscan) that utilize pressure sensors to measure gait parameters are more practical than camera-based systems and are validated for research. Comparatively low-cost wearable technology, such as inertial measurement units (IMUs) that contain gyroscopes, accelerometers, and inclinometers, is rapidly replacing these camera-based systems and pressure sensor technologies enabling researchers to still collect relevant and validated gait parameters in the laboratory. However, gait and mobility assessment in the clinic or laboratory is not an accurate representation of typical daily life as patients exhibit increased attention, alertness, and effort to perform when under examination. Using these IMUs in a home setting can detect differences between freezers and non-freezers' quality of gait, such as variability and consistency, rather than the quantity of walking and turning, which are similar between these two populations.[72] Further research into the accuracy of wearable sensors to detect FOG episodes and the usefulness of collected data in the community setting is warranted.[72]

1.3 Progressive supranuclear palsy

Progressive supranuclear palsy (PSP) encompasses a range of behavioural, movement and language abnormalities. The most common form of atypical parkinsonism is PSP Richardson's syndrome (PSP-RS) characterized by the rapid progression of these more frequently reported clinical features: speech and swallowing difficulties, axial bradykinesia, rigidity, vertical supranuclear gaze palsy, unsteady gait, FOG, postural instability, and executive dysfunction.[3] However, the slowing of vertical saccades rather than horizontal saccades is a diagnostic and defining feature of PSP-RS. There are other symptomatic PSP phenotypes such as: PSP-parkinsonism where patients have early features of PD and a more benign disease course than PSP patients usually have, PSP with progressive gait freezing where pure akinesia with gait freezing occurs before development of other PSP-RS features, PSP-corticobasal syndrome (CBS) includes CBS diagnosis and pathology that resembles PSP-RS motor features, PSP-speech language that has predominant speech/language disorder before developing PSP-RS motor features, PSP with frontal presentation includes initial development of frontotemporal dementia followed by PSP-RS cardinal features, PSP with predominant cerebellar ataxia, which is a rare clinical phenotype with patients initially presenting with ataxia before PSP-RS features, and PSP with mixed pathology involving co-pathologies such as Alzheimer's disease with PSP.[3]

Pathological criteria of PSP are mainly tau lesions in the basal ganglia and brainstem.[3] PSP syndromes with more severe cortical symptoms have shown widespread cortical tau pathology as seen in PSP-CBS patients. Longitudinal neuroimaging using diffusion tensor imaging showing atrophy of the midbrain and superior cerebellar peduncles is a marker for differentiating PSP-RS from other parkinsonian syndromes.[73] Although there is a need for diagnostic biomarkers that can detect PSP pathology in the pre-symptomatic/early symptomatic stages of disease, disease-modifying approaches that target tau and effective therapies for PSP are major unmet needs.

1.3.1 Similarities between Parkinson's disease and Richardson's syndrome

In PSP-RS, FOG occurrences increasing with disease duration are similarly seen in PD.[10] This pattern is less consistent in the later stages as most PSP-RS patients are unable to walk whereas advanced PD patients may still have limited mobility; giving rise to the short PSP-RS prognosis of approximately 6 years.[74] Onset of FOG occurs within the first 4 years of disease in at least 70% of PSP-RS patients and FOG is associated with rigidity, bradykinesia, gait, and posture clinical features.[74] Symptoms of FOG, bradykinesia, rigidity, and speech abnormalities seen in PSP-RS are also observed in the PIGD PD phenotype and in advanced PD patients who do not typically respond well to levodopa therapy.[3,4] Hence, dopaminergic-resistant gait impairments and FOG symptoms in PSP-RS and PD syndromes may possess related pathologies within networks involving the striatal efferents to the globus pallidum, subthalamic nucleus,[10] and the PPN. A recent study by Davidsson *et al* demonstrated that PD and AP patients have distinguishable patterns of striatal dopaminergic neuronal loss detected using a DaTSCAN single-photon emission computed tomography (SPECT) imaging technique.[75,76] DaTSCAN uses a radioactive tracer ([123I]FP-CIT; 123I-ioflupane) with a high binding affinity for presynaptic striatal dopamine transporter (DAT) and provides a quantitative measure of the number of functioning dopaminergic neurons in the striatum.[75] Early PD patients tend to have an egg shape pattern (posterior-anterior degeneration pattern) whereas AP patients have a more global and severe degeneration pattern (burst striatum).[75] Both AP and PD syndromes have degeneration of dopaminergic innervation, but DAT levels decline twice as fast in AP compared to PD patients. Thus, a burst striatum pattern seen in AP syndrome reflects a more severe and widespread neurodegeneration than is seen in the early stages of PD. However, the marked loss of dopamine transporter binding in the striatum, consistent with the loss of nigrostriatal neurons does not account for the poor response of dopaminergic replacement therapies for gait and FOG in both PD and AP syndromes.[77]

Notably, both PD and PSP populations have been shown to have PPN pathologies. Animal models with selective cholinergic depletion in the PPN show increased FOG

severity suggesting the vital role of the PPN in PD and in the much more affected population of PSP patients.[78] DBS targeting the PPN (PPN-DBS) and dual-targets of PPN and GPi report gait improvement and reduced falls at 12-months in PSP patients[79] and at 6-months in PD patients with dopaminergic-resistant gait[80] and in advanced PD patients with predominant axial features and FOG without levodopa (see section 1.4.2).[81] The PPN plays a vital role for appropriate planned movement to be initiated (e.g. posture and gait) by receiving and regulating somatosensory information from the thalamus and cerebral cortex to locomotor generators in the spinal cord. Thus, the degeneration of PPN cholinergic neurons early in PSP-RS and progressively in PD patients contribute to the presence of FOG and falls. Thus, effective therapies that may stimulate or reactivate the cholinergic pathway may be required to treat PSP-RS and PD patients with dopaminergic-resistant axial features.[15]

1.4 Therapeutics for parkinsonian gait impairments

Proper management of gait impairments especially FOG is important due to its major source of disability and fall risks in parkinsonism syndromes. However, the various treatment approaches available have inconsistent and limited benefits for axial features including gait, FOG, and postural instability, thereby leaving a large population of patients sub-optimally managed. The two general therapeutic classes are pharmacological and surgical options. Pharmacotherapy is the mainstay treatment and is adjusted over the disease course whereas surgical therapy is only tried in a fraction of patients due to strict inclusion criteria. Experimental approaches such as non-invasive transcranial stimulation techniques are explored when symptoms are resistant to pharmacotherapy and when surgical intervention is not an option or is deemed ineffective for alleviating axial features. Non-medical management of FOG/gait including physiotherapy and occupational therapy is used as preventative strategies or in mild cases. Non-medical strategies include the use of cues that can overcome FOG or improve gait rhythmicity, and recommendations to maintain sufficient physical activity (e.g. boxing therapy, cycling). Other preventative strategies include shifting weight to one leg before swinging for gait initiation, taking wide turns or using C loop turns instead of narrow turns, creating wider spaces or decluttering of the home with an occupational therapist,

attentional focus on gait (e.g. not dual-tasking), and limiting mobility in crowded environments.[20]

1.4.1 Pharmacotherapy

The gold-standard treatment for PD, dopamine replacement (e.g. levodopa), is used to correct imbalances from the loss of dopaminergic neurons within the BG. Levodopa/carbidopa (Sinemet) or other levodopa formulations such as Stalevo that includes entacapone, and dopamine agonists (pramipexole and ropinirole) are effective for alleviating appendicular motor features such as rigidity, bradykinesia, and tremor. However, the effects of dopamine replacement pharmacology for treating axial motor features are limited.[33] Levodopa has been found to improve gait pace but worsen rhythm and postural control gait parameters,[34] while dopamine agonists have been shown to improve gait initiation and turning.[33] However, dopamine agonists are not the first choice for drug-naïve patients due to the elevated risk of developing FOG and other adverse side effects such as sedation and increased fall risks compared to starting with levodopa.[20]

Dopaminergic medication can typically alleviate FOG that occurs during the OFF-medication or during wearing OFF states, denoted as dopaminergic-responsive FOG, more effectively than when FOG occurs during the ON-medication state (OFFON-FOG).[20] Contrasting dopaminergic-responsive FOG, dopaminergic-induced FOG (ONOFF-FOG) can persist or even worsen in the ON-medication state compared to the OFF-medication state.[82] This type of FOG is distinctive and is not a result of inadequate dopaminergic therapy.[82] Higher levodopa dosages are required to suppress dopaminergic-responsive FOG than those dosages required for managing cardinal motor features. Chronic use or high dosages of levodopa can induce side effects such as levodopa-induced dyskinesia (LID) and wearing off fluctuations (more frequent “wearing off” periods), which can be more disabling than the PD symptomologies.[83] Intraduodenal levodopa gel (Duodopa) and subcutaneous apomorphine infusions can be tried as these approaches provide more continuous levodopa administration to reduce fluctuations and can be considered for managing dopaminergic-responsive FOG.[20] However, OFFON-FOG and other axial symptoms such as speech and oral motor control, balance and

stability are typically not responsive to dopaminergic medication over time leaving a large patient population sub-optimally managed.

With disease progression and increased disease duration, dopaminergic-resistant gait and FOG symptoms predominant, even in most patients with initially dopaminergic-responsive FOG.[20] Amantadine, an N-Methyl-D-aspartate antagonist, may be tried as an add-on therapy for dopaminergic-resistant FOG, although side effects are common in elderly patients and evidence is inconclusive, thus more studies are needed to better determine the efficacy for gait and FOG.[84] As altered cholinergic activity is implicated in parkinsonian gait and cognition, the use of acetylcholinesterase inhibitors (ChI; e.g. donepezil, galantamine, and rivastigmine) has been considered for symptomatic treatment. ChIs may improve cognitive impairments but there is inconclusive evidence that falls are reduced, and ChIs may worsen other motor features.[85] Thus, the use of non-dopaminergic drugs for treating levodopa-resistant gait and FOG is disappointing and no meta-analyses or randomized controlled trials exist.[20]

1.4.2 Non-pharmacological treatments

Due to the multiple neural networks involved with FOG, gait automaticity and rhythmicity, invasive or non-invasive neuromodulation of the central nervous system is of growing interest.[86] Invasive neuromodulation techniques include the use of DBS targeting the STN or GPi, or a more experimental target of the PPN or multiple targets. Currently, only a small fraction of PD patients are eligible for DBS due to strict inclusion criteria and DBS candidates in particular must have dopaminergic-responsive motor symptoms. The effect of DBS is well established for treating appendicular symptoms including bradykinesia, rigidity, and tremor and for alleviating levodopa-induced dyskinesia.[87] However, DBS for treating axial features such as levodopa-responsive gait/FOG is less clear.[87] Long-term (1+ years) studies show no amelioration of axial motor symptoms and may induce or aggravate FOG, postural instability, and falls.[4,86] However, DBS in the short-term is effective for improving gait and reducing levodopa-responsive FOGs.[4,86] Interestingly, a study has shown synergistic benefits of STN-DBS and levodopa for axial symptoms within the first year.[88] STN-DBS intervention in 35 levodopa-responsive PD patients significantly improved clinical symptoms with reduced

UPDRS scores and reduced levodopa doses within the first year.[89] In this study, STN-DBS patients demonstrated no increases in DAT binding but rather a reduction in DAT at a rate of 6.7% per year, which is comparable to the declining rate of DAT binding observed in non-operated PD patients. DBS targeting the STN or GPi may not slow nigrostriatal neuronal degeneration despite beneficial short-term clinical effects. This study concluded that electrode implantation and STN stimulation may not induce a neuroprotective effect.[89] Thus, the exact mechanism of action of STN-DBS is unknown and it is unclear whether an increased release of dopamine in the striatum takes part. Ultimately, DBS does not offer satisfactory control of FOG, which encourages investigation into other targets.

DBS of the PPN has been considered as a non-dopaminergic treatment as the PPN is part of the MLR consisting of cholinergic and glutamatergic neurons involved in gait initiation and FOG.[90] However, PPN-DBS is still considered investigational due to inter-individual variability in gait response.[4] Further research to determine the best DBS target (caudal versus rostral PPN), optimal stimulation parameters, and patient selection is needed.[4] Multi-target DBS such as PPN and STN have shown promising beneficial effects for gait, postural instability[91] and FOG[92] that exceed effects observed from PPN-DBS or STN-DBS alone. Another experimental target of DBS is the zona incerta, which has shown gait improvement 10-13 months post-surgery in a small cohort of patients.[93] In summary, STN-DBS may have better gait improvements than GPi-DBS, but GPi-DBS has a milder decline in response over time where new non-dopaminergic targets such as the PPN and zona incerta for gait remain elusive.

Non-invasive neuromodulation approaches such as transcranial magnetic or electrical stimulation can modulate activity of cortical sites that are anatomically connected to deeper target sites without the need for invasive surgery. Repetitive transcranial magnetic stimulation (rTMS)[94] and high-frequency TMS over the lower leg area of the M1 reduced subjective FOG and improved gait and 180-degree turning performance.[95] Low frequency rTMS over the M1 or DLPFC has shown no FOG improvements, and a study was inconclusive due to several patients withdrawing due to stimulation discomfort.[96] Although intermittent theta burst stimulation over the cerebellum improved gait speed

and reduced FOG, 10% of patients discontinued due to the discomfort and pain from the stimulation.[97] Thus, the rate of stimulation discomfort and the variability of improvements for FOG raises concerns as to whether rTMS techniques should be used in clinical practice.[47]

Transcranial direct current stimulation (tDCS) has the potential to be translated to clinic compared to rTMS due to its portability, greater safety profile, lower cost, and being more user-friendly. A double-blinded, cross-over, randomized sham-controlled study demonstrated that 5 consecutive days of a 20-minute, 2 mA anodal tDCS stimulation over the M1 significantly reduced dopamine-resistant FOG in 10 PD patients for up to 1 month following treatment.[98] Furthermore, dual-target of tDCS over the M1 and left DLPFC improved objectively measured FOG in 20 patients compared to sham stimulation or single-target of tDCS.[99] Although there are only a limited number of studies and albeit no longitudinal reports regarding the use of tDCS for FOG, these preliminary results for a non-invasive stimulation approach are promising.[47]

1.5 Spinal cord stimulation for gait impairments

Novel treatment options for symptoms that are unresponsive to current available therapies, such as gait impairments and FOG, have emerged. One alternative treatment is epidural, dorsal column spinal cord stimulation (SCS) that is a minimally invasive, programmable, out-patient procedure used for several decades to treat certain types of chronic neuropathic pain syndromes.[100] SCS induces paresthesias, a tingling or numbness sensation, to cover the body areas affected by pain. In open label trials, the therapeutic effect of SCS has been tested for various movement disorders such as dystonia, multiple sclerosis tremor, and orthostatic tremor albeit with limited improvements.[101] SCS has gained recognition for treating motor symptoms in parkinsonian animal models and recently in more robust clinical trials. However, despite promising clinical findings, its use for treating parkinsonian gait impairments is still in its infancy. Heterogeneity of methodologies and small sample sizes have challenged the robustness of the clinical evidence to support SCS as a viable therapy.[102]

SCS involves implanting epidural electrode leads that are connected to an implantable pulse generator and are placed along the medial dorsal part of the spinal cord through the dura matter.[101] The pattern of stimulation is important for successful responses as various pulse width, pulse frequency, and current intensity (comprised of the applied voltage and the impedance) parameter combinations have different effects in target structures.[103] Thus, the type of sensory fibres activated is dependent on the pattern of stimulation.[104] Electrical pulses with shorter pulse widths may primarily activate large-diameter (low threshold) afferent fibres such as mechanoreceptors that send sensory information to the ventral posterolateral thalamus and primary somatosensory cortex.[101,105] Increased stimulation times with longer pulse widths may induce a depolarization of deeper structures and its effect can be more prominent in the upper thoracic spinal cord.[106] As the dorsal column is formed by nerve fibres of varying sizes, the refractory period of a single neuron determines the frequency rate that can generate a new action potential.[103] For example, low frequency stimulation can stimulate most nerve fibres since the rate is lower than the refractory period of the slowest nerve fibre in the dorsal column.[103] Current clinical reports have suggested that identifying optimal stimulation parameters (the pattern of stimulation thereby the type of dorsal column nuclei activated) by individualizing SCS programming to each patient's symptoms may be an important factor influencing the clinical response.[103] Nevertheless, the therapeutic success of SCS may also depend upon the sensory fibres activated leading to areas or dermatomes being covered by paresthesias, such as the lower limbs and feet to treat gait impairments.[107,108] Thereby, the placement of electrode leads (e.g., thoracic or cervical) can influence motor response.[103] SCS may generate its therapeutic effects locally at the dorsal horn by pain-generating mechanisms (e.g., gate-control theory),[109] by restoring activity imbalances at the dorsal horn level[103] or by modulating the activity of central pattern generators (CPGs).[5] In addition, SCS may influence distantly by modulating suprasegmental circuits such as the thalamus, somatosensory, premotor, anterior cingulate cortex, prefrontal areas, and brainstem structures.[101,103] However, the underlying mechanism of SCS for treating PD motor symptomologies such as the modulation of the thalamo-cortico-striatal or the cortico-subthalamic-PPN-PMRF pathways is still unclear.

1.5.1 Pre-clinical use of SCS in Parkinson's disease

A preliminary report on the effects of high thoracic SCS applied in dopamine-depleted mice and rats significantly improved locomotion.[107] Fuentes *et al* observed momentarily after stimulation was switched on, that the modulation of oscillatory brain activity measured by local field potentials in the motor cortex and basal ganglia nuclei (putamen, GPi, STN, and thalamus) coincided with improvements in locomotor behaviour.[107] In non-human primate PD models treated with high thoracic SCS, Santana *et al* found that improvements in freezing, bradykinesia, rigidity, and hypokinesia are strongly associated with the desynchronization of cortico-basal ganglia circuitry and the reduced activity of beta band oscillations.[105] Correspondingly, cortical desynchronization occurs by stimulating afferent fibres within the dorsal column of the spinal cord that input to the PPN, thalamic nuclei and the cerebral cortex.[105,107,110] Thus, these studies suggest that SCS improves gait impairments and freezing that is associated with the disruption of these pathological synchronized oscillatory activities.

In addition to changes in electrophysiological activity associated with gait and FOG improvements, SCS may induce a dopaminergic neuroprotective effect. Preliminary results of chronic (6-weeks), upper thoracic, high frequency (333 Hz) SCS in a 6-hydroxydopamine (6-OHDA) rat PD model has shown protection of nigrostriatal dopaminergic neurons, quantified by striatal tyrosine hydroxylase (TH) immunoreactivity, and an increased neuronal cell count in the SNpc, compared to the sham control group.[111] Another study has observed 6-OHDA rats treated with upper cervical, low frequency (50 Hz) SCS produced a neuroprotective effect by significantly preserving nigro-striatal dopaminergic neurons and upregulating vascular endothelial growth factor compared to the sham control group.[112] Thus, these findings suggest that dorsal column SCS may have a chronic therapeutic and possibly a neuroprotective effect increasing its potential as an alternative therapy for gait features in parkinsonian patients.

1.5.2 Clinical use of SCS in Parkinson's disease

With the pioneering use of SCS in rodent and primate PD models, numerous clinical case studies over the last decade have reported axial motor improvements, such as gait and

FOG. Table 1-1 displays an overview of the 19 recent studies and the heterogenous effects of SCS in these clinical populations totaling 84 patients. These clinical case studies included patients with: PD with and without pain or those with a loss of efficacy to both dopaminergic replacement medications and DBS, primary progressive FOG, and AP syndromes such as multiple systems atrophy (MSA) and vascular PD (VPD). Out of the known 19 studies summarized in Table 1-1, 12 studies included parkinsonian patients with treatment resistant pain, of which 6 out of the 12 studies included PD patients with prior DBS, 2 studies included pain-free PD patients with DBS, and 3 studies included AP patients. Heterogeneous results may have occurred due to differences in the type of patients selected such as those with PD or AP syndromes, those with various predominant PD symptoms and those with or without former DBS therapy. Furthermore, the variability in SCS outcomes may be due to the inclusion of patients with different causes of treatment resistant pain as pain can affect various body parts (e.g. neck, lower back, or legs). These studies that included patients with pain did not control for bias, as pain alleviated by SCS can also improve gait symptoms. Besides, these early clinical case studies also had differences in the placement of electrode leads (cervical versus thoracic). Failure of SCS to improve gait may be due to lead placement along the spinal cord, as pre-clinical studies with positive effects localized leads in the upper thoracic spinal segments.[105,107] Another reason for the heterogenous effects of SCS is the broad spectrum of stimulation parameters implemented. Pre-clinical studies highlight the importance of the pattern of stimulation (high frequency versus low frequency or high/low pulse width combinations) to activate ascending nerve fibres and modulate cortical activity.[105,107]

The lack of objective gait measures and the reliance upon using clinical scales as gait outcome measures (e.g. UPDRS motor items for axial features or timed-up and go tasks) in these pilot clinical studies do not provide the granularity necessary for understanding how SCS affects the different aspects of gait (e.g. pace, rhythm, asymmetry, and variability). In addition, many studies summarized in Table 1-1 have various follow-up time-points ranging from 2 weeks to 2.5 years making conclusive results of SCS very challenging. However, studies that did report improvements in gait speed and FOG occurring at follow-up time points of 2 weeks, 5 months, 6 months, 12 months, and 24 months[6-8,113-115] have been criticized with skepticism as these parameters are very

sensitive to a placebo effect.[116] A method to minimize placebo effects and to blind patients is to test multiple stimulation settings and ultimately select the setting that best improves an individual's gait symptoms.[117] Furthermore, another approach to minimize placebo effects is burst stimulation. This has been explored in 3 recent studies and permits the use of SCS at a subthreshold intensity, thus the patients do not feel paresthesias.[8,115,118] Kobyashi *et al* demonstrated burst stimulation improved MDS-UPDRS-III (motor items) score, specifically the gait and posture features, in a PD patient with back pain.[115] Mazzone *et al* reported the effects of tonic (continuous, suprathreshold) stimulation compared to burst stimulation for refractory pain in a mixed population of parkinsonian patients with PD, AP and VPD.[8] This study concluded that burst stimulation improves gait symptoms acutely and improvements continued for up to 12 months, but that tonic stimulation required a longer latency prior to seeing motor benefits.[8] However, both tonic and burst stimulation approaches demonstrate improvements in gait speed, cadence, and step length for PD and AP patients, which also required a mean reduction in daily levodopa dose by 100 mg.[8]

Evidence of SCS modulating cortical activity to alleviate FOG has been suggested in one study by de Lima-Pardini *et al*.[114] De Lima-Pardini *et al* used the cohort of 4 chronically treated STN-DBS patients, who exhibited significant gait improvements with 300 Hz and 90 μs stimulation,[113] to compare the effects of low (60 Hz) and high (300 Hz) stimulation frequencies on FOG and APAs.[114] Both frequency parameters reduced FOG and the time of APAs but failed to improve reactive postural responses, albeit greater benefits were achieved with 300 Hz than 60 Hz stimulation.[114] APA mechanisms are dependent on the activity of the thalamo-cortical-striatal pathway and are influenced by attentional and environmental factors.[114] Thus, SCS may influence cortical input to the striatum by modulating cortical areas involved in planning of movement (e.g. SMA) that are required for APAs.[114] Furthermore, when DBS was switched off, SCS still improved FOG and APAs further pointing to the non-dopaminergic effect of SCS for improving movement control.[113,114] The potential non-dopaminergic effect of SCS for gait was also documented in 2 recent studies including a MSA patient[7] and a primary progressive FOG patient,[6] as FOG and gait symptoms are characteristically unresponsive to dopaminergic medications in these syndromes. SCS improved FOG and gait in the MSA and primary progressive

FOG patients for up to 6-months[7] and 24-months of therapy,[6] respectively. As the use of SCS continues to be investigated globally, future studies should employ objective measures of gait, parkinsonian patients with ON-medication freezing, blinded testing of stimulation parameters to minimize placebo effects, and to follow these patients within the first year and annually to understand the longitudinal effect of this promising therapy.

Table 1-1: Overview and results of the clinical use of SCS for parkinsonian symptoms

				Stimulation parameters				
Study	No. of pts / Mean age (years) / YWD (years) / DBS prior to SCS	Indication for SCS	SCS level	Freq (Hz)	PW (μs)	Intensity	Outcomes	F/U
Thevathasan et al., 2010[119]	2 / 76 / N/A / No	Advanced PD	C2	130 and 300	200 and 240	2-3 and 3-4 V	Unchanged UPDRS-III score: from 37.8 to 35.4 (subthreshold) and to 37.4 (suprathreshold); unchanged 10-m walk	10 days
Weise et al., 2010[120]	1 / 72 / 17 / STN-DBS	PD with Chronic back pain	Cervicothoracic	N/A	N/A	N/A	Unchanged UPDRS-III score	N/A
Fenelon et al., 2011[121]	1 / 74 / 5 / No	PD with Failed back surgery syndrome	T9-T10	100 to 300	410	3.5 V	UPDRS-III decreased from 56.7 to 29.7 (OFF-levodopa/ON-SCS), 26 (ON-levodopa/OFF-SCS) and 22 (ON-levodopa/ON-SCS)	29 months

Agari et al., 2012[122]	15 / 71 / 17 / Yes in N = 7	PD and chronic low back and leg pain	T7-T12	5 to 20	210 to 330	0 to 4 V	UPDRS-III reduced from 23.5 to 18.9 at 3-months and 21.3 at 12-months, assessed ON-levodopa/ON-SCS	12 months
Landi et al., 2012[123]	1 /65 / 8 / STN-DBS	Advanced PD and chronic intractable leg pain	T9-T10	30	250	1.8 to 2.5 V	Unchanged UPDRS-III score	16 months
Hassan et al., 2013[124]	1 / 43 / 8 / No	PD with Chronic neuropathic neck and upper limb pain secondary to trauma	C2	40	500	0.3 to 1.1	UPDRS-III score reduced from 28 to 22 (12-months) and 16 (24-months) assessed ON-levodopa/ON-SCS	24 months
Soltani & Lalkhen., 2013[125]	1 / 68 / N/A / No	PD with Post laminectomy syndrome	T9-T11	60	300	1.5 V	Improved UPDRS-III	N/A
Mitsuyama et al., 2013[126]	2 / N/A / 7 to 10 / No	PD Chronic low back pain	Midthoracic	N/A	N/A	N/A	Unchanged UPDRS-III score	N/A
Nishioka et al., 2015[127]	3 / 74 / 9 / No	PD with Radiculopathy, herniated disc, failed back surgery syndrome	T8-L1	5 to 20	60 to 450	0.6 to 5.8 V	UPDRS-III score reduced from 37 to 25 (12-months) assessed ON-meds/ON-SCS	12-months

Pinto de Souza et al., 2017[113]	4 / 64/ N/A / STN-DBS	Advanced PD with treatment resistant PIGD	T2-T4	300	90	2.0 to 3.6 V	UPDRS-III improved from 33 to 22 (1-month), 16.2 (3-months), and 19.7 (6-months) assessed ON-DBS/ON-meds/ON-SCS; FOG-Q improved by 56.4% and improved berg balance score; TUG improved by 63.2%, 20-m walk time improved by 63.3%; Stride length increased by 17.0%	6-months
Akiyama et al., 2017[128]	1 / 65 / 12 / Yes	PD with back pain	T8	7	250 and 450	2.5 to 3.5 V	Unchanged UPDRS-III, UPDRS-II improved from 25 to 12; TUG improved from 15 sec to 7 sec	1-month
Rohani et al., 2017[6]	2 / 60 and 75 / 5 and 7 / No	PD with resistant gait disorders and/or FOG	T10-T11	60 and 70	60 and 90	2.5 and 7 V	FOG improvement perceived by 1 patient at 24-months and clinical evaluation of improved FOG at 5-months	5-months and 24-months

de Lima-Pardini et al., 2018[114]	4 / 64 / N/A / STN-DBS	PD with PIGD	T2-T4	60 or 300	N/A	N/A	APA measured at step initiation reduced in all patients under 300 Hz SCS, where APA reduced for 2 of the 4 patients under 60 Hz SCS suggesting SCS influences SMA activity; FOG reduced in 2 patients under 300 Hz as 2 patients did not have FOG episodes during assessment; reactive postural control did not change	Tested each setting 1-week apart
Kobyashi et al., 2018[115]	1 / 74 / 3 / No	PD with back pain	T6-T8	40 with 5 spikes of 500	1000	0.6 to 0.8 mA	UPDRS-III improved from 20 to 6; improved gait and posture	2 weeks
Hubsch et al., 2019[129]	5 / 69 / 15 / No	PD with resistant gait disorders and/or FOG	T10-T11	100	300	N/A	UPDRS-III improved by 23% OFF-levodopa and by 37% ON-levodopa as axial items improved by 29.8% (OFF-levodopa/ON-SCS) and by 42.5% (ON-levodopa/ON-SCS) at 2-months; reduced number of steps by 20% (ON-levodopa/ON-SCS); PDQ-39 improved from 72 to 57; at 2.5	2-months and 2.5 years

							years of therapy, 3 of the 5 patients kept same program with maintained long-term benefit	
Mazzone et al., 2019[8]	18 / 65 / 11 / STN-DBS in N = 1; PPN-DBS in N = 2	PD with low back pain (N = 4), AP with pain (N = 4), VPD with pain (N = 10); Tonic stimulation included 3 PD, 1 AP and 2 VPD and burst stimulation included 1 PD, 3 AP and 8 VPD patients	C2-C3	13 to 185 (N = 6 tonic); 250 to 500 (N = 12 burst)	60 to 210 (tonic); 1000 (burst)	1.3 to 4.0 V (tonic); 0.2 to 0.9 mA (burst)	Tonic stimulation produced a delayed effect at 3-12 months; burst stimulation produced acute effects and continued up to 12-months. DBS/SCS PD patients improved motor and gait scores acutely and at 3-, 6- and 12-months with burst and tonic stimulation groups requiring reduced daily levodopa dose by a mean 100 mg; gait speed, cadence, step length improved for both tonic and burst stimulation groups up to 12-months	12-months

Chakravarthy et al., 2020[118]	15 / 74 / 17/ STN-DBS in N = 8	Refractory pain in 2 tremor-dominant and 13 akinetic rigid PD; tonic stimulation for N = 1; burst stimulation for N = 7; burst and cycle stimulation for N = 7	Thoracic in N = 14, cervical in N = 1	10 (tonic); 40 / 500 (burst and burst + cycle); cycling mode included on time 10 sec and off time 30 sec	350 (tonic); 1000 (burst and burst + cycle)	2.6 mA (tonic); 0.15 to 1.45 mA (burst and burst + cycle)	Unchanged UPDRS-III scores; TUG time improved by 21% in 7 of the 11 patients and 18% improvement with burst stimulation but 7% worsening in burst + cycle mode	22 months (ranged from 4 to 33 months)
Prasad et al., 2020[116]	6 / 31 to 76 / 12 to 18/ No	Pain-free PD with significant axial symptoms	T10	50 to 130	50 to 450	N/A	Unchanged UPDRS-III scores; UPDRS-II OFF-levodopa slightly improved from 27 to 22 up to 12-months; gait velocity, step length, and variability of step length and swing time did not improve up to 3-months and worsened at 12-months; step asymmetry, stride width, stance and swing gait phases did not change up to 12-months	12-months

Zhang et al., 2020[7]	1 / 70 / 6 / No	Multiple systems atrophy	T10-T12	60	200	1.0 V	Significant FOG reduction with ON-SCS for 2-weeks; UPDRS-III improved 38% and FOG-Q improved 63% at 6-months; PET imaging at 5-months showed increased glucose metabolism in bilateral frontal-parietal lobes compared to baseline	6-months

Abbreviations: AP = atypical parkinsonism; C = cervical; FOG-Q = freezing of gait questionnaire; Freq = frequency; F/U = follow-up; Hz = hertz; N = sample size; PDQ-39 = Parkinson's disease questionnaire; PET = positron emission tomography; PW = pulse width; T = thoracic; TUG = timed-up and go test; UPDRS-II = Unified Parkinson's disease rating scale activities of daily living score UPDRS-III = Unified Parkinson's disease rating scale motor score; V = voltage; VPD = vascular Parkinson's disease

1.6 Rationale and Summary

Gait impairments and FOG in patients with PD and PSP-RS are typically unresponsive to current available pharmacotherapies (e.g. dopaminergic replacement therapies). Furthermore, both of these syndromes are not eligible for surgical interventions (e.g. STN- or GPi-DBS) due to the lack of levodopa responsiveness of these axial motor features (levodopa responsiveness is a criteria for DBS intervention) and because long-term (1+ years) DBS can worsen gait. Thus, a large population of patients are sub-optimally treated resulting in a significant unmet need for a novel, effective therapy for dopaminergic-resistant gait symptoms.

It is theorized that dopaminergic-resistant FOG is a sensorimotor processing issue and may not be solely related to basal ganglia (nigrostriatal) dysfunction. PD freezers have decreased activation of cortical areas associated with motor planning and execution when

compared to non-freezers. Non-invasive stimulation of motor planning cortical areas, such as the DLPFC, SMA, and M1 or dual-target stimulation, can reduce FOG supporting that there is an impaired central, cortical network underlying FOG. The loss of dopaminergic innervation to the posterior putamen, which receives sensorimotor cortical inputs based on the conserved spatio-topographical organization of the neural circuitry, reduces connectivity between cortical and subcortical areas and may cause visual-motor performance errors due to perceptual impairments. External proprioceptive feedback using sensory cues can also alleviate FOG and improve gait features such as speed and step length suggesting an association between enhancing visual-motor control and reducing FOG. Furthermore, the upper brainstem, particularly the PPN, is a sensorimotor integration centre that may contribute to FOG due to the decoupling of pre-planned motor programs and motor responses. PPN stimulation has been shown to restore motor planning programs, improve gait speed and reduce FOG occurrence. As the mechanism of FOG is multidimensional, a therapeutic intervention that can access and modulate cortical and subcortical pathways involved in sensory processing, motor planning and coordination, and gait execution to alleviate dopaminergic-resistant gait symptoms is warranted. The hypothesis of the research tested in this thesis is that mid-thoracic, dorsal SCS intervention effectively reduces FOG by modulating the sensory processing system in gait and may have a dopaminergic effect in individuals with FOG. SCS may influence multiple projection pathways to the brainstem, cerebellum, basal ganglia, thalamus, and cortical areas besides acting on local and integrated spinal circuitries to alleviate FOG.[5]

The first aim of the current thesis, reported in **Chapter 2**, was to understand the relationship between FOG, visual-motor performance and changes in cortical activity and striatal dopaminergic innervation with up to 6-months of SCS therapy in PD participants. Visual-motor performance was assessed by using robotic reaching target choice tasks that extracted upper limb speed, reaction time and accuracy of targeting shapes on the screen. Four tasks including 12 trials per task were completed by the PD participants who were required to move the robot (connected to a toggle that moved a cursor on a computer screen) to each target that appeared. Tasks involved 1) a stationary target, 2) stationary but toggle exerted resistive/assistive forces requiring the participant to provide more/less force to move the cursor to each target, 3) target appeared on the screen for 0.25 seconds

requiring the participant to move the cursor to wherever the target appeared, and lastly 4) each participant had to find a shape on the screen and avoid distractor shapes requiring visual discrimination capabilities. DaTSCAN brain imaging and resting-state EEG recordings were conducted at pre-surgery and at 6-months of SCS use to quantify DAT binding, a marker for striatal dopaminergic innervation, and changes in cortical activity by quantifying power spectral density in cortical areas relating to FOG (sensorimotor areas), respectively.

The second aim of this thesis was to understand the short and long-term effects of SCS for alleviating dopaminergic-resistant (ON-levodopa) FOG and gait dysfunction in PD and PSP-RS participants. The rationale for investigating the alleviation of FOG in both parkinsonian syndromes is that the pathogenesis of dopaminergic-resistant FOG and gait symptoms is not disease specific and both syndromes have sensorimotor deficits. FOG and gait impairments in early PSP-RS and progressively observed in PD patients or in PD patients with the PIGD phenotype may likely originate from similar changes in non-dopaminergic neural activity, such as cholinergic dysfunction in the PPN that is part of the MLR and required for initiation and regulation of motor control. The outcomes of the second aim are described in **Chapters 3 and 4**. **Chapter 3** reported the changes in clinical scores and objective gait and FOG parameters from pre-surgery to 1-year with SCS therapy in 3 PSP-RS participants. **Chapter 4** reported the changes in clinical scores and gait parameters from pre-surgery to 6 months and a long-term update of 3 years with SCS therapy in PD participants. In **Chapters 3 and 4**, self-paced, straight walking tasks were performed on a Protokinetics Zeno Walkway and gait features were extracted using the gait analysis software (PKMAS). FOG assessments included quantifying the total number of FOG episodes and the duration per FOG episode that were captured using the gait carpet during straight walking tasks. All participants performed walking tasks employing multiple SCS programs to optimize and personalize the setting that best improved gait features for each participant to use daily at home during the follow-up periods.

Overall, it was predicted that the reduction in FOG in PD would be associated with improvements in upper limb visual-motor performance and with the modulation of

cortical activity in sensorimotor areas. It was also predicted that improvements in visual-motor performance would be associated with changes in striatal dopaminergic innervation (DAT binding) in PD. Lastly, it was predicted that SCS would reduce FOG severity in both PD and PSP-RS cohorts.

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Chapter 2

2 Neurophysiology and neuroimaging changes related to freezing of gait and visual-motor performance following SCS therapy in Parkinson's disease

2.1 Introduction

Freezing of gait (FOG) is a highly disabling symptom commonly seen in Parkinson's disease (PD) that responds poorly to pharmacological (dopaminergic replacement therapies such as levodopa) and surgical interventions.[1] Non-invasive transcranial direct stimulation over the primary motor cortex (M1)[2] or dual-target stimulation of the M1 and the dorsolateral prefrontal cortex[3,4] have produced variable yet promising effects, however longitudinal studies are still warranted. Recently in a limited number of robust clinical reports, tonic and burst spinal cord stimulation (SCS) have shown efficacious short-term (2-weeks to 6-months) and longitudinal (up to 24-months) effects for treating levodopa-resistant gait dysfunction and FOG in PD and atypical parkinsonism syndromes.[5-7] Although the exact mechanism of SCS for PD gait is still unclear, pre-clinical studies involving rodent and non-human primate PD models have shown that SCS restores locomotion and improves other motor symptoms by disrupting low-frequency, synchronized oscillatory activity and altering neuronal firing rates within the cortico-basal ganglia-thalamic circuit.[8,9] Furthermore, upper thoracic SCS may induce a neuroprotective effect by maintaining a higher density of dopaminergic innervation in the striatum and neuronal cell count in the substantia nigra pars compacta (SNpc) observed in the rat PD model when compared to the sham control group.[10] Thus, SCS may induce structural and activity changes within pathways associated to FOG and gait dysfunction.

FOG events can be triggered by environmental factors,[11] and sensory cueing approaches can alleviate FOG by providing external sensory feedback. These factors suggest that proprioceptive deficits may drive the dysfunctional cortical and subcortical networks underlying these gait impairments.[12] De Lima-Pardini *et al* suggested that improvements in anticipatory postural adjustments and FOG severity may be related to the influence of SCS modulating the supplementary motor area (SMA) cortical activity.[13] Hence, the

hypothesis that SCS treatment for FOG is multidimensional and possibly involves the modulation of cortical activity, enhancing sensory feedback, and the maintenance of nigrostriatal dopaminergic neuronal density.

The central effects of mid-thoracic SCS for treating levodopa-resistant FOG in PD patients were studied by measuring changes in sensorimotor cortical activity and striatal dopaminergic innervation over a 6-month treatment period. The relationship between these central effects and changes in FOG severity and visual-motor performance following SCS therapy has not been investigated. This current study aims to highlight the underlying mechanisms of SCS and FOG impairments in PD. The findings suggest that FOG improvements are related to changes in cortical activity within the sensorimotor areas. Improvements in upper limb visual-motor performance following SCS are associated to changes in striatal dopaminergic innervation. Thus, SCS may influence both non-dopaminergic and dopaminergic pathways for axial and appendicular motor PD features, respectively.

2.2 Methods

2.2.1 Subjects and study design

Seven pain-free PD participants with significant FOG and gait dysfunction while ON-levodopa were recruited for this non-randomized study from the London Movement Disorders Centre in London, Ontario. Inclusion criteria were participants with idiopathic PD meeting the UK Brain Bank criteria with II-IV Hoen-Yahr stage while on oral medications, history of falls, gait and balance dysfunction despite optimized medication management, and no significant secondary causes. Exclusion criteria were participants with a history of stroke or other neurological diseases, and moderately severe parkinsonism in the context of unstable pharmacological treatment. Twelve healthy, age-matched (between 60 and 75 years) control participants with no history of neurological trauma or neurological disease, no mobility deficits or spinal cord injury that would affect mobility, or on any anti-psychotic or anti-seizure medications were assessed at a one-time visit.

FOG severity was examined using 360-degree turning on the spot tasks in both directions in all PD participants at pre-surgery (baseline), and at 3-months and 6-months of SCS therapy while participants were OFF-levodopa (levodopa withheld for at least 12-hours) and ON-levodopa (assessed 1-hour following 1.5x morning dose of levodopa medication intake) with SCS turned on (ON-SCS) to each participant's best setting. Visual-motor performance was assessed by utilizing robotic target reaching choice tasks while participants were in the ON-levodopa/ON-SCS state at all time-points. Resting-state electroencephalography (EEG) recordings were performed while participants were OFF- and ON-levodopa medication with SCS switched off for 48 hours at all time-points. DaTSCAN (GE Healthcare®, Chicago, IL, USA) brain imaging, performed by the London Health Science Center's (LHSC) Nuclear Medicine (NM) department, was conducted while participants were ON-levodopa at pre-surgery and at 6-months of SCS use. Movement Disorders Society Unified Parkinson's disease rating scale motor items (MDS-UPDRS-III) was conducted at baseline to capture the most affected side and the levodopa response.

Healthy control subjects completed turning tasks, visual-motor performance assessments, and resting-state EEG recordings. Healthy control participants were not subjected to a DaTSCAN as the DaTSCAN analysis software, DaTQUANT (GE Healthcare®, Chicago, IL, USA), has an embedded healthy age-matched control database.

2.2.2 Ethics

This open-label, investigational, single-center pilot study was approved by the Western University Health Sciences Research Ethics Board (REB#: 107451) (Appendix A). All participants provided signed informed consent (Appendices B, C). The first participant's first visit and the last participant's last visit occurred in August 2018 and June 2021, respectively.

2.2.3 Spinal cord stimulation programming and intervention

Epidural dorsal SCS (Boston Scientific® Precision Spectra, Marlborough, Massachusetts, USA) with 2 cylindrical percutaneous electrode leads were placed mid-thoracically (T8-T9 spinal segments) and a rechargeable implantable pulse generator was implanted in the

right flank, as per standard surgical procedures. Electrode lead position was confirmed by ensuring paresthesias covered both lower limbs and the feet of each participant. A week following surgery, participants completed 3 full-day (~5 - 6 hours) programming visits that involved testing 6 SCS setting programs per programming visit. A total of 9 SCS settings (pulse widths: 200 μs, 300 μs, and 400 μs combined with frequencies: 30 Hz, 60 Hz and 130 Hz) were tested twice in a randomized fashion at different programming visits and at different times of the day (morning and afternoon). Each setting was turned on for 30 minutes at a medium suprathreshold intensity (~3% or 1mA higher than paresthesia threshold while participants were seated) before walking and turning tasks were conducted. For each tested setting, paresthesias covering both lower limbs and feet while sitting and standing was confirmed. The SCS setting to produce the greatest improvement in FOG (360-degree on the spot turns) and straight walking (e.g. stride velocity, step length, gait cycle phases) was used by each participant daily (~12 hours per day; during all waking hours) at a medium suprathreshold intensity over the 6-month follow-up period.

2.2.4 Freezing of gait assessment

FOG episodes were provoked by narrow 360-degree turning on the spot tasks in both clockwise (CWT) and counterclockwise (CCWT) directions;[14] no assistive devices were used for turning and the assessor stood behind the participant to ensure safety during turning tasks. All FOG episodes were captured on a Protokinetics Zeno Walkway (Zenometrics LLC, Peekskill, NY, USA) and the Protokinetics gait analysis software (PKMAS) extracted total turning time, center of pressure (COP) path length, and center of mass estimated (COMe) path length for each turning task. All 360-degree turning tasks were conducted while OFF-levodopa and ON-levodopa with SCS turned on (ON-SCS) for all participants at all time-points. Healthy control participants performed 3 complete 360-degree turns per direction and mean turning time, COP path length and COMe path length were extracted from PKMAS.

2.2.5 EEG recording, pre-processing, and analysis

Resting state, eyes-closed (lights switched off), 5-minute EEG (32-electrode Nautilus system, g.Tec Neurotechnology, Graz, Austria) recordings were performed using the g.Recorder EEG acquisition software (g.Tec Neurotechnology, Graz, Austria) while participants while OFF-levodopa and ON-levodopa with SCS switched off (OFF-SCS) at all time-points. Offline pre-processing involved re-referencing (common average), application of a notch filter to eliminate 60 Hz noise, automatic artifact rejection using Fieldtrip, and electrode interpolation. Absolute spectral power at frequencies 1 to 65 Hz were extracted from each of the 32-electrodes. Relative spectral power was calculated (e.g. alpha relative power at the Cz electrode = sum of absolute power in alpha frequencies divided by sum of absolute power in the remaining frequencies) per electrode for each frequency band: delta (2 – 4 Hz), theta (4 – 8 Hz), alpha (8 – 12 Hz), beta (13 – 30 Hz), low gamma (30 – 50 Hz), and high gamma (50 – 65 Hz). Data analyzed from electrodes placed over cortical areas representing the primary motor cortex (C3, Cz, and C4), premotor (FC5, FC1, FC2, and FC6), prefrontal (F3, Fz, and F4), primary somatosensory (CP5, CP1, CP2, CP6), and parietal (P3, Pz, and P4) were reported. According to the 10-20 electrode placement map, electrodes associated with the lower limbs are Cz, FC1, FC2, Fz, CP1, CP2, and Pz where electrodes associated with left and right upper limbs are those with even (#4 and 6) and odd (#3 and 5) numbered electrodes, respectively. For analysis, neighboring electrodes were clustered together by averaging the relative power of all the electrodes per cluster for each frequency band (Figure 2-1): “F1” (F3, FC5, C3), “F2” (F4, FC6, C4), “C1” (Fz, FC1, FC2, Cz), “C2” (CP1, CP2, Pz), “P1” (CP5, P3), and “P2” (CP6, P4).

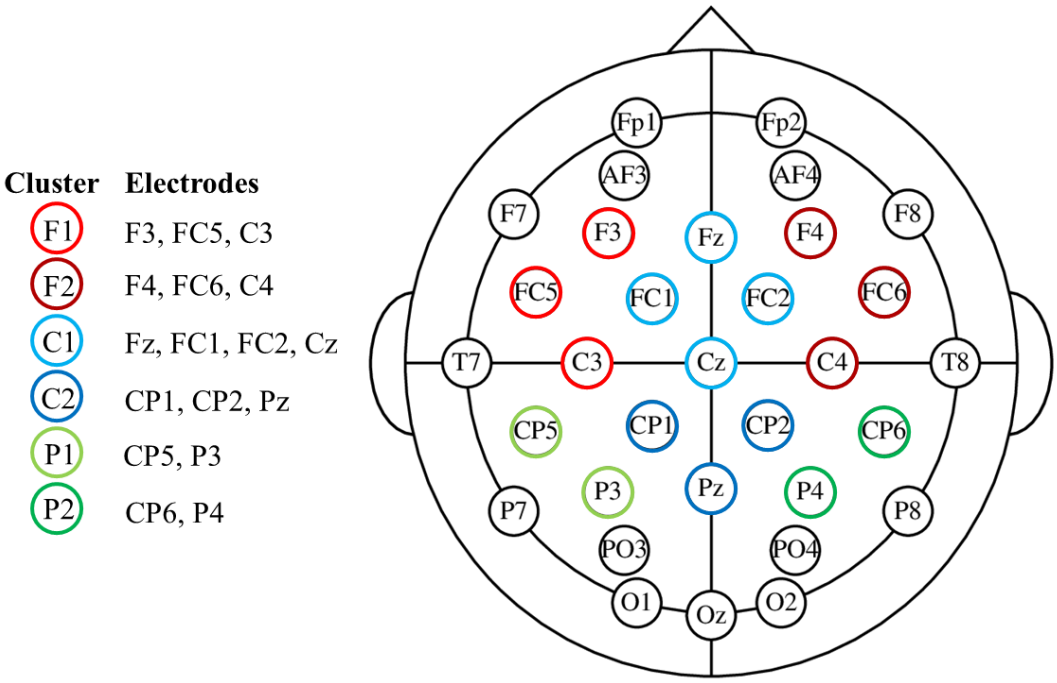

Figure 2-1. Schematic illustration of the electrode montage. Each cluster consisted of 2 to 4 neighbouring electrodes. Clusters were numbered from left hemisphere (F1, P1), central hemisphere (C1, C2), and right hemisphere (F2, P2) according to their location along the anterior-posterior dimension.

2.2.6 DAT imaging and analysis

Four of the seven participants underwent a SPECT-DaTSCAN at baseline and at 6-months of SCS therapy. The brain scan was conducted approximately 3.5 hours following intravenous injection of 170 - 180 MBq radioactive tracer [^{123}I] FP-CIT (ioflupane), administered by a NM nurse. One hour prior to ioflupane injection and to avoid thyroid accumulation, each participant was administered 80 mg of Radblock™ (potassium iodide tablets). DAT images were acquired using a Discovery 670 SPECT/CT (GE Healthcare®, Chicago, IL, USA) using standard DaTSCAN imaging procedures as per the LHSC NM department. Participants were supine positioned with the head on an off-the-table headrest and the circular orbit for the detector heads was set to a radius of at least 15 cm for SPECT acquisition.

Specific binding ratio (SBR) values were calculated (ratio of specific striatal uptake to non-specific uptake) using DaTQUANT software (version 2.0, GE Healthcare®, Chicago, IL, USA). The data was registered to a DaTSCAN template. The images were reoriented, if the image was tilted, to align with the anterior commissure-posterior commissure (ACPC) orientation using the software's green locators. Standard volume of interest template of the caudate and putamen regions was applied. If the striatal and background region of interests (ROIs) required editing, the software only permitted ROI shifts as the shape and size of the ROIs were not modifiable. All images underwent Chang attenuation correction and ordered subset expectation maximization (OSEM) reconstruction type, as the data was reconstructed by DaTQUANT. Measured SBR values were extracted from each analyzed image per (right and left) striatal ROI: caudate, putamen, anterior putamen, and posterior putamen, putamen to caudate ratio per hemisphere (e.g. Right putamen SBR / Right caudate SBR), and caudate and putamen asymmetries (e.g. Right caudate SBR / Left caudate SBR).

2.2.7 Visual-motor performance assessment

Upper limb visual-motor performance was assessed by target reaching choice tasks using a robotic device[15] for each upper limb in 4 of the 7 participants while ON-levodopa and ON-SCS at all time-points (Figure 2-2a). The four tasks involved moving a white cursor on the screen controlled by handling a toggle attached to the robot. The tasks are: 1) reaching towards the middle of a stationary green square target, 2) adapting resistive/assistive forces exerted onto the toggle of the robot and reaching to the middle of a stationary green target, 3) moving the cursor to a space where the participant perceived a green target that appeared on the screen for 0.25 seconds, and 4) moving the cursor to find the correct shape (upright equilateral triangle) and avoiding distractor shapes (Figure 2-2b-e). For tasks #1 and 2, the green target would disappear once the participant moved the white cursor into the middle of the target and another a green "home" target would appear in the middle of the screen starting the next trial, totaling 12 targets (6 horizontally and 6 vertically placed). The tasks were designed to assess deficits in target selection (accuracy; distance from the center of the target where a threshold accuracy of 1.5 cm or less indicated the cursor was in the center of the target), reaction

time (time taken to move the cursor towards the target), and speed (mean velocity from the central “home” target to the external target). The visual-motor performance measures were extracted using a custom written MatLab® (version 2015b, MathWorks, Natick, MA, USA) code that enabled the integration of a Quarc interface (Quanser®, Markham, Ontario, Canada) with a virtual runtime environment for the communication between the robot and the visual display of the tasks, respectively.

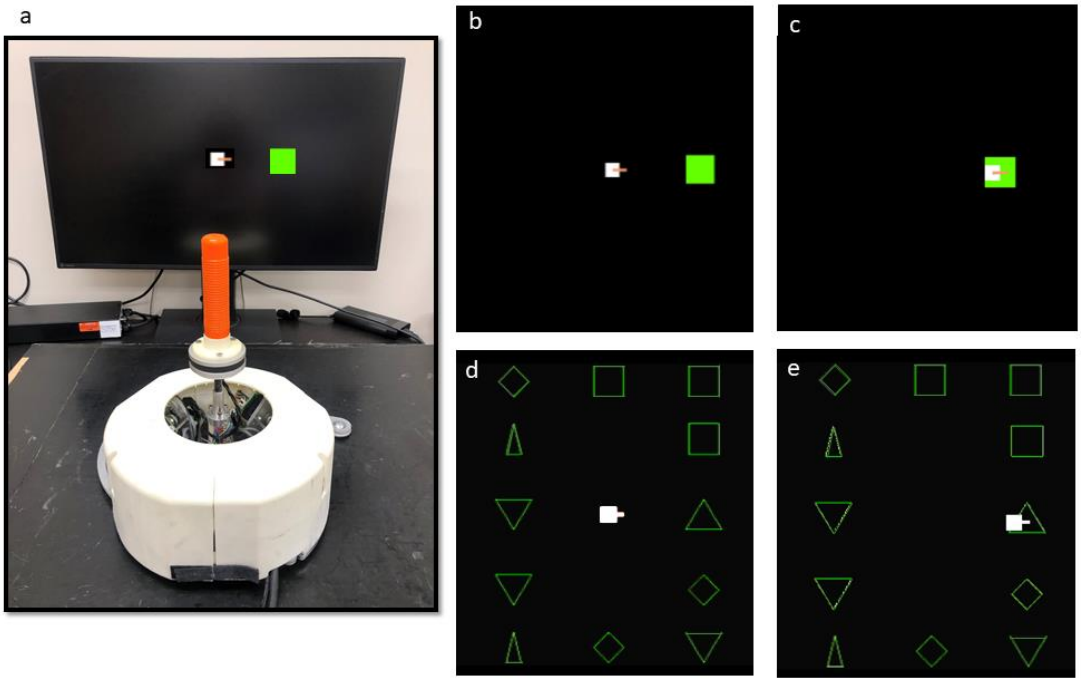

Figure 2-2. The set-up of the robotic device (a) and the visual display of the target reaching choice tasks (b-e).

A 27” monitor displayed the target reaching choice tasks that involved participants to move the white cursor to the green square target (b,c) or to the correct shape (upright equilateral triangle) and to avoid the distractor shapes (d,e) using the orange toggle stick on the robotic device (a).

2.2.8 Statistical analysis

Quantitative measures of FOG (turning time, COP and COMe path lengths were log-transformed for statistical testing), relative spectral power per frequency band for each of the 6 electrode clusters, striatal DAT (SBR values per hemisphere for each ROI), and visual-motor performance (mean accuracy, reaction time and speed per arm) were plotted

as mean ± standard deviations. Differences between OFF-levodopa and ON-levodopa states for FOG and relative power measures were tested using a paired t-test (open-source statistical software, R (version 4.1.1) package “t.test”). Differences between PD participants and age-matched healthy controls for FOG, relative power and visual-motor performance measures were tested using an independent t-test.

The effects of SCS on FOG, relative power, DAT, and visual-motor performance were analyzed in separate linear mixed models via the maximized likelihood estimation (R “lmerTest” package). Measures collected from baseline to 3- and 6-months of SCS therapy were compared. Estimated comparisons of least square means and 95% confidence intervals (95%CI) for each fixed effect in a linear mixed model were calculated and multiple comparisons were adjusted using Tukey’s method (R “lsmeans” package; p-value < 0.05). Each fixed effect was separately tested in a linear mixed effects model; fixed effects included: FOG: turning time, COP and COMe path length per direction, relative power per electrode cluster for each frequency band, and mean speed, reaction time and accuracy per visual-motor task. Linear mixed model analysis allowed adding participants as a random effect to resolve issues of independence among repeated measures by controlling for individual variation among participants. Post hoc power analysis was conducted using R package “power.t.test” function.

Measures of FOG, relative power, DAT, and visual-motor performance were further analyzed with four linear mixed models via the maximized likelihood estimation (“lmerTest” package). Clinical outcome variables such as clockwise turning or left arm visual-motor performance were analyzed with central (e.g. C1, C2) and contralateral (e.g. right hemisphere) electrode clusters (e.g. F2, and P2) or with contralateral DAT predictor variables (e.g. Right putamen SBR). The first linear mixed model analyzed mean turning time per participant for repeated measures with covariates: visual-motor performance (tasks 3 and 4) parameters of mean speed, reaction time and accuracy, time (baseline, 3- and 6-months) as a fixed effect, and participants as a random effect. The second linear mixed model analyzed mean turning time per participant for repeated measures with covariates: relative power per central and contralateral electrode cluster per frequency band, time (baseline, 3- and 6-months) as a fixed effect, and participants as a random

effect. The third linear mixed model analyzed mean turning time per participant for repeated measures with covariates: striatal DAT binding per ROI per contralateral hemisphere, time (baseline, 3- and 6-months) as a fixed effect, and participants as a random effect. The fourth linear mixed model analyzed visual-motor performance parameters (mean speed, reaction time and accuracy for tasks 3 and 4) per participant per upper limb for repeated measures with covariates: DAT binding per ROI per contralateral hemisphere, time (baseline, 3- and 6-months) as a fixed effect and, participants as a random effect. All data values were rescaled by centering (subtracting by the mean) and dividing by 2 standard deviations (SD) using R package "arms" to ensure estimated coefficients were on the same scale. *P*-values < 0.05 indicated statistical significance.

2.3 Results

2.3.1 Study demographics

Demographics of the 7 participants (12 ± 7 years with disease, 2 females) are displayed in Table 2-1. Participants #4 - 7 completed all study assessments and participants #1 - 3 completed FOG and EEG assessments only. Five of the seven participants best improved with the SCS setting of 400 µs pulse width combined with a frequency of 60 Hz and continued to use this setting at-home over the treatment period. All participants did not improve on low frequencies (30-60 Hz) combined with a pulse width of 200 µs. One participant (#6) required a reduction in daily levodopa dose due to worsening of FOG while ON-levodopa. No side effects from the SCS therapy were reported.

Table 2-1. Demographics, clinical features and the SCS setting that best improved FOG and gait for each study participant

						MDS-UPDRS-III score			
ID	**Sex**	**Age (years)**	**YWD**	**DLD (mg)**	**Most affected side[b]**	**OFF**	**ON**	**L-dopa response (%)[c]**	**SCS setting[d]**

1	M	72	23	800	Left	27	23	-15	200/130
2	F	66	10	600	Left	38	28	-26	400/60
3	F	74	20	800	Left	50	48	-4	400/60
4	M	77	3	1100	Left	29	21	-28	400/60
5	M	69	9	1200	Left	44	41	-7	400/30
6	M	74	10	900[a]	Left	34	30	-12	400/60
7	M	78	8	1200	Left	36	35	-3	400/60
Mean	2F/ 5M	73	12	950	7 Left	37	32	-13	
SD		4	7	251		8	10	10	
Median		74	10	950		36	30	-12	
Range (low)		66	3	600		27	21	-28	
Range (high)		78	23	1200		50	48	-3	

[a]Daily levodopa dose reduced to 650 mg at the 3-month follow-up for Participant #6; [b]total UPDRS-III sub-scores per right and left sides while OFF- and ON-levodopa medication and the side with the highest number is reported; [c]change in OFF/ON levodopa medication response in percent; [d]SCS setting (pulse width (μs)/frequency (Hz)) that was used for testing and used daily at-home. Abbreviations: DLD Daily levodopa dose; F Female; L-dopa Levodopa; M Male; OFF off levodopa medication; ON on levodopa medication; YWD Years with disease

2.3.2 Freezing of gait outcomes

2.3.2.1 Comparing PD participants and healthy controls

Mean turning time, COP path length and COMe path length for CWT and CCWT directions was 5±1 sec, 178±31 mm, and 112±28 mm, respectively, in age-matched healthy controls. PD participants at baseline were a mean difference of +97±18 sec in turning time, +2333±89 mm in COP path length, and +735±19 mm in COMe path length compared to controls for both turning directions. However, at the 6-month follow-up, the mean difference in turning time, COP and COMe path lengths reduced by 55±6% (mean difference was +43±5 sec), 36±12% (+1555±296 mm) and 41±18% (+433±126 mm), respectively, comparing PD participants to controls.

2.3.2.2 Effect of SCS therapy on freezing of gait

While PD participants were OFF-levodopa, the effect of SCS significantly reduced CWT time from 137±119 sec at baseline to 62±48 sec (t[14]=-2.079, p=0.038, 95%CI -0.65,-0.02, difference 55%, post-hoc power = 0.94) at 3-months and to 67±61 sec (t[14]=-

2.222, *p*=0.026, 95%CI -0.67,-0.04, difference 51%, post-hoc power = 0.97) at 6-months (Figure 2-3a). CCWT time significantly reduced from 130±98 sec at baseline to 63±47 sec (t[14]=-2.079, *p*=0.007, 95%CI -0.54,-0.09, difference 51%, post-hoc power = 0.99) at 3-months and to 61±69 sec (t[14]=-2.222, *p*=0.007, 95%CI -0.54,-0.09, difference 53%, post-hoc power = 0.99) at 6-months (Figure 2-3b).While ON-levodopa, CWT time significantly reduced from 115±101 sec at baseline to 51±38 sec (t[14]=-2.079, *p*=0.007, 95%CI -0.54,-0.09, difference 51%, post-hoc power = 0.99) at 3-months and to 52±41 sec (t[14]=-2.222, *p*=0.007, 95%CI -0.54,-0.09, difference 51%, post-hoc power = 0.98) at 6-months (Figure 2-3a**)**. CCWT time significantly reduced from 89±72 sec at baseline to 40±34 sec (t[14]=-2.079, *p*=0.001, 95%CI -0.87,-0.28, difference 55%, post-hoc power = 1.0) at 3-months and to 50±37 sec (t[14]=-2.222, *p*=0.004, 95%CI -0.72,-0.13, difference 44%, post-hoc power = 1.0) at 6-months (Figure 2-3b).

While participants were OFF-levodopa, COP path length, measured by the change in total pressure between both feet, during CWT was significantly reduced from 2761±1805 mm at baseline to 1646±781 mm (t[14]=-2.215, *p*=0.027, 95%CI -0.63,-0.04, difference 40%, post-hoc power = 0.97) at 6-months (Figure 2-3c). COP path length during CCWT significantly reduced from 3200±2384 mm at baseline to 1754±1134 mm (t[14]=-2.215, *p*=0.002, 95%CI -0.57,-0.12, difference 45%, post-hoc power = 0.99) at 6-months (Figure 2-3d). While participants were ON-levodopa, COP path length during CWT significantly reduced from 2571±1568 mm at baseline to 2012±1768 mm (t[14]=-1.909, *p*=0.027, 95%CI -0.50,-0.03, difference 22%, post-hoc power =0.97) at 3-months and to 1726±1031 mm (t[14]=-2.215, *p*=0.016, 95%CI -0.52,-0.05, difference 33%, post-hoc power =0.98) at 6-months (Figure 2-3c). COP path length during CCWT significantly reduced from 2452±1166 mm at baseline to 1329±894 (t[14]=-1.909, *p*=0.002, 95%CI -0.88,-0.20, difference 33%, post-hoc power = 1.0) at 3-months (Figure 2-3d).

COMe path length during CWT non-significantly reduced by a mean of 33% from 724±844 mm at baseline to 492±605 mm over the 6-months while participants were OFF-levodopa and ON-levodopa (Figure 2-3e). COMe path length during CCWT non-significantly reduced by a mean of 48% from 817±1118 mm at baseline to 423±610 mm over the 6-months (Figure 2-3f).

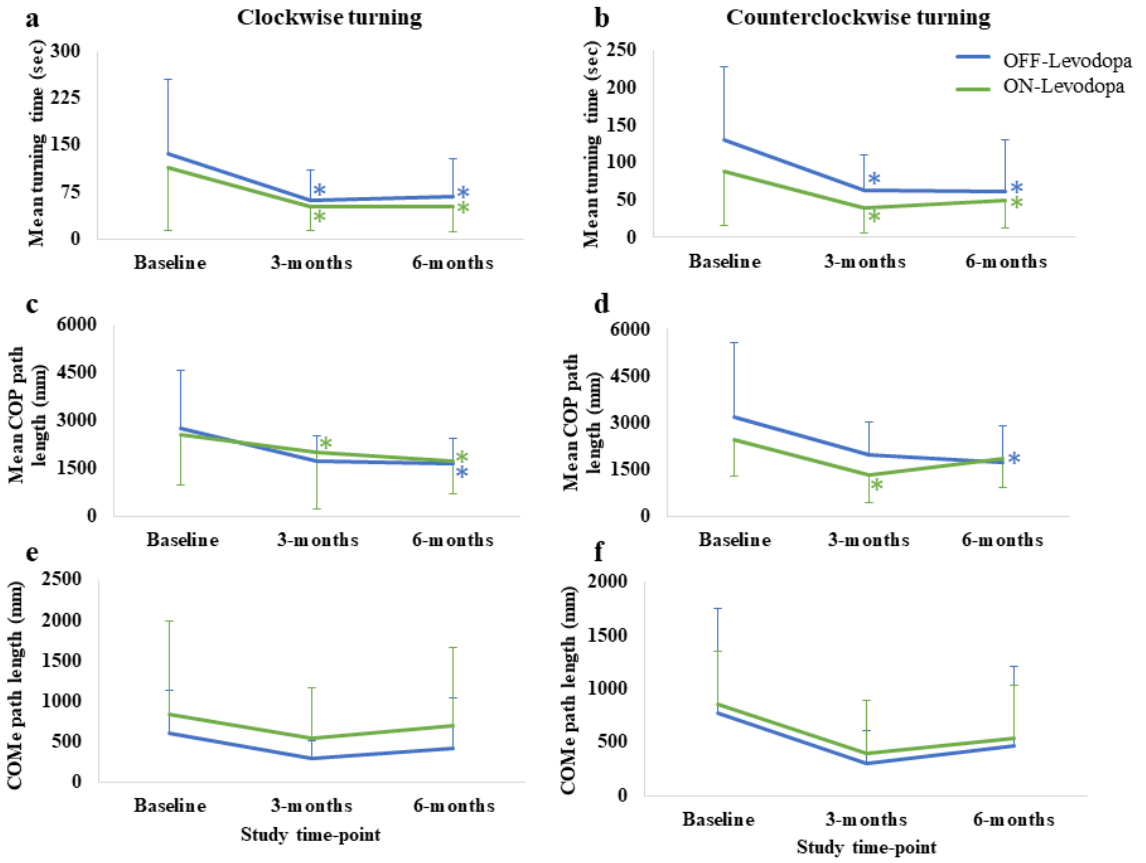

Figure 2-3. 360-degree narrow turning on the spot in both directions was utilized to measure FOG over the 6-month SCS treatment period in all 7 participants while OFF-levodopa (blue line) and ON-levodopa (green line). Turning time (a, b), COP (c, d) and COMe (e, f) path lengths were extracted from the gait analysis software (PKMAS). Coloured asterisks represent statistically significant differences compared to baseline (p-values <0.05) and error bars represent standard deviation.

2.3.3 Changes in cortical EEG activity

2.3.3.1 Comparing PD participants and healthy controls

Mean relative theta band power from the "P1" electrode cluster was significantly higher by a mean of 27% (t[22] = 2.479, 95%CI 0.006,0.07, p = 0.022) in PD participants while OFF-levodopa and ON-levodopa (0.19±0.04) compared to controls (0.15±0.03) at all time-points. Mean relative beta band power from all electrode clusters was significantly lower by a mean of 16% (t[22] = -2.406, 95%CI -0.16,-0.02, p = 0.025) in PD

participants while ON-levodopa (0.41±0.01) at baseline and at 6-months (0.40±0.02) compared to controls (0.48±0.08). However, mean relative beta band power was not significantly different from the "F1" (p = 0.059) and "C1" (p = 0.052) electrode clusters at 3-months between PD and control participants. No significant differences in relative power between PD participants and controls were observed in the alpha, delta, low gamma, and high gamma frequency bands. Furthermore, no significant differences in relative power in the beta frequency band for all electrode clusters while participants were OFF-levodopa.

2.3.3.2 Effect of SCS therapy on cortical activity

Mean relative power for each electrode cluster per frequency band while participants were OFF-levodopa (Figure 2-4) and ON-levodopa (Figure 2-5) are illustrated. While participants were OFF-levodopa, a significant reduction in relative beta band power from the "F2" electrodes by a mean of 15% (t[14] = 2.765, p = 0.04, 95%CI -0.6,0.2, post-hoc power = 0.89) occurred at 3-months (0.40±0.02 Hz) compared to baseline (0.47±0.04 Hz) (Figure 2-4b). A significant reduction in relative alpha band power from the "C1" electrodes by a mean of 13% (t[14] = 2.747, p = 0.04, 95%CI -0.5,0.3, post-hoc power = 0.97) occurred at 6-months (0.12±0.01 Hz) compared to baseline (0.14±0.01 Hz) (Figure 2-4c). From the "C2" electrodes, a non-significant reduction in relative beta band power by a mean of 13% occurred at 3-months (t[14] = 2.305, p = 0.09, 95%CI -0.5,0.3, post-hoc power = 0.67) and 6-months (t[14] = 2.464, p = 0.07, 95%CI -0.6,0.3, post-hoc power = 0.98) compared to baseline (Figure 2-4d). There was a significant increase in relative delta band power from the "P2" electrodes by a mean of 20% (t[14] = -2.802, p = 0.03, 95%CI -0.2,0.7, post-hoc power = 0.62) at 3-months (0.10±0.02 Hz) compared to baseline (0.08±0.02 Hz) (Figure 2-4f). There were no significant changes in relative power from the "F1", "C2" and "P1" electrode clusters **(**Figure 2-4a,d,e) and no significant changes in the theta, low gamma and high gamma frequency bands. While participants were ON-levodopa, there were no significant changes in relative power in any of the frequency bands from the 6 electrode clusters (Figure 2-5).

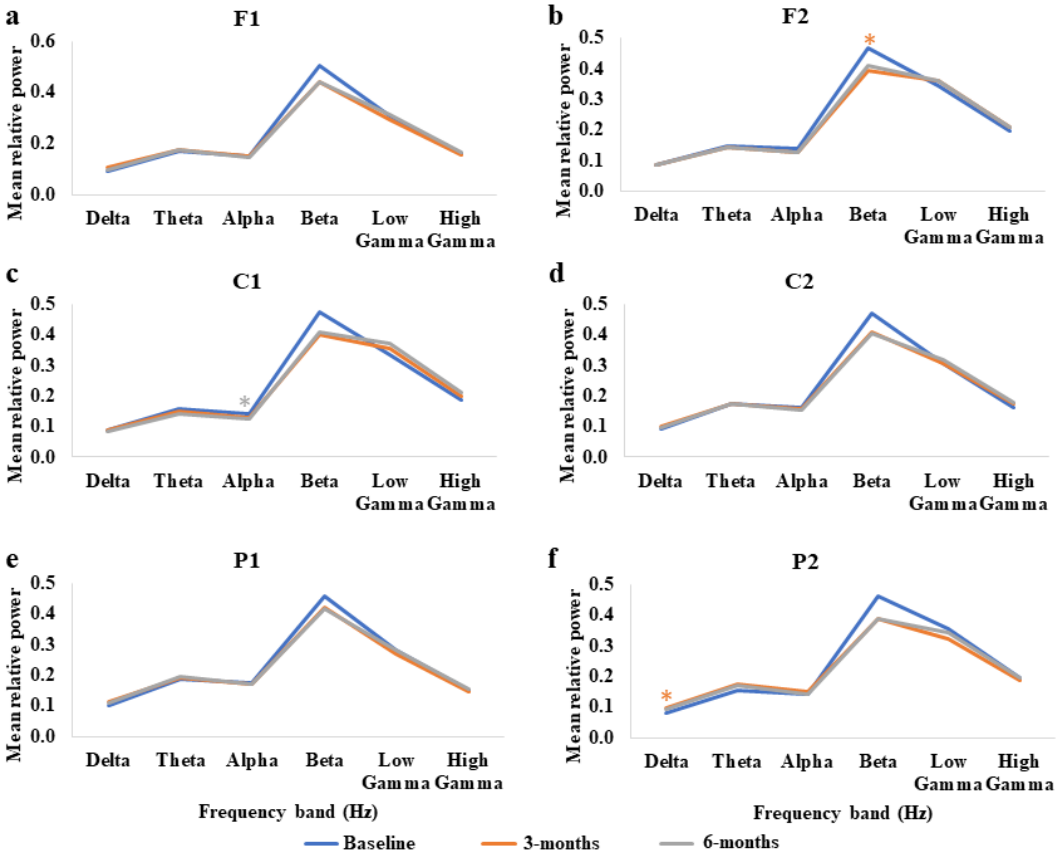

Figure 2-4. Mean relative power per electrode cluster (a-f) for each frequency band in all participants while OFF-levodopa from baseline (blue line) to 3-months (orange line) and 6-months (gray line) of SCS therapy. Coloured asterisks represent *p*-value < 0.05 compared to baseline.

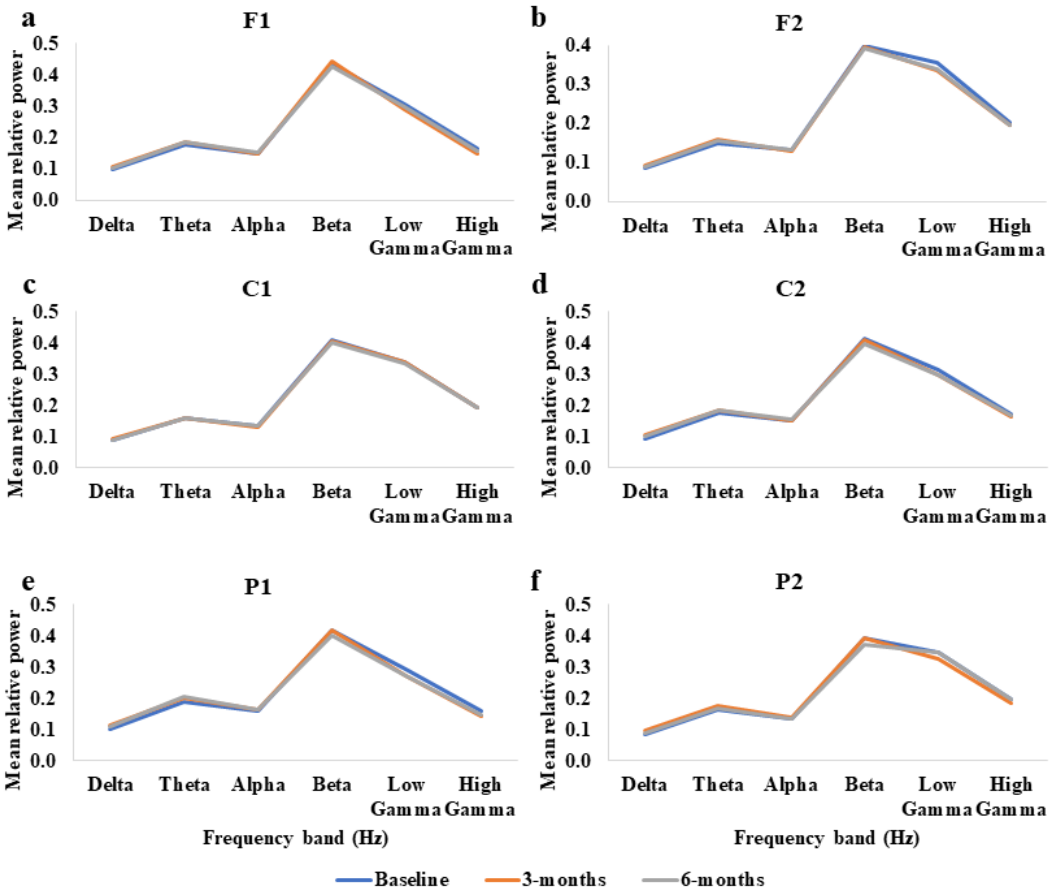

Figure 2-5. Mean relative power per electrode cluster (a-f) for each frequency band in all participants while ON-levodopa from baseline (blue line) to 3-months (orange line) and 6-months (gray line) of SCS therapy.

Linear mixed models (e.g. lmer(med_cluster_band ~ time + (1 | participant) where med_cluster_band represents the relative frequency band power from an electrode cluster while participants were either OFF-levodopa or ON-levodopa) revealed the estimates of the fixed effect of time (SCS therapy) on the relative power per frequency band from each electrode cluster while PD participants were OFF-levodopa or ON-levodopa medication. While participants were OFF-levodopa, a model revealed the coefficient of $\beta = 0.48$ ($p = 0.017$, 95%CI -0.9,-0.08) and $\beta = 0.65$ ($p = 0.002$, 95%CI -1.1,-0.2) indicated that a 2 SD change at 3- and 6-months, respectively, was associated with a reduction in β * 2 SD in "C1" alpha band relative power. The model revealed a coefficient of $\beta = 0.46$ ($p = 0.027$, 95%CI -0.9,-0.05) and $\beta = 0.44$ ($p = 0.04$, 95%CI -0.9,-0.01) indicated that a

2 SD change at 3- and 6-months, respectively, was associated with a reduction in β * 2 SD in “F2” alpha power. In the beta band, the model revealed a coefficient of $\beta = 0.39$ ($p = 0.011$, 95%CI -0.7,-0.09) and $\beta = 0.45$ ($p = 0.006$, 95%CI -0.8,-0.1) indicated that a 2 SD change at 3- and 6-months, respectively, was associated with a reduction in β * 2 SD in “C2” relative power. The model revealed a coefficient of $\beta = 0.45$ ($p = 0.002$, 95%CI -0.7,-0.2) and $\beta = 0.32$ ($p = 0.014$, 95%CI -0.6,-0.1) indicated that a 2 SD change at 3-months was associated with a reduction in β * 2 SD in “F2” and “P2” beta power, respectively. In the delta band, the model revealed a coefficient of $\beta = 0.44$ ($p = 0.002$, 95%CI 0.2,0.7) indicated that a 2 SD change at 3-months was associated with an increase in β * 2 SD in “P2” relative power. No significant associations of the effect of SCS with relative power in the theta, low gamma, and high gamma frequency bands nor from the “F1” and “P1” electrode clusters were observed.

While ON-levodopa, the model revealed the coefficient of $\beta = 0.26$ ($p = 0.024$, 95%CI -0.5,-0.03) indicated that a 2 SD change at 3- and 6-months was associated with a reduction in β * 2 SD in “P1” low gamma band relative power. The model revealed the coefficient of $\beta = 0.21$ ($p = 0.034$, 95%CI -0.4,-0.02) and $\beta = 0.19$ ($p = 0.006$, 95%CI 0.06,0.3) indicated that a 2 SD change at 3-months was associated with a reduction in $\beta = 0.21$* 2 SD in “P2” low gamma and an increase in $\beta = 0.19$ * 2 SD in “P2” theta band relative power, respectively. No significant associations of the effect of SCS therapy with relative power in the delta, alpha, beta, and high gamma frequency bands nor from the “F1”, “F2”, “C1”, or “C2” electrode clusters were observed.

2.3.4 Striatal DAT outcomes

2.3.4.1 Comparing PD participants and healthy controls

Striatal DAT binding in PD participants was lower by a mean of 86±4% compared to the age-matched controls (mean DAT binding of 2.29±0.23 SBR in all ROIs from the DaTQUANT database). Furthermore, asymmetry ratios between the right and left hemispheres in the caudate, putamen, anterior putamen, and posterior putamen ROIs was a mean 0.81±0.29 at baseline and 1.27±0.24 at 6-months in PD participants. Thus, DAT binding was 21% less in the right versus the left striatum at baseline and 24% greater in

the right versus the left striatum at 6-months of therapy when compared to the mean right/left ratio of 1.03±0.01 in the age-matched controls.

In controls, the DAT binding ratio between the anterior and posterior putamen per hemisphere was a mean of 1.22±0.02 indicating greater DAT binding in the anterior compared to the posterior putamen. This was similarly observed in the PD participants where the ratio of anterior/posterior putamen DAT binding was greater by a mean 5% at baseline (mean 1.3±0.4 SBR) and by a mean 42% at 6-months (mean 1.8±0.6 SBR).

2.3.4.2 Effect of SCS therapy on striatal DAT binding

DAT binding (SBR values) in the ROIs from the right hemisphere did not significantly change between baseline and 6-months in the 4 PD participants. However, comparing striatal DAT per participant from baseline to 6-months of SCS use (Figure 2-6), participants #4 and #7 had a mean SBR increase by 45% (difference of +0.10 SBR) and 40% (+0.12 SBR) in the right putamen and anterior putamen ROIs, respectively (Figures 2-6c,e). For participants #5 and #7, a 700% (+0.07 SBR) and 33% (+0.05 SBR) increase of DAT in the right posterior putamen, respectively, was observed (Figure 2-6g). Participant #5 had an increase of 50% (+0.10 SBR) and 100% (+0.10 SBR) in the right and left caudate ROIs, respectively (Figures 2-6a,b). There was no significant effect of time as a predictor for right hemispheric striatal DAT binding.

In the left hemisphere, a significant reduction in the putamen (t[4] = -7.839, p = 0.0008, 95%CI -0.7,-0.07, difference 44%, post-hoc power = 1.0), anterior putamen (t[4] = -5.485, p = 0.001, 95%CI -0.8,0.03, difference 47%, post-hoc power = 0.91) and posterior putamen (t[4] = -4.667, p = 0.009, 95%CI -0.8,0.04, difference 33%, post-hoc power = 0.97) ROIs was observed in all 4 participants between baseline and 6-months (Figures 2-6d,f,h). However, no significant change in the caudate (t[4] = -1.633, p = 0.21, 95%CI -0.7,0.5, difference 21%) was observed (Figure 2-6b). A linear mixed model revealed (e.g. lmer(hemi_ROI ~ time + (1 | participant) where hemi_ROI represents a SBR value from a striatal ROI per hemisphere) there was a significant effect of time (SCS therapy) with DAT binding in the putamen by a coefficient of β = -0.8001 (p = 0.001, 95%CI -1.00,-0.60), anterior putamen by β = -0.6155 (p = 0.012, 95%CI -0.9,-0.51), and posterior

putamen by β = -0.7144 (p = 0.009, 95%CI -1.01,-0.41). Thus, 3 of the 4 participants had increased DAT binding in the right striatum and all participants had decreased DAT binding in the left striatum.

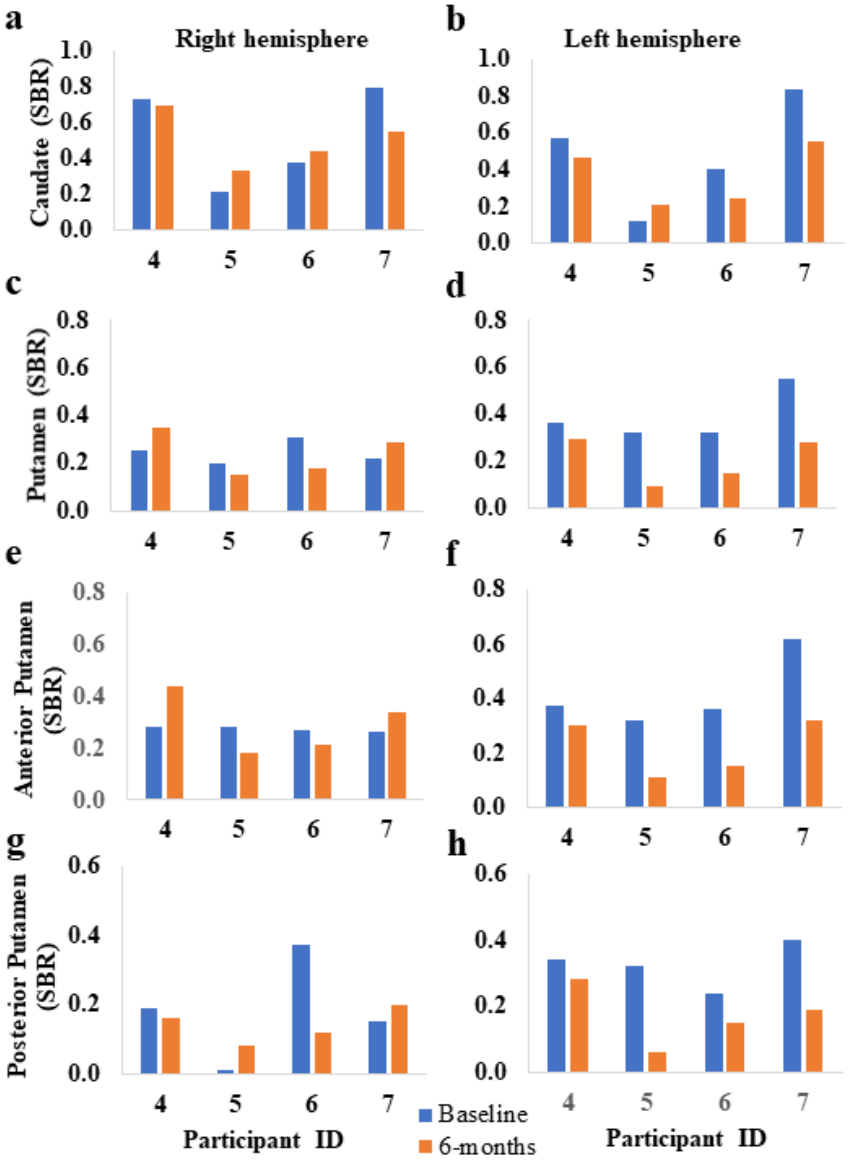

Figure 2-6. SBR values of striatal DAT binding in the caudate (a-b), putamen (c-d), anterior putamen (e-f) and posterior putamen (g-h) in the right (a,c,e,g) and left (b,d,f,h) hemispheres per participant (#4 to 7) at baseline (blue) and at 6-months of SCS use (orange).

For each participant, SBR values, specific binding of the tracer to a ROI divided by the non-specific binding (background ROI), were quantified by GE DaTQUANT software.

At baseline, asymmetry of striatal DAT binding between the right and left hemispheres was significantly different in the putamen (p = 0.009, 95%CI -0.7,-0.09, difference +60%, post-hoc power = 0.91) and anterior putamen (p = 0.009, 95%CI -1.1,-0.5, difference +56%, post-hoc power = 0.92), with no significant differences between the right and left caudate (p = 1.000, 95%CI -0.2,0.2, difference -10%) and posterior putamen (p = 0.17, 95%CI -0.7,0.2, difference +67%) (Figure 2-7a). At 6-months, there was a significant difference between the right and left caudate (p = 0.03, 95%CI -0.4,0.8, difference -25%, post-hoc power = 0.67) and anterior putamen (p = 0.004, 95%CI -0.4,0.8, difference -23%, post-hoc power = 0.58) (Figure 2-7b**).** However, there were no significant differences between the right and left putamen (p = 0.21, 95%CI -0.4,0.7, difference -18%) and posterior putamen (p = 0.62, 95%CI -0.7,0.6, difference +42%). A linear mixed model (e.g. lmer(ROI ~ side*time + (1 | participant) where ROI represents SBR values from a specific ROI) involving an interaction between time (baseline and 6-months) and side (right and left hemisphere), SBR values from the putamen (β = 0.89, p = 0.001, 95%CI 0.4,-1.4) and the anterior putamen (β = 0.99, p = 0.007, 95%CI 0.4,-1.5) were significantly different indicating DAT binding in these ROIs vary with time and per side following SCS therapy.

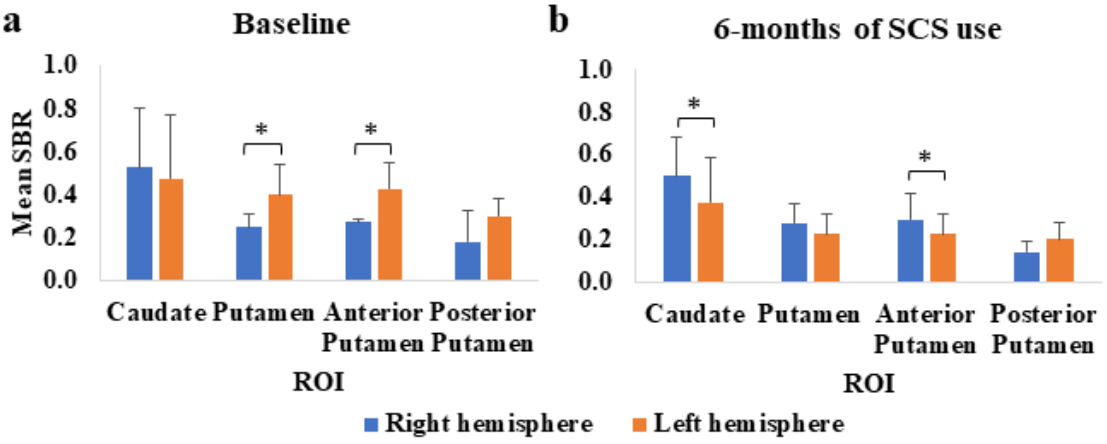

Figure 2-7. Mean DAT binding (SBR values) in each striatal ROI per hemisphere at baseline (a) and at 6-months of SCS use (b) in all 4 participants. Asterisks represent p-value < 0.05 and error bars represent standard deviation.

2.3.5 Visual-motor performance outcomes in PD participants following SCS therapy and comparing to healthy controls

The visual-motor task 1, mean speed of moving the cursor to the target for both arms was significantly slower by 58% (left upper limb: $t[14] = -4.325$, $p = 0.001$, 95%CI -0.6,-0.2; right upper limb: $t[14] = -3.841$, $p = 0.002$, 95%CI -0.6,-0.2) in PD participants compared to healthy controls at baseline (Figure 2-8a left column). Changes in upper limb speed, reaction time or accuracy did not significantly change over the 6-month SCS treatment (Figure 2-8a).

Task 2, involving the robot exerting a resistive force, PD participants were significantly slower by a mean of 61% (left: $t[14] = 5.84$, $p < 0.001$, 95%CI 0.2,0.4; right: $t[14] = 4.27$, $p = 0.001$, 95%CI 0.2,0.6) compared to healthy controls (Figure 2-8b, left column). In addition, bilateral upper limb reaction time was significantly slower by a mean of 134% (left: $t[14] = -7.479$, $p < 0.001$, 95%CI -0.6,-0.3; right: $t[14] = -6.396$, $p < 0.001$, 95%CI -0.6,-0.3) in PD participants compared to controls (Figure 2-8b center). The effect of SCS therapy significantly increased mean speed in both arms by 46% (left: $p = 0.02$, 95%CI -0.5,0.4; right: $p = 0.04$, 95%CI -0.6,0.5) from 0.1±0.02 cm/s at baseline to 0.2±0.05 cm/s at 6-months. Mean reaction time in the right upper limb significantly reduced by a mean of 36% ($p = 0.01$, 95%CI -0.7,-0.03, post-hoc power = 0.65) from 1.3±0.6 sec at baseline to 0.8±0.1 sec at 3- and 6-months. Mean accuracy in the right upper limb significantly improved by a mean of 73% ($p = 0.04$, 95%CI -0.8,0.2, post-hoc power = 0.72) from 5.3±5.7 cm at baseline to 1.4±1.4 cm at 6-months. No significant changes in left upper limb reaction time or accuracy were observed over the 6-months.

Task 2 with assistive forces, PD participants were significantly slower in both upper limbs by a mean of 59% (left: $t[14] = -6.22$, $p < 0.001$, 95%CI -0.6,0.3; right: $t[14] = -9.722$, $p < 0.001$, 95%CI -0.5,-0.3) compared to controls (Figure 2-8c left column). Additionally, right upper limb reaction time was significantly slower by 88% ($t[14] = 2.22$, $p = 0.043$, 95%CI 0.003,0.2) in PD compared to controls (Figure 2-8c center). The effect of SCS therapy significantly reduced right upper limb reaction time by 34% ($p = 0.02$, 95%CI -0.5,0.4, post-hoc power = 0.99) from 1.1±0.4 sec at baseline to 0.7±0.2 sec

over the 6-months. No significant changes in bilateral upper limb speed or accuracy and left upper limb reaction time were observed over the 6-months.

For task 3, involving participants to notice the target appear on the screen for 0.25 seconds and move the cursor to the target location, PD participants were significantly slower in right upper limb reaction time by a mean of 31% (right: $t[14] = 1.604$, $p = 0.022$, 95%CI 0.03,0.3) compared to controls (Figure 2-8d center). In addition, bilateral upper limb accuracy was significantly worse by 168% (left: $t(14) = 3.671$, $p = 0.003$, 95%CI 0.1,0.6; right: $t[14] = 4.29$, $p = 0.001$, 95%CI 0.2,0.6) in PD compared to controls (Figure 2-8d right column). The effect of SCS therapy significantly worsened speed in the left arm by a mean of 20% ($p = 0.04$, 95%CI -0.02,0.8, post-hoc power = 0.71) from 0.2±0.03 cm/s at baseline to 0.18±0.02 cm/s at 3- and 6-months (Figure 2-8d left column). No significant changes in bilateral upper limb reaction time or accuracy were observed in PD over the 6-months.

Task 4, involving participants to move the cursor to the correct shape and to avoid the distractor shapes, PD participants were significantly slower in mean speed and reaction time by a mean of 54% (left: $t[14] = -5.122$, $p < 0.001$, 95%CI -0.5,-0.2; right: $t[14] = -5.787$, $p < 0.001$, 95%CI -0.5,-0.2) and by 54% (left: $t[14] = 2.579$, $p = 0.022$, 95%CI 0.04,0.5; right: $t[14] = 2.247$, $p = 0.041$, 95%CI 0.01,0.3), respectively, compared to controls (Figure 2-8e left column and center). The effect of SCS therapy significantly improved mean accuracy in both arms by a mean of 91% ($p = 0.045$, 95%CI -0.9,0.03, post-hoc power = 0.82) from 17.6±13.7 cm at baseline to 1.5±0.1 cm at 6-months (Figure 2-8e right column). No significant changes in bilateral upper limb speed or reaction time were observed over the 6-months.

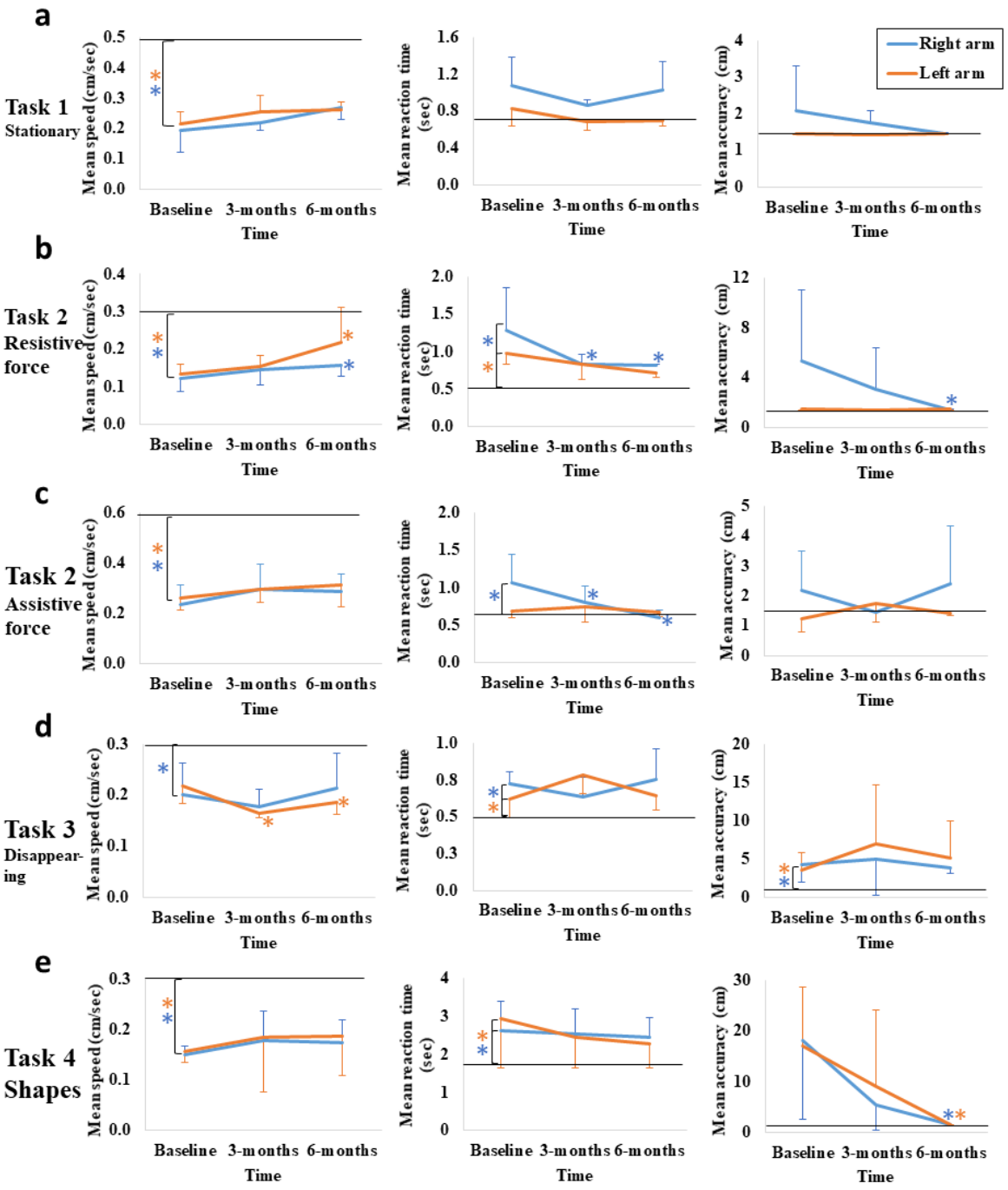

Figure 2-8. Mean speed (left column), reaction time (middle column) and accuracy (right column) measures from the visual-motor performance tasks (a-e) in the right (blue) and left (orange) upper limbs of all 4 PD participants from baseline to 3- and 6-months of SCS use.

Task 1 (a) involved participants to move the cursor into the middle of a stationary target, task 2 involved stationary targets but the robot exerted a resistive (b) or an assistive (c)

force requiring greater or lesser force, respectively, to be applied to the robot to move the cursor to the target, task 3 (d) involved participants to move the cursor to the place on the screen that the target appeared for 0.25 seconds, and task 4 (e) required participants to move the cursor to the correct shape (upright equilateral triangle) and to avoid distractor shapes. Black horizontal lines indicate mean healthy control values per task, error bars represent standard deviation, coloured asterisks denote statistical significance ($p < 0.05$) compared to baseline within PD participants and vertical bars indicate significant differences between PD and controls at baseline.

2.3.6 Relationship between changes in clinical and neurophysiological measures with SCS therapy

2.3.6.1 Freezing of gait and visual-motor performance

A linear mixed model (e.g. lmer(FOG ~ arm_robot*time + (1 | participant) where FOG represents CWT or CCWT turning time and arm_robot represents a visual-motor performance variable from a specific task per upper-limb with an interaction with time (SCS therapy)) revealed that changes in CWT time while participants were ON-levodopa as the dependent variable was significantly associated to changes in accuracy (Task #4 for targeting the correct shape) in both upper limbs (left: $\beta = 0.36$, 95% CI 0.15,0.56, $p = 0.001$; right: $\beta = 0.30$, 95% CI 0.06,0.55, $p = 0.015$) as the covariate over the 6-months. The model revealed that changes in the dependent variable, CCWT time was significantly associated to changes in reaction time (Task #4) in both upper limbs (left: $\beta = 0.21$, 95% CI 0.03,0.38, $p = 0.022$; right: $\beta = 0.45$, 95% CI 0.33,0.56, $p < 0.001$). Thus, the reduction in turning time was significantly associated with improvements in accuracy for visual discrimination of shapes and for motor control.

2.3.6.2 Freezing of gait and cortical activity

A linear mixed model (e.g. lmer(FOG ~ med_cluster_band*time + (1 | participant)) examined the outcome of turning time (CWT or CCWT directions) with electrode clusters “C1”, “C2”, “F1” and “F2” per frequency band as covariates comparing baseline and post-SCS time-points (3- and 6-months) while participants were either OFF-levodopa or ON-levodopa. While participants were OFF-levodopa, the model revealed the coefficients of $\beta = -1.17$ (95% -1.9,-0.45, $p = 0.002$), $\beta = -1.18$ (95% -2.12,-0.25, $p = 0.013$), and $\beta = 2.14$ (95% 1.15,3.13, $p < 0.001$) indicated that a 2 SD change in “C1”, “C2”, and “F2” relative alpha band power, respectively, was associated with a β * 2 SD

change in CCWT time over the 6-months. Furthermore, the model also revealed that CCWT time as the outcome was significantly associated with relative beta band power from the "C1" (β = 3.62, 95% CI 2.36,4.89, $p < 0.001$), "C2" (β = -1.44, 95% CI -2.24,-0.63, $p < 0.001$), and "F2" (β = -1.74, 95% CI -2.67,-0.82, $p < 0.001$) electrode clusters as the covariates. A model with CCWT time was significantly associated with changes in relative theta band power from the "C1" (β = -1.74, 95% CI -2.13,-1.34, $p < 0.001$), "C2" (β = 1.97, 95% CI 1.41,2.52, $p < 0.001$), and "F2" β = 0.74, 95% CI 0.41,1.06, $p < 0.001$) electrode clusters. A model with CWT time was significantly associated with changes in relative theta band power from "C2" (β = -1.34, 95% CI -2.17,-0.51, $p = 0.002$) and "F1" (β = 1.80, 95% CI 1.27,2.33, $p < 0.001$) electrode clusters as the covariates. Thus, changes in relative alpha, beta, and theta band power from the "C1", "C2", and "F2" clusters were significantly associated to changes in OFF-levodopa turning time (reduced FOG).

While participants were ON-levodopa, the model revealed that CCWT time as the outcome was significantly associated with relative alpha band power from "C1" (β = -1.27, 95% CI -1.94,-0.60, $p < 0.001$), "C2" (β = 0.54, 95% CI 0.03,1.05, $p = 0.038$), and "F2" (β = 0.92, 95% CI 0.23,1.60, $p = 0.009$) electrode clusters as the covariates over the 6-months. Furthermore, the model revealed that CWT time as the outcome was significantly associated with relative alpha band power from "C1" (β = -0.94, 95% CI -1.56,-0.31, $p = 0.003$) and "C2" (β = 1.29, 95% CI 0.69,1.89, $p < 0.001$) electrode clusters as the covariates. Thus, changes in relative alpha band power from "C1", "C2" and "F2" clusters were significantly associated to changes in ON-levodopa turning time.

2.3.6.3 Freezing of gait and striatal DAT binding

A linear mixed model (e.g. lmer(FOG ~ hemi_ROI*time + (1 | participant) where hemi_ROI represents a SBR value from a striatal ROI per hemisphere) revealed that changes in CWT time while participants were OFF-levodopa as the dependent variable was significantly associated to DAT binding in the anterior putamen of the right hemisphere (β = -0.83, 95% CI -1.28,-0.37, $p < 0.001$) as the covariate over the 6-months. Thus, this model indicated that a reduction in turning time (reduced FOG severity) was significantly associated to increased DAT binding in the right anterior putamen. No

significant associations were observed between CCWT time and striatal DAT binding in either hemisphere.

2.3.6.4 Visual-motor performance and striatal DAT binding

A linear mixed model (e.g. lmer(arm_robot ~ hemi_ROI*time + (1 | participant) where arm_robot represents a visual-motor performance variable from a specific task per upper-limb) revealed a main interaction effect between DAT binding in the anterior putamen for the right and left hemispheres as the outcome with speed (Task #4) in the left (β = -1.42, 95% CI -1.77,-1.07, $p < 0.001$) and right upper limbs (β = -0.38, 95% CI -0.69,-0.07, p = 0.016), respectively, as the covariates over the 6-months. Thus, changes in upper limb speed for visual discrimination was significantly associated with changes in anterior putamen DAT over the SCS treatment period.

A model revealed a main interaction effect between DAT binding in the left posterior putamen as the outcome with right upper limb accuracy (β = -1.43, 95% CI -1.77,-1.10, $p < 0.001$) and speed (β = 0.73, 95% CI 0.60,0.86, $p < 0.001$) for visual discrimination (Task #4) over the 6-months. However, a model revealed a main interaction effect between DAT binding in the right posterior putamen as the outcome with left upper limb reaction time (β = 0.88, 95% CI 0.41,1.35, $p < 0.001$) for Task #4 and speed (β = 1.21, 95% CI 0.38,2.05, p = 0.004) for Task #3. Thus, changes in upper arm speed, reaction time and accuracy were significantly associated with DAT binding in the posterior putamen over the SCS study treatment duration. No significant associations between speed, reaction time and accuracy with DAT binding in the caudate and putamen were observed over the 6-months.

2.4 Discussion

This is the first study to investigate the modulation of sensorimotor cortical activity and striatal dopaminergic innervation by dorsal column SCS at the thoracic level of the spinal cord to treat FOG and improve upper limb visual-motor performance. SCS significantly reduced FOG severity while participants were OFF-levodopa and ON-levodopa and improved upper limb speed, reaction time and accuracy for visual discrimination (targeting the correct shape) and tasks that required adapting to resistive forces. The

change in FOG was significantly associated with upper limb visual-motor improvements. FOG improvement was significantly associated with the modulation of resting-state sensorimotor cortical activity, particularly regions of the SMA and lower limb areas of the M1, while PD participants were OFF-levodopa. However, reduced FOG was not associated with changes in striatal dopaminergic innervation. These findings suggest that FOG may originate from impaired activity within these non-dopaminergic cortical pathways responsible for motor planning and execution, rather than an involvement of nigrostriatal subcortical pathways. Furthermore, SCS may modulate the activity of these pathways ultimately reducing FOG severity. Improvements in upper limb visual-motor performance was significantly related with changes in striatal dopaminergic innervation, particularly in the posterior putamen. These findings suggest that SCS may enhance appendicular motor control relating to upper limb freezing mediated by dopaminergic, sensorimotor pathways.

SCS has been shown to improve different aspects of gait, such as effecting changes in stride velocity, step length, and asymmetry and variability of gait, and reducing FOG frequency during walking (see **Chapter 4**). In this present study, SCS also significantly reduced FOG during turning while participants were OFF-levodopa and ON-levodopa. This highlights that SCS may improve the efficiency of turning by reducing the number of steps (reduced COP path length) mediated by acting on non-dopaminergic pathways, as there were improvements while participants were OFF-levodopa with no synergistic effects between medication and SCS use. A similar methodology for the individualization of SCS programming, described in **Chapter 3**, was utilized by determining the optimal SCS setting that best improved motor response, such as turning on the spot which is an effective provoker of FOG.[14] A low frequency (30-60 Hz) combined with a high pulse width (400 μs) SCS setting was most effective for reducing turning FOG as no improvements were observed using low frequencies with a lower pulse width (200 μs). Similar optimal SCS settings for straight walking tasks were reported in the pilot study with advanced PD patients (see **Chapter 4**). De Souza *et al* also demonstrated similar gait effects in PD patients using a low pulse width combined with a high frequency stimulation pattern over the 6-months of SCS therapy.[7] Minimizing placebo effects by blinding participants to each setting being tested[16] expanded our knowledge of effective

SCS parameters and advanced our understanding of the importance of the pattern of stimulation.

Restoration of locomotion and reduced freezing by upper thoracic SCS is correlated with the reduction of low-frequency cortical and basal ganglia oscillatory activity and changes in neural firing patterns reported in rat[8] and non-human primate[9] PD model pre-clinical studies. Santana *et al* demonstrated that SCS reduced the local field potential power in the M1, putamen, subthalamic nucleus, and thalamus, and that the desynchronization of these beta oscillations within the cortico-basal ganglia-thalamic circuit was the key underlying factor that brought the brain network closer to a normal state.[9] In this present study, SCS also induced significant reductions in low-frequency (delta, alpha, and beta) cortical activity within the SMA, M1 representation of the lower limbs, and frontal areas compared to baseline while participants were OFF-levodopa over the 6-month treatment period. These changes in low-frequency sensorimotor activity (theta, alpha and beta bands) were significantly associated with the reduction in FOG while participants were OFF-levodopa but were not observed with ON-levodopa FOG improvements. This corroborates the de Lima-Pardini *et al* study suggesting that SMA dysfunction underlies FOG and may be influenced by SCS due to improvements in anticipatory postural adjustments and freezing observed in PD patients.[13] In addition, significant associations between changes in right hemispheric ("F2" and "P2" electrode clusters) and central ("C1" and "C2") sensorimotor cortical activity with SCS therapy (time) were observed. However, no associations with the left hemispheric ("F1" and "P2") cortical activity with SCS therapy were observed indicating that SCS may influence cortical activity corresponding with the most affected side for all participants, which was the left side of body based on the MDS-UPDRS-III score and the reduced striatal DAT in the right hemisphere. Thus, this study is the first to demonstrate that SCS may directly modulate the cortical function of the primary sensory and motor areas to alleviate FOG. SCS may disrupt the connection between the dysfunctional basal ganglia, PPN and cortical areas that result in poor performance when trying to achieve tasks[17] and automatic movement responses that resemble FOG events.[18]

EEG slowing and reduced functional connectivity in the alpha frequency band is associated with non-dopaminergic disease severity in PD.[19] However, PD patients with freezing exhibit less efficient fronto-striatal pathways and attentional networks[20] and increased alpha activity, predominantly in the prefrontal and centro-parietal areas compared to PD patients without freezing.[21] A quantitative EEG study demonstrated that defective dopaminergic networks are involved in abnormal oscillatory alpha and beta cortical activity.[22] This present study corroborates the Melgari *et al* study where PD patients with freezing may exhibit defective dopaminergic networks as ON-levodopa cortical activity within the beta frequency band was significantly lower compared to controls.[22] As beta frequency band activity in the ON-levodopa state was not associated with SCS therapy, this suggests a slowing of neural activity is extensive in PD, and may not be a useful biomarker of FOG.[23] While participants were in the OFF-levodopa state, cortical activity within the delta, alpha and beta frequency bands from the "C1", "C2", "F2" and "P2" electrode clusters (sensorimotor areas) were significantly associated with FOG reductions over the 6-month SCS treatment period. Furthermore, no consistent associations between FOG reduction and striatal dopaminergic innervation were observed. Thus, SCS may primarily modulate non-dopaminergic, low frequency oscillatory sensorimotor cortical networks that may contribute to FOG and axial motor features of PD. This may be mediated by non-dopaminergic pathways[20] involving the connection between the PPN and thalamus with these cortical regions that need to function together for the fine-tuning and execution of gait.[24]

Deficits in the sensorimotor system that integrates information from the environment to guide motor decisions are prominent in PD patients with freezing.[25-27] As environmental factors can trigger FOG events and sensory cueing can ameliorate FOG, impaired visuospatial, perceptual processing and dopaminergic-resistant FOG may be connected.[25,26,28] Impairments of visual-motor performance in PD can be measured using tasks involving decisional factors (recognition of visual features) and automaticity, such as tasks involving simple reaching toward spatial targets as they appear in a workspace.[29] This study utilized a similar approach to quantify upper limb sensorimotor performance with minimal requirement of cognitive processes. The tasks utilized in this study were useful in the evaluation of movement impairments as both upper limbs in PD participants

exhibited slower speed and reaction times and were less accurate compared to healthy controls, as corroborated by previous studies.[29,30] SCS therapy improved speed, reaction time and accuracy in both upper limbs for visual discrimination tasks and tasks that required adaptation to resistive forces. The effect of SCS for visual-motor performance contrasts with the effect of levodopa medication in PD. Previous studies have shown that levodopa does not consistently improve the accuracy of sensorimotor performance[29,30] and may not significantly improve vision and displacement perceptual abilities.[31,32] Thus, visuospatial perception required for accurate visual-motor control may be mediated by similar non-dopaminergic pathways that contribute to FOG and is accessible by SCS therapy.[26,28]

Striatal dopaminergic denervation primarily affecting the posterior putamen, which receives sensorimotor cortical input, is thought to cause the shift from automatic to goal-directed motor control in PD.[33] In the rat PD model, SCS induced preservation of striatal dopaminergic density signifying a neuroprotective effect that was correlated with motor improvements.[10] However, in this present study, SCS may not induce a neuroprotective effect as a decrease in left striatal dopaminergic innervation was observed. Interestingly, the improvements in upper limb visual-motor performance were significantly associated with the changes in striatal dopaminergic innervation within the anterior and posterior putamen regions. SCS may modulate the balance of functional striatal dopaminergic cells between the anterior and posterior putamen of both hemispheres. This may contribute to changes in attentional and sensorimotor integration networks, which are areas affected in PD patients with freezing.[12,20] Thus, appendicular motor dysfunction and sensory processing deficits that may contribute to FOG and the loss of gait automaticity may be attributed to dopaminergic deficiency within the cortico-basal ganglia-thalamic pathway.

The value of this research study was limited by being an open-label study with a small sample size. Moreover, the assessment of visual-motor performance was only tested in the ON-levodopa state due to time constraints and participant fatigue; ideally these tasks would also be performed by participants while in the OFF-levodopa state. This additional assessment may further support the conclusions that appendicular motor control is mediated by dopaminergic pathways, but accuracy and visual perception is mediated by

non-dopaminergic pathways. Future studies should employ a larger sample size and explore tasks that measure proprioception (perception of passive motion) to confirm the influence of SCS for enhancing sensory feedback to alleviate FOG.

In summary, this study demonstrated that SCS reduced FOG severity and improved upper limb visual-motor performance in this advanced PD cohort with dopaminergic-resistant FOG. Dysfunction within the non-dopaminergic, sensorimotor cortical network may contribute to FOG impairment and SCS may modulate this network to alleviate FOG. Deficits in visual-motor performance may be facilitated by the non-dopaminergic network that contributes to FOG. SCS improved appendicular visual-motor control that may be mediated by changes in striatal dopaminergic innervation. Thus, these axial and appendicular motor improvements may be related to non-dopaminergic and dopaminergic neurophysiological changes within the cortico-subthalamic-PPN-PMRF and cortico-striatal-thalamo pathways, respectively.

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Chapter 3

3 Spinal cord stimulation therapy for gait dysfunction in progressive supranuclear palsy patients

3.1 Introduction

Richardson syndrome progressive supranuclear palsy (PSP-RS) is the most common form of atypical parkinsonism characterized by a rapid progression of clinical features including early postural instability, recurrent falls, freezing of gait (FOG), speech and swallowing difficulties, axial bradykinesia and rigidity, and vertical supranuclear gaze palsy.[1-3] FOG and postural instability present early in the disease course with limited to no response to levodopa (L-dopa) in PSP-RS. Spinal cord stimulation (SCS) is a standard, minimally invasive procedure for refractory pain, however recent studies suggest SCS has positive effects on locomotion and FOG symptoms resistant to L-dopa.[4-7] In this article, we report using SCS as a novel treatment for gait dysfunction in three patients with PSP-RS.

3.2 Methods

This monocentric pilot study was approved by Western University Health Sciences Research Ethics Board (REB#107451; Appendix A) and registered on clinicaltrials.gov registry (NCT03079310). Three female PSP-RS participants (3.2±1.3 years with disease) with significant FOG were recruited from the London Movement Disorders Centre in London, Ontario. Epidural SCS was implanted (Boston Scientific® Precision Novi) and leads were placed at the top of T8-T9 spinal segments. Participants provided signed informed consent (Appendix B). This study was carried out in accordance with the Code of Ethics of the World Medical Association.

Participants were assessed at pre-SCS, and 3-, 6- and 12-months post-SCS while OFF-L-dopa (≥12 hours since last dose) and ON-L-dopa (1-hr after a 1.5x dose). SCS programming was conducted over 2 visits involving random and repeated testing of 6 programs (300 and 400 μs combined with 30, 60 and 130 Hz) was completed <1-month following SCS implantation (SCS was only turned on in the lab). Subsequently, each

participant used their best tested SCS program, as previously described,[4] daily at a comfortable suprathreshold intensity over the 12-months. Paresthesias coverage of both lower limbs and feet was confirmed for all programming.

Participants completed 4 passes of self-paced, straight walking across the Protokinetics Zeno Walkway (Zenometrics LLC, Peekskill, NY) and spatiotemporal gait measures were extracted using the Protokinetics Software (PKMAS).[4] FOG detection using a custom-written MatLab (MatLab® v.2018b) algorithm was utilized and FOGs were confirmed using digital video recordings.[4] To capture turning FOG, narrow 360-degree turning on the spot in both directions was conducted at all visits and if no FOG was captured on the first trial, at least three trials were performed. All participants required their own assistive devices and continued to use the same assistive devices throughout the study.

Primary endpoints were changes in duration and number of FOG episodes captured on the carpet, duration of 360-degree turning, and mean z-score changes in spatiotemporal gait parameters that were grouped together based on the expectation to increase (step length, stride velocity, single support time and swing time) and to decrease (stride width, gait cycle time, stance time and double support time) with SCS turned on at 3-, 6- and 12-months of SCS use compared to pre-SCS.[4] Clinical endpoints were collected at all visits: activities-specific balance confidence (ABC) scale, MDS-UPDRS-III, FOG questionnaire (FOG-Q), Montreal Cognitive Assessment (MoCA) and global impression of change in quality of life (GISC; 0: no improvement; 10: highest most imaginable improvement) (Appendices D-H).

3.3 Results

3.3.1 Participant demographics

Detailed participant demographics are displayed in Table 3-1. Participant #3 was treated with L-dopa without any improvement and subsequently stopped L-dopa >6-months prior to study initiation. At baseline, mean turning time (both directions), a measure of turning FOG, improved by 30.8±0.04% from OFF- to ON-L-dopa (L-dopa response) in participants #1 and #2 at pre-SCS. However spatiotemporal parameters (STPs), step

length and stride velocity, worsened while ON-L-dopa by 6.7±0.01% and 28.2±0.01%, respectively; no L-dopa effect was observed for mean gait asymmetry and variability.

Table 3-1. Participant demographics and baseline gait and clinical scores while OFF- and ON-L-dopa

Participant ID#	OFF/ON L-dopa				
	#1	#2	#3	Mean	SD
Age	82	71	76	76.3	5.5
Years with disease	3	4.5	2	3.2	1.3
Daily levodopa dose (mg)	600	800	n/a	700.0	141.4
UPDRS-III score	33/29	17/13	38/–	29.3/21.0	11.0/11.3
ABC (%)	60	8	25	31.0	26.5
FOG-Q (/24)	14	23	19	18.7	4.5
MoCA (/30)	25	26	23	24.7	1.5
Mean 360° turning (sec)	46.1/33.3	179.2/118.7	110.1	111.8/76.0	66.6/60.4
Mean FOG time (sec)	0/2.9	47.0/15.9	10.4	19.1/9.4	24.7/9.2
Number of FOGs	0/2.0	10.0/6.0	10.0	6.7/4.0	5.8/2.8
Step length (cm)	22.3/20.6	29.5/21.2	14.9	22.2/20.9	7.3/0.4
Stride velocity (cm/s)	30.7/28.9	51.9/37.2	25.1	35.9/33.0	14.1/5.9
GA (%)	25.5/31.2	16.9/20.9	24.7	22.4/26.0	4.8/7.3
CV (%)	12.0/12.5	43.3/39.6	40.2	31.8/26.0	17.2/19.2

ABC activities-specific balance confidence scale, CV% coefficient of variability (gait variability), GA gait asymmetry, L-dopa levodopa, MoCA Montreal Cognitive Assessment, OFF-L-dopa: participants tested ≥ 12 h since last dose, ON-L-dopa participants tested 1 h after 1.5 × dose, SD standard deviation, Sec seconds, UPDRS-III Unified Parkinson's Disease Rating Scale for motor symptoms

3.3.2 SCS programming

Best SCS setting that produced the greatest improvement in gait and in both FOG phenotypes (straight walking and turning) was utilized by each participant for the 12-month post-SCS period: participant #1, 400μs/60Hz; participant #2, 300μs/60Hz; participant #3, 400μs/130Hz. However, participant #1 performed well on 4 of the 6 settings (excluding 400μs/60Hz and 130Hz), participant #2 also demonstrated improved gait at 400μs settings and 300μs/60Hz, and participant #3 improved on all settings especially at stimulation frequency of 30Hz.

3.3.3 Freezing of gait outcomes

Duration of 360-degree turning in both directions was improved by a mean 50.0±11.0% and by 37.7±14.7% change while OFF and ON-L-dopa, respectively, in participant #1 over the 12-months compared to pre-SCS (Figure 3-1). A mean 40.2±20.2% reduction of clockwise turning duration was observed in participant #2 while OFF and ON-L-dopa up to 12-months. However, inconsistencies in the effect of SCS occurred during counterclockwise turning as duration worsened by 78.8±9.0% at 6-months while OFF- and ON-L-dopa but improved by 44.4% only when OFF-L-dopa at 12-months, indicating an improvement in "OFF" state FOG. For participant #3, duration of 360-degree turning remained similar up to 6-months and worsened by 63.9±79.7% at 12-months.

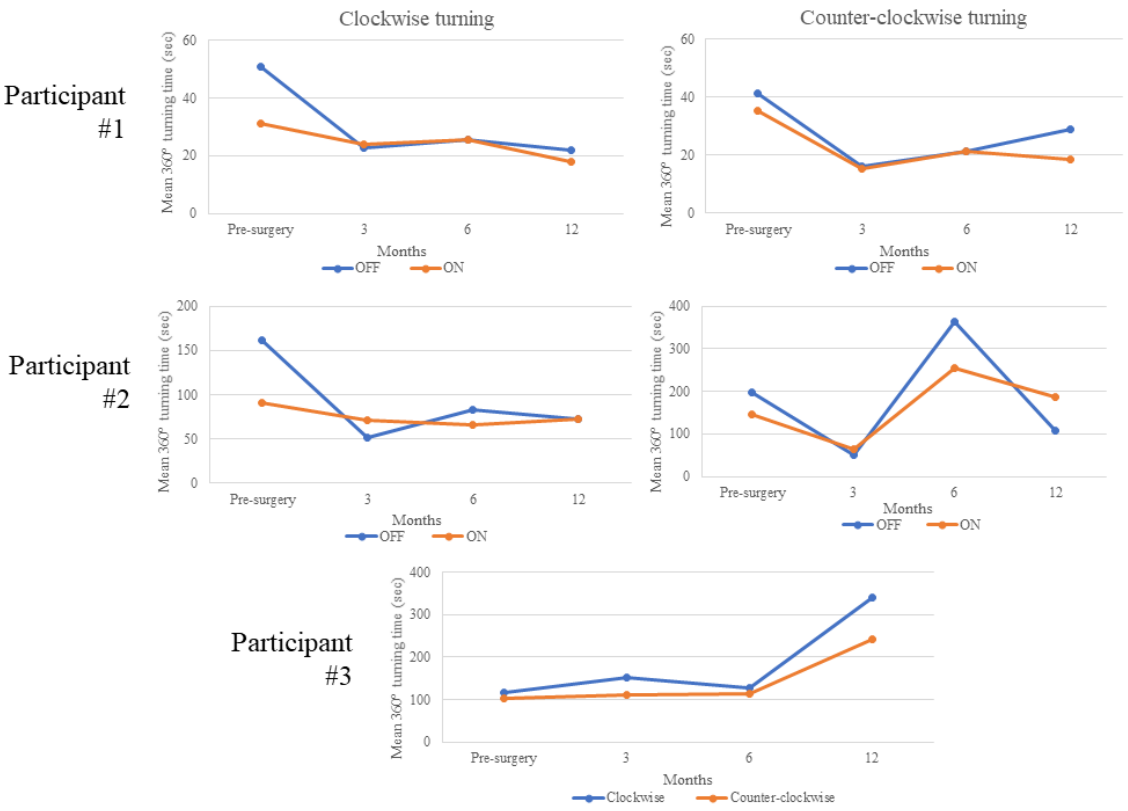

Figure 3-1. Mean duration of 360-degree turning on the spot in clockwise and counterclockwise directions for each participant while OFF- and ON-L-dopa medication (except participant #3 who was only assessed while OFF-L-dopa).

Participant #1 was more affected by FOGs during turning on the spot tasks (Figure 3-1) rather than during walking as no FOGs were captured while OFF-L-dopa at pre-SCS. However, two FOGs were captured while OFF-L-dopa at 12-months (Figure 3-2). Daily use of SCS after 6- and 12-months reduced mean FOG frequency and duration by 75.0±35.4% and 33.0±94.7%, respectively, while ON-L-dopa during straight walking across the gait carpet. Mean FOG frequency was reduced by 40.6±33.7% while OFF- and ON-L-dopa in participant #2 over the 12-months, however mean FOG duration worsened by 151.4±8.8% while ON-L-dopa but remained the same OFF-L-dopa at 12-months. Both mean FOG frequency and duration improved by 77.6±26.2% after 3- and 6-months of SCS use, but mean FOG duration worsened by 121.6% at 12-months for participant #3.

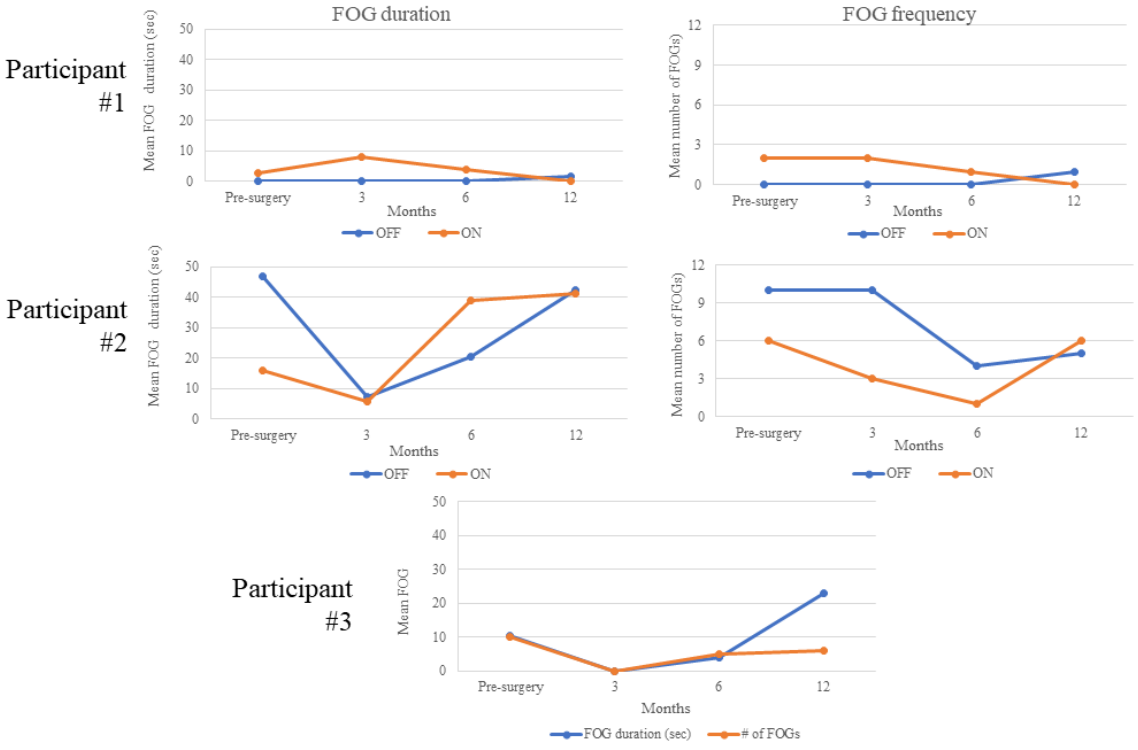

Figure 3-2. Mean number of FOG episodes and mean duration per FOG episode for each participant while OFF and ON L-dopa medication (except participant #3 who was only assessed while OFF L-dopa). FOG episodes were captured on the gait carpet during ambulatory straight walking.

3.3.4 Ambulatory gait outcomes

Changes in STPs during ambulatory straight walking were compared using mean z-scores and % changes of gait measures (step length, stride velocity, swing time and single support time) per participant. Participant #1 demonstrated a mean z-score of +2.7±0.3 (25.4±10.5%) while OFF-L-dopa and +1.0±0.3 (21.8±13.5%) while ON-L-dopa over the 12-months (Figure 3-3). Participant #2 had a mean z-score (change in gait measures) improvement of +1.6±1.2 (30.7±15.0%) and +0.4±0.6 (10.6±9.9%) while OFF- and ON-L-dopa, respectively, where at 12-months overall ON-L-dopa mobility worsened but improvements continued while OFF-L-dopa. Participant #3 improved by a mean +0.9±0.1 (31.6±5.4%) up to 6-months but worsened by -1.4±0.8 (69.5±27.7%) at 12-months. Mean stride width, stance and double support gait phases (negative z-scores) were reduced up to 12-months for participant #1 while OFF- and ON-L-dopa, up to 12-months for participant #2 while OFF-L-dopa and up to 6-months for participant #3 (Figure 3-3).

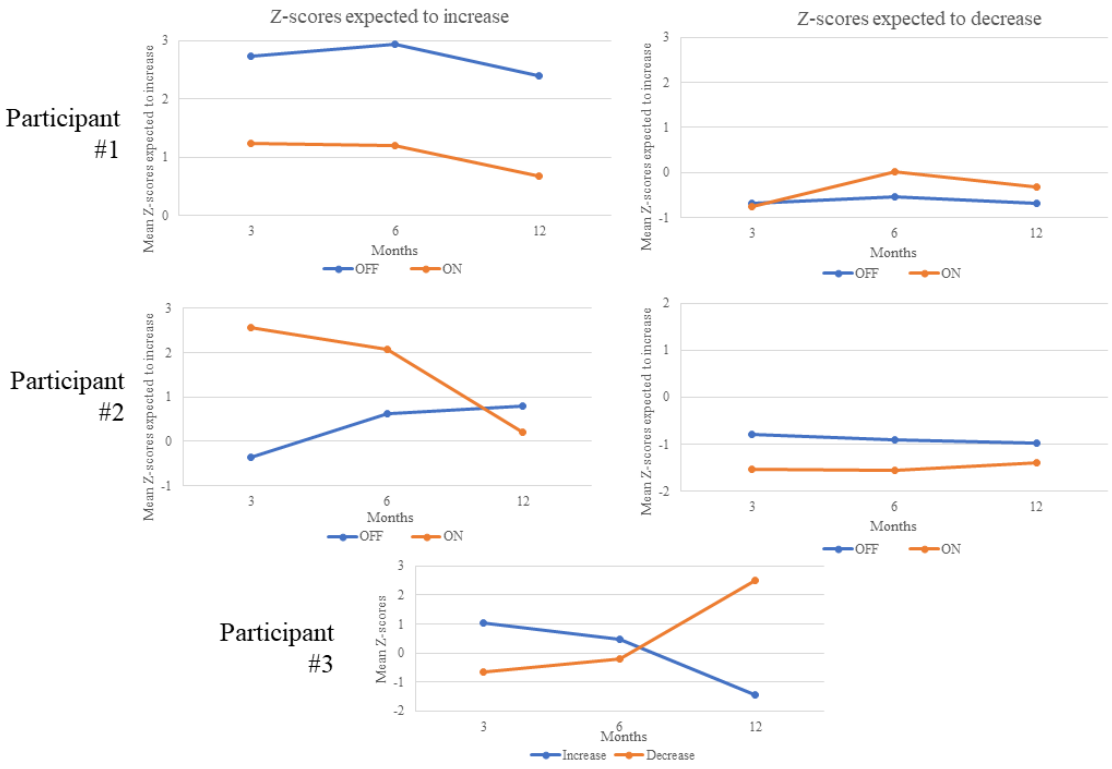

Figure 3-3. Mean z-scores plotted for gait measures expected to increase after SCS use (left column) and measures expected to decrease after SCS use (right column) for each participant while OFF- and ON-L-dopa medication (except participant #3 who was only assessed while OFF-L-dopa).

The z-scores for gait variables expected to increase, thus we expect positive z-scores, were step length, stride velocity, single support time and swing time. The z-scores for gait variables expected to decrease, thus we expect negative z-scores, were stride width, gait cycle time, stance time and total double support time. The z-scores presented represent the best SCS setting tested during programming (<1-month post-SCS implantation): participant #1, 400 µs/60Hz; participant #2, 300 µs/60Hz; participant #3, 400 µs/130Hz and utilized at post-SCS follow-ups.

For participant #1, mean gait asymmetry improved at 6-months by a mean 15.4% while OFF- and ON-L-dopa compared to pre-SCS (Figure 3-4). Mean gait asymmetry was reduced by a mean 7.8% while ON-L-dopa at 3- and 6-months that was not sustained at 12-months, and gait asymmetry while OFF-L-dopa worsened by 13.3% in participant #2. Mean gait asymmetry improved by a mean 9.8% at 3- and 6-months for participant #3 but worsened by 8.0% at 12-months. Mean gait variability (CV%) did not change significantly over the treatment course while OFF- and ON-L-dopa for participant #1,

however was improved by a mean 14.9% at 6-months for participant #2 while OFF- and ON-L-dopa and by a mean 15.7% for participant #3 over the treatment course.

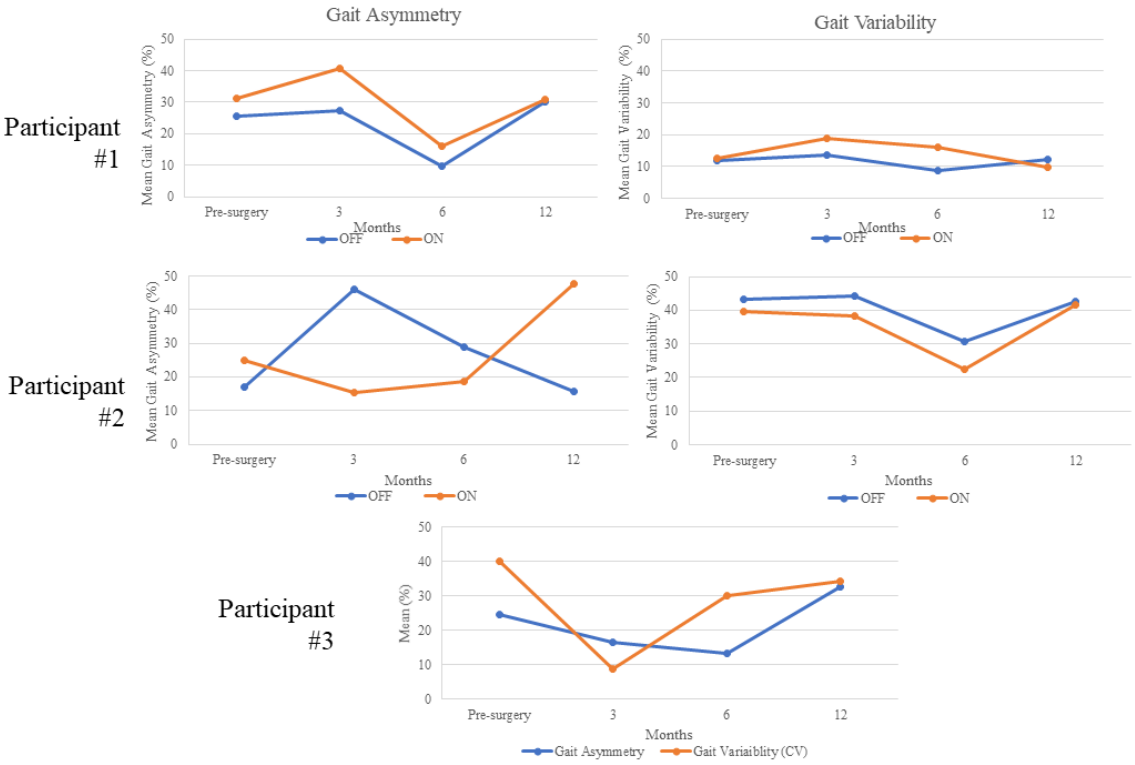

Figure 3-4: Mean gait asymmetry (left column) and gait variability (right column) changes for participants #1 (row 1), #2 (row 2) and #3 (row 3) while OFF- and ON-L-dopa medication (except for participant #3 who was only assessed while OFF-L-dopa).

Mean gait asymmetry was calculated by averaging asymmetry of step length, step time, swing time, and single support time. Mean gait variability was calculated by averaging coefficient of variability (CV%) of stride time, stance time, swing time, and total double support time.

3.3.5 Clinical scale outcomes

Participant #1 rated the highest global impression of change score (GICS) of 6/10 at 3- and 6-months and continued with a score of 7/10 at 12-months. Participant #2 rated a global improvement of 1/10 at 3-months but did not perceive improvement at 6- and 12-months. Participant #3 found a global improvement of 3/10 over the 12-months.

MDS-UPDRS-III score was reduced by a mean 14.5% (-5 points) while maintaining a 12.0% L-dopa response in participant #1. For participant #2, L-dopa response was reduced from 23.5% to 1.9%; total MDS-UPDRS-III score was reduced by 23.5±16.6% (-4 points) up to 6-months while OFF-L-dopa that worsened at 12-months by 11.8% (+2 points) and 38.5% (+5 points) while OFF- and ON-L-dopa, respectively. MDS-UPDRS-III score worsened by 18±21.9% (+7 points) in participant #3. Mean MoCA scores did not change over the treatment course. Confidence of daily activities (ABC scale) was reduced by 15% change to an ABC score of 45.0% in participant #1, increased by 10% to 16.3% for participant #2 and reduced by 20% to 5.6% in participant #3 at 12-months. FOG-Q scores stayed the same for participants #1 and #2 and worsened by 4 points to a total of 23 points for participant #3. No side effects were reported during the study course.

3.4 Discussion

Progressive supranuclear palsy (PSP) has a short median survival from 5 to 10 years from disease onset, and those with Richardson's syndrome progressive supranuclear palsy (PSP-RS) subtype have a shorter median disease duration and higher mortality risk than in PSP-parkinsonism.[8] Severe gait dysfunction including freezing of gait (FOG) and early falls are hallmarks of PSP-RS causing significant morbidity. Most patients are tried on levodopa (L-dopa) but usually stop due to a limited to no response. Thus, there are no effective treatments available for PSP. This is the first-to-date study to use spinal cord stimulation (SCS) for the treatment of FOG and gait dysfunction in 3 PSP-RS (~3 years of disease) participants over 12-months. We found SCS reduced FOGs and improved straight walking in all 3 participants, however improvements depended on each participant's response to L-dopa and progression of their disease.

In this study we utilized the most effective way to provoke FOGs in a laboratory setting (on the spot, narrow 360-degree turning) in addition to assessing FOGs while straight walking.[9,10] At baseline, turning duration, FOGs during straight walking and MDS-UPDRS-III score improved with L-dopa in participants #1 and #2 (participant #3 was not taking L-dopa prior to study start), however gait measures worsened when ON-L-dopa in both participants. After SCS, participant #1 continued to have a positive L-dopa response

(OFF/ON-L-dopa MDS-UPDRS-III score change) and demonstrated a consistent reduction in turning duration and frequency and duration of walking FOGs, and ambulatory gait improved while OFF- and ON-L-dopa up to 12-months. However, for participant #2, clockwise turning and FOG frequency while walking improved both OFF- and ON-L-dopa with SCS up to 12-months, but L-dopa response was now minimal, and overall gait and counterclockwise turning worsened ON-L-dopa, while improvements in gait and counterclockwise turning were observed when OFF-L-dopa. These findings are interesting as it suggests two possible outcomes when combining SCS and dopaminergic therapies. In participant #1, dopamine and SCS have a synergistic effect for treating FOG and gait which has also been observed in pre-clinical and clinical PD studies.[5,11,12] Thus, in this case, SCS is beneficial as an adjunct therapy. The second scenario as observed in participant #2 is a switch in L-dopa effect as worsening of gait symptoms occurred only when ON-L-dopa. Although rare, drug-induced or "ON" FOG is also reported in PD and after subthalamic deep brain stimulation when combined with levodopa administration.[13-17] This suggests L-dopa possibly induced an interfering or worsening effect with SCS. Thus, SCS can be a monotherapy as a dose reduction or elimination of L-dopa should be considered as in participant #2. For participant #3 (only OFF-L-dopa), SCS improved both gait and straight walking FOG up to 6-months, but the gradual loss of response to SCS, worsened gait and UPDRS-III score at 12-months, suggests disease progression. This highlights possible mechanisms of SCS acting on: 1) non-dopaminergic pathways for gait, as seen in our cohort while OFF-L-dopa and in previous studies including patients with FOG refractory to dopaminergic therapy,[18,19] multiple systems atrophy (MSA),[6] and primary FOG,[20] and 2) the synergistic effect of SCS with dopamine where electrical stimulation of the spinal cord sends signals to the basal ganglia circuits to release stored dopamine.[5,18]

A personalized approach to SCS programming was applied and participants were blinded to which stimulation settings were being tested. Only participant #3 improved on all settings whereas, participants #1 and #2 improved on 4 of the 6 tested settings. This suggests that SCS for gait is not solely based on the effects of sensing paresthesias. This corroborates our pilot PD study results[4] as there is uncertainty as to whether SCS is effective, especially in consideration of FOG.[21,22] Recent studies using burst stimulation,

a new programming technique that provides effect without paresthesias, has shown significant motor improvements in two trials with PD and atypical parkinsonism patients.[19,23] Thus, burst stimulation minimizes placebo-effects of SCS for gait improvements. However, with tonic stimulation, a high amplitude stimulation or inducing paresthesias at a suprathreshold intensity may improve outcomes due to increased possibilities of dorsal horn and column activation.[22] Furthermore, stimulation patterns of longer pulse widths with shorter frequencies that has shown benefit in our PD and PSP cohorts may be due to the electrodynamics of less excitable structures and deeper structures that are likely to be activated.[21,24] It should be noted that while the majority of SCS studies have been positive for gait/FOG in PD,[5] variability of therapeutic outcomes (e.g. magnitude of improvement and gait parameters affected), especially in the long-term, could be attributed to disease phenotypes, symptoms responding to L-dopa, severity of non-motor symptoms, and the technology/programming (e.g. parameters, burst or tonic stimulation) and hardware (device/electrodes) used. Similarly, most short-term studies of external sensory cueing (e.g. visual or auditory) in PD patients with FOG are positive but in the long-term, success depends on disease profile when simultaneously learning and doing new tasks.[25] Hence this demonstrates that SCS may influence the same pathways as external cues by intrinsically and indirectly modulating cortical areas responsible for planning and execution of movement.[25,26]

The value of this study is limited by: 1) being an open-label study with a small sample size and the necessity to report results case by case, 2) not testing an OFF-stimulation condition, as it is difficult to identify when a true OFF-stimulation occurs or to determine a stimulation wash out period, and 3) the possibility of a placebo effect and bias associated with SCS-induced paresthesias. Future studies could utilize a blinded crossover design,[18] double blinding during programming and follow-up assessments, or apply a placebo/sham stimulation protocol design[27] to minimize bias. Additionally, the episodic nature of FOG might impact accuracy of in-laboratory assessments, thus future studies focusing on FOG might utilize in-home wearable sensors to overcome laboratory-setting biases.

Overall, SCS programmed to each patient's symptoms reduced FOG and gait dysfunction severity using tonic, suprathreshold stimulation. SCS may be an effective approach for treating refractory FOG symptoms in PSP-RS and may be considered early in the disease course (such as at time of FOG onset and initial reporting of falls) regardless of L-dopa response (even with a minimal L-dopa response). Furthermore, the effect of L-dopa on gait symptoms should be monitored to optimize SCS outcomes (whether to apply SCS as a monotherapy or as an adjunct therapy). Further clinical studies with trial designs that include PSP-RS patients with dopaminergic-resistant FOG, monitoring FOG and gait symptoms OFF- and ON-L-dopa when combined with SCS therapy, and placebo-stimulation protocols (e.g. sufficient wash out between testing different SCS settings or burst versus tonic stimulation) should be investigated.

3.5 References

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Chapter 4

4 Spinal cord stimulation therapy for gait dysfunction in advanced Parkinson disease patients

4.1 Introduction

In patients living with Parkinson disease (PD) for an average of 10-15 years, axial motor symptoms, such as gait dysfunction, freezing of gait (FOG), and postural instability, are common late phenomena and induce significant disability.[1-3] Axial symptoms are largely resistant to dopamine replacement therapy.[1,3] Benefits of deep brain stimulation (DBS) targeting subthalamic nucleus (STN) or globus pallidus interna (GPi) for axial symptoms is limited and unpredictable and this intervention is only available to a fraction of patients.[3-10] DBS of the pedunculopontine nucleus (PPN) for axial symptoms is still experimental as outcomes are variable.[5,11,12] A novel therapeutic intervention is a significant unmet need for alleviating axial disability in advanced PD patients.

Progress in the therapeutic use of dorsal spinal cord stimulation (SCS) has produced significant motor and gait improvements in 5 non-human primate models of PD and in 24 human PD case studies; though many cases included patients with chronic pain which limits significance of reported gait improvements.[13-20] High frequency SCS in 4 PD patients previously treated with STN-DBS was well tolerated and significantly improved gait.[21] However, short- and long-term effects of SCS in patients that have typical PD related FOG and the optimal therapeutic SCS settings need to be refined. Finally, quantitative gait analysis is necessary to understand which affected gait domains improve with SCS.[22-24]

In this open-label, non-randomized pilot study, the primary endpoint was to evaluate SCS efficacy by clinical evaluation and objective gait analysis from pre-surgery to 6-months and the long-term gait effect up to 3-years with SCS therapy. The secondary endpoint was a randomized, single-blinded (participant) evaluation by gait analysis of different frequency and pulse width combinations at a suprathreshold intensity at weeks 2,4,6,8,10,12, and 16 weeks (1-4m) after surgery. SCS was performed in PD patients

without pain but with significant gait dysfunction and FOG despite optimization of dopaminergic medication.

4.2 Methods

4.2.1 Subjects

A convenience sampling of 5 PD participants with significant gait dysfunction and postural instability while ON medication were recruited for this non-randomized study from the London Movement Disorders Centre in London, Ontario, Canada. Inclusion criteria were: participants with idiopathic PD meeting the UK Brain Bank criteria with II-IV Hoehn-Yahr stage while "ON" oral medications, a history of falls, gait and balance dysfunction and postural instability despite optimized treatment with medications, and no significant secondary causes. Participants with a history of stroke, or any other neurological diseases, moderately severe parkinsonism in the context of unstable pharmacological treatment were excluded.

Of the 5 male advanced PD participants who completed the 6-month study, four participants were re-assessed while ON-levodopa (~1-1.5 hours after dose) after 3-years of SCS (a long-term update).

4.2.2 Ethics

Western University Health Sciences Research Ethics Board (REB#: 107451) approved this investigational, pilot study protocol (Appendix A). The study was registered at ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT03079310) as an open-label, single-centre, pilot study. All participants provided signed informed consent (Appendix B). First participant's first visit and last participant's last visit occurred in February 2016 and December 2016, respectively. Appendix I outlines study design and analysis in a CONSORT flowchart up to the 6-month follow-up. Four of the five participants were re-assessed between April 2019 and July 2019. This study was carried out in accordance with the Code of Ethics of the World Medical Association and all ongoing and related trials for this intervention are registered.

4.2.3 Study design

Clinical rating scales and ambulatory walking tasks captured objectively by the gait mat were completed pre- and post-operatively. Figure 4-1 outlines the study timeline and design up to 6-month follow-up. Eleven frequency (30,60,130Hz) and pulse width (200,300,400,500µs) SCS combinations (the device did not allow program 500µs/130Hz to be programmable) at a supra-threshold intensity were single-blinded to the participant and randomly selected using a randomization table. SCS settings selected were based on previously published studies involving PD gait therapy using SCS.[16,18-21] Post-operative study visits lasted approximately 4-5 hours and were conducted at weeks 2,4,6,8,10,12, and 16 (1-4m) while participants were on-medications (dopaminergic; +LD/+SCS). Firstly, clinical scales were completed in the morning followed by assessing one or two SCS settings; if the participant was fatigued due to length of visit, then one SCS setting was assessed. Each SCS setting was programmed 1-hour before participants conducted ambulatory walking tasks. At the end of each study visit, the assessor considered the participant's feedback, and the objective analysis of gait (spatiotemporal parameters) that were best improved with SCS setting(s) tested until that point to determine which setting the participant should use till the next visit. At the end of the 8th post-operative visit at week 16, the SCS setting to produce the best motor response was objectively selected by the assessor using gait analysis and was confirmed by the participant subjectively. At week 24 (6m), clinical scales and the effects of SCS was collected using the gait mat with the device turned-on and programmed to their best setting for at least 1-hour before assessment and on medication (+LD/+SCS). Thus, a total of nine study visits over a 25-week duration were completed.

Following approximately 3-years of SCS therapy, clinical rating scales and walking tasks were collected in a single visit by the same assessor for 4 of the 5 participants.

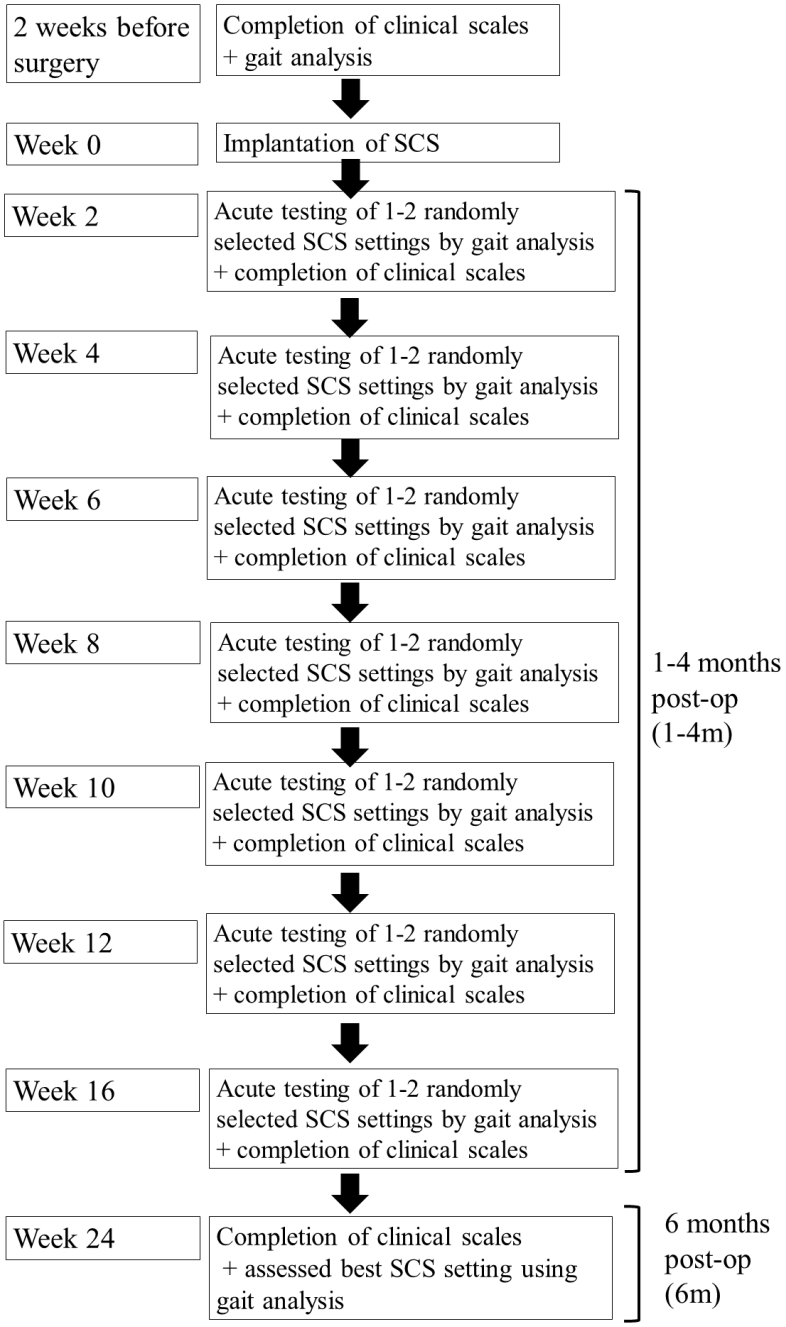

Figure 4-4-1. Flowchart outlining the study timeline and design up to 6-months following surgery.

4.2.4 Spinal cord stimulation intervention

Two cylindrical, percutaneous electrodes, with 8 contacts per lead, (Boston Scientific® Precision Novi) were implanted in the medial, epidural space at T8-T10 spinal segments,

with the electrode positioned to produce paresthesias fully covering the lower trunk and lower extremities including both legs and feet. One week following implantation, all participants were initially set to 400μs/60Hz inducing paresthesia fully covering both lower limbs and feet. For all gait assessments with the device switched ON to medium suprathreshold intensity, the exact stimulation intensity varied per setting per participant. Participants were instructed to use the device daily set to a tolerated supra-threshold intensity (~3-5% higher than the minimum intensity to produce paresthesia perceived by the participant while the participant was standing) using the Boston Scientific remote control.

4.2.5 Gait analysis

For each visit and SCS setting assessed, participants (without shoes) walked across the 20-foot Protokinetics Zeno walkway (Zenometrics LLC, Peekshill, NY) over two trials each with two passes to-and-fro, totaling four passes to capture ambulatory walking episodes; gait initiation and turning was conducted off-mat. Three of the five participants required assistive walking aids (2 with canes, 1 with a walker). No auditory or visual cues were provided, the testing environment with a plain floor and whitewashed walls was kept constant and participants were tested at approximately the same time of the day or at least 1-hr before or after taking oral medications to ensure participants were assessed while “ON” medications. The sensors embedded in the walkway detect and relay each footfall to the Protokinetics Movement Analysis Software (PKMAS). PKMAS is a reliable method for processing footstep patterns and provides accurate and validated measurements of various gait parameters.[25-27] Approximately 10% of footfalls were incomplete (partial footfalls were captured at the carpet ends) and were removed from analysis using PKMAS. Spatiotemporal gait parameters including step length, stride width, stride velocity, step time, stance, swing, single and double support phases of a gait cycle are known variables to be affected in PD, which were extracted using PKMAS. Z-scores were calculated for each parameter to determine which setting (frequency/pulse width combination) provided the best improvement per participant. The z-score was calculated based on the average and standard deviation of all the tested SCS settings. For

instance, to calculate participant#1's z-score for step length with the SCS device programmed to 400μs/60Hz:

$$Z^{P1}_{SL-400/60} = \frac{SL^{P1}{}_{400/60} - SL^{P1}{}_{all\ SCS\ settings}}{\sigma^{P1}{}_{all\ SCS\ settings}}$$

where $Z^{P1}{}_{SL\text{-}400/60}$ is participant#1's z-score for step length, $SL^{p1}{}_{400/60}$ is participant#1's mean step length on 400μs/60Hz, $SL^{P1}{}_{\text{all SCS settings}}$ is the average step length of all tested SCS settings for participant#1, and $\sigma^{P1}{}_{\text{all SCS settings}}$ is the standard deviation of the step length gait variable of all tested SCS settings for participant#1. Mean z-scores for gait parameters expected to increase (step length, stride velocity, swing %, single support %) or decrease (stride width, step time, gait cycle time, stance %, double support %) following SCS intervention were grouped together and plotted for each subject. Within subject means and standard deviation from left and right lower limbs, left/right ratio of gait variables representing percent gait asymmetry (100x(|ln(left/right)|) and percent gait variability represented as coefficient of variance (CV; (SD/mean)*100) were calculated.[28,29]

A custom-written MatLab algorithm provided automatic detection of the number of FOG episodes and the duration (seconds) of each episode was calculated based on left and right foot pressure changes exported from PKMAS; number of FOG episodes was visually confirmed using the generated PKMAS footfalls and video recordings of each walk pass. Total number of FOG episodes from the gait-mat (2 trials) and the mean FOG duration of each episode were calculated for each participant under each condition: pre-operative, best setting tested between 1-4m (+LD/+SCS), and 6m (+LD/+SCS) after SCS. Timed sit-to-stand (STS) (time in seconds for a participant to arise from a chair to standing position) over 4 trials were recorded for each participant under each assessment condition.

4.2.6 Clinical outcome measures

Unified Parkinson Disease rating scale motor scores (UPDRS III),[30] Parkinson disease questionnaire (PDQ-8) (Appendix J), freezing of gait questionnaire (FOG-Q), and activities-specific balance confidence scale (ABC) were completed at the beginning of

each study visit while participants were on their oral medications for all nine visits. Changes in clinical scale ratings (PDQ-8, FOG-Q, and ABC) were based on the period of time at-home between the current and previous study visit or in the last week up to the current visit where participants were using SCS settings that produced the best motor response. Each participant was accompanied by their spouse/family member living with participant/care-giver who aided in answering the questionnaires.

4.2.7 Statistical analysis

Clinical data from all subjects were pooled and mean and standard deviations were plotted for all nine visits. For each gait parameter exported from PKMAS, the mean and standard deviations of all footfalls from the left, right and average of both sides were calculated for all walking sessions (pre-operative (+LD)), best setting between 1-4m (+LD/+SCS), and 6m (+LD/+SCS). A Friedman test (IBM SPSS Statistics version 20) was conducted to determine if there were statistical differences in clinical scores and gait variables during the 6m SCS intervention. Pairwise comparisons were performed with Bonferroni correction for multiple comparisons. The null hypothesis assumed that mean clinical scores, and scores for each gait variable, calculated from PKMAS outputs, between pre-operative and post-operative time-points (1-4m and 6m conditions) were not statistically different (α=0.05).

4.3 Results

4.3.1 Demographics

Study demographics of the five male PD participants are outlined in Tables 4-1 and 4-2; all participants had a history of falls and FOG and participant#3 had lower limb/feet dyskinesia. Three of the five participants required a mean reduction in daily levodopa dose by 115mg by 6-months due to presence of dyskinesias following 6-months of SCS use. All participants tolerated the procedure and no adverse events relating to surgery or hardware were reported.

Table 4-1. Demographics, best SCS setting tested between 1 and 4 months, and total UPDRS motor score from preoperative to 6-months postoperatively for all study participants.

ID	Age	YWD	Best SCS setting tested at 6m	Daily levodopa dose (mg)		Total UPDRS motor score	
			Pulse width/Frequency	Pre-op (+LD)	6m (+LD/+SCS)	Pre-op (+LD)	6m (+LD/+SCS)
1	63	14	400µs/60Hz	1500	1350	23	16
2	78	18	300µs/30Hz	2000	1825	29	21
3	64	15	300µs/130Hz	1000	750	21	13
4	66	8	300µs/30Hz, 300µs/130Hz, 400µs/130Hz	900	900	39	17
5	85	15	400µs/60Hz	1250	1250	49	40
Mean	71	14	-	1330	1215	32	21
SD	10	4	-	441	420	12	11
Range (low)	63	8	-	900	900	21	13
Range (high)	85	18	-	2000	1825	49	40

Abbreviations: +LD: ON oral (dopaminergic) medications; +LD/+SCS: ON oral (dopaminergic) medications and SCS turned on for more than 1 hour before assessment; 6m: 6-months after SCS surgery; PD: Parkinson disease; Pre-op: Pre-operative (baseline) measurements; SD: standard deviation of population; UPDRS: Unified Parkinson disease rating scale; YWD: years with disease.

Table 4-2. Mean quantitative gait measure values from preoperative to on-stimulation 6-months postoperatively for all study participants.

ID	Step Length (cm)		Stride Velocity (cm/sec)		Swing %		Single Support %		Double Support %	
	Pre-op +LD	6m +LD/+SCS	Pre-op +LD	6m +LD/+SCS	Pre-op +LD	6m +LD/+SCS	Pre-op +LD	6m +LD/+SCS	Pre-op +LD	6m +LD/+SCS
1	28.6	43.8	63.2	108.4	32.2	35.2	30.1	34.5	37.5	28.0
2	8.3	34.3	8.4	60.8	20.9	33.0	21.7	32.3	57.4	33.7
3	51.4	51.9	114.2	126.4	37.0	35.9	34.6	33.8	26.0	27.9
4	31.3	45.2	88.8	84.0	37.3	38.3	36.4	35.6	24.7	23.6
5	18.3	16.4	9.0	24.3	10.1	24.2	7.8	21.6	74.5	54.4
Mean	27.6	38.3	56.7	80.8	27.5	33.3	26.1	31.6	44.0	33.5
SD	16.1	13.8	47.4	40.1	11.8	5.4	11.7	5.7	21.5	12.2

Range (low)	8.3	16.4	8.4	24.3	10.1	24.2	7.8	21.6	24.7	23.6
Range (high)	51.4	51.9	114.2	126.4	37.3	38.3	36.4	35.6	74.5	54.4

Abbreviations: +LD: ON oral (dopaminergic) medications; +LD/+SCS: 6m: 6-months after SCS surgery; Double support % is the double support time expressed as a percentage of the gait cycle time; ON oral (dopaminergic) medications and SCS turned on for more than 1 hour before assessment; Pre-op: Pre-operative (baseline) measurements; PD: Parkinson disease; SD: standard deviation of population; Single support % is single support time expressed as a percentage of the gait cycle time; Swing % is swing time presented as a percentage of the gait cycle time.

4.3.2 Clinical rating outcomes up to 6-months

All participants experienced a significant improvement in clinical rating outcomes except for non-statistically significant changes in PDQ-8 and FOG-Q over the SCS intervention course (Figure 4-2). A declining trend in mean FOG-Q scores was reported demonstrating a mean change of 26.8% at week 24 (6-months; 15.0±3.9; median=15.0; p=0.06) compared to pre-operative (20.5±1.0; median=20.0). By week 24, 2 of the 5 participants improved in their worst state (from needing assistance to walking almost normally), 3 of the 5 participants reported ADLs were moderately, rather than severely, affected by gait dysfunction, and 4 of the 5 participants reported FOG occurred less frequently: often rather than always (pre-operative).

Significant improvement (X^2_8=23.317; p=0.003) in all participants' confidence to complete daily activities (ABC), especially around and outside the house, occurred at week 6 (median=69.7%; p=0.02) and improvements were maintained following week 10 resulting in a mean improvement by 71.4% at week 24 (65.0±22.2%; median=72.5%; p=0.002) compared to pre-operative (Figure 4-2). By the end of the study, participant#2 reported discontinuation of using a wheelchair and solely uses a walker.

Mean total UPDRS motor scores while on-medication/on-stimulation were significantly improved (X^2_8=22.949; p=0.003) at weeks 16 and 24 by 32.3% (21.8±10.8; median=16; p=0.03) and 33.5% (21.4±10.8; median=17; p=0.02) compared to pre-operative (Table 4-1 and Figure 4-2). UPDRS items 23 to 25 scores (assess upper limb bradykinesia) for all participants were reduced from mean 7.4±5.6 (median=6.0) at pre-operative to 4.8±4.0 (median=4.0) at week 24 (6-months after SCS).

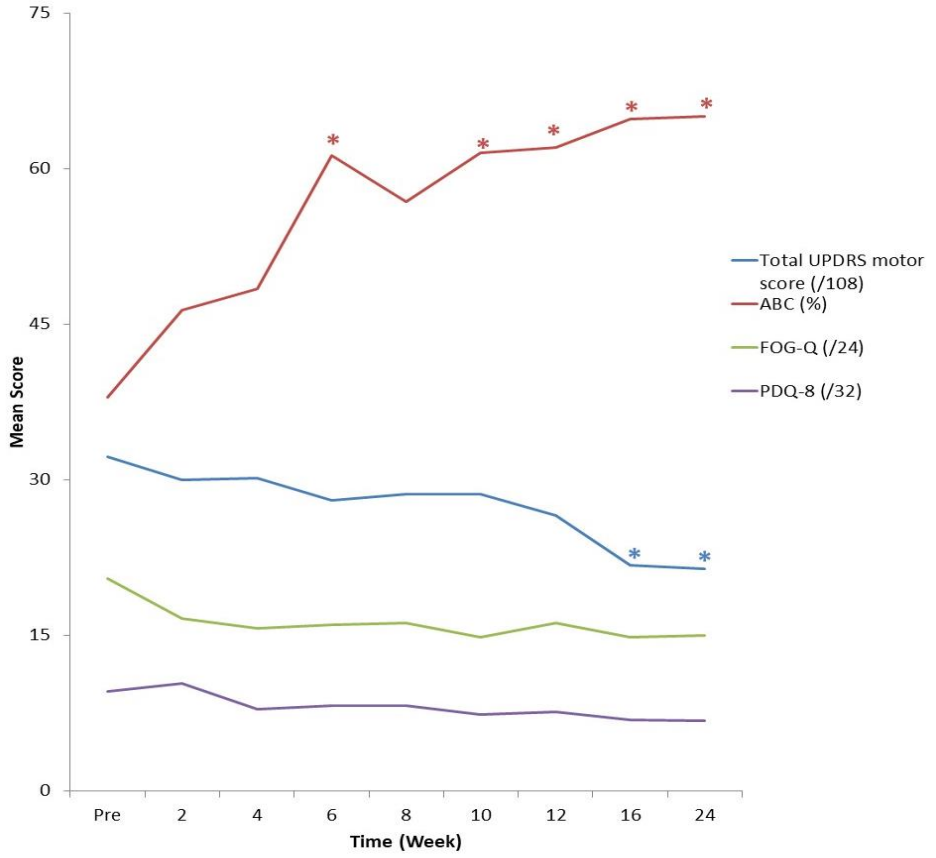

Figure 4-2. Improvements in clinical rating scales from preoperative to 6 months after SCS use.

Red line, mean clinical rating scores for ABC; blue line, total UPDRS motor items while participants were on-medication/on-stim (+LD/+SCS); green line, FOG-Q; purple line, PDQ-8. Color-coordinated asterisks represent statistically significant differences in clinical outcomes compared with preoperative ("pre").

4.3.3 Gait analysis evaluation of SCS for gait dysfunction at 1-4 and 6-months follow-up

Mean z-scores allow quantitative evaluation of which SCS combination(s) best improved gait per participant (Figure 4-3). Frequency 130Hz combined with 200µs and 300µs was not tolerated by participant #1; program 300µs/130Hz was not tolerated by participant #2 due to excessive feeling of imbalance and increased freezing and thus these settings were not assessed. Participants#1 and #5 improved the most (highest positive and negative mean z-scores) set to 400µs/60Hz. Participant#2 demonstrated best gait on SCS setting 300µs/30Hz, whereas participant#3 improved the most on setting 300µs/130Hz.

Participant#4 demonstrated similar gait improvements on 300μs/30Hz, 300μs/130Hz and 400μs/130Hz and results from setting 400μs/130Hz were plotted in Figure 4-3. There were no defining trends within or between subjects when correlating changes in pulse width/frequency to gait outcome measures (e.g. increasing frequency from 30 to 60Hz demonstrated both increases and decreases in mean z-score values).

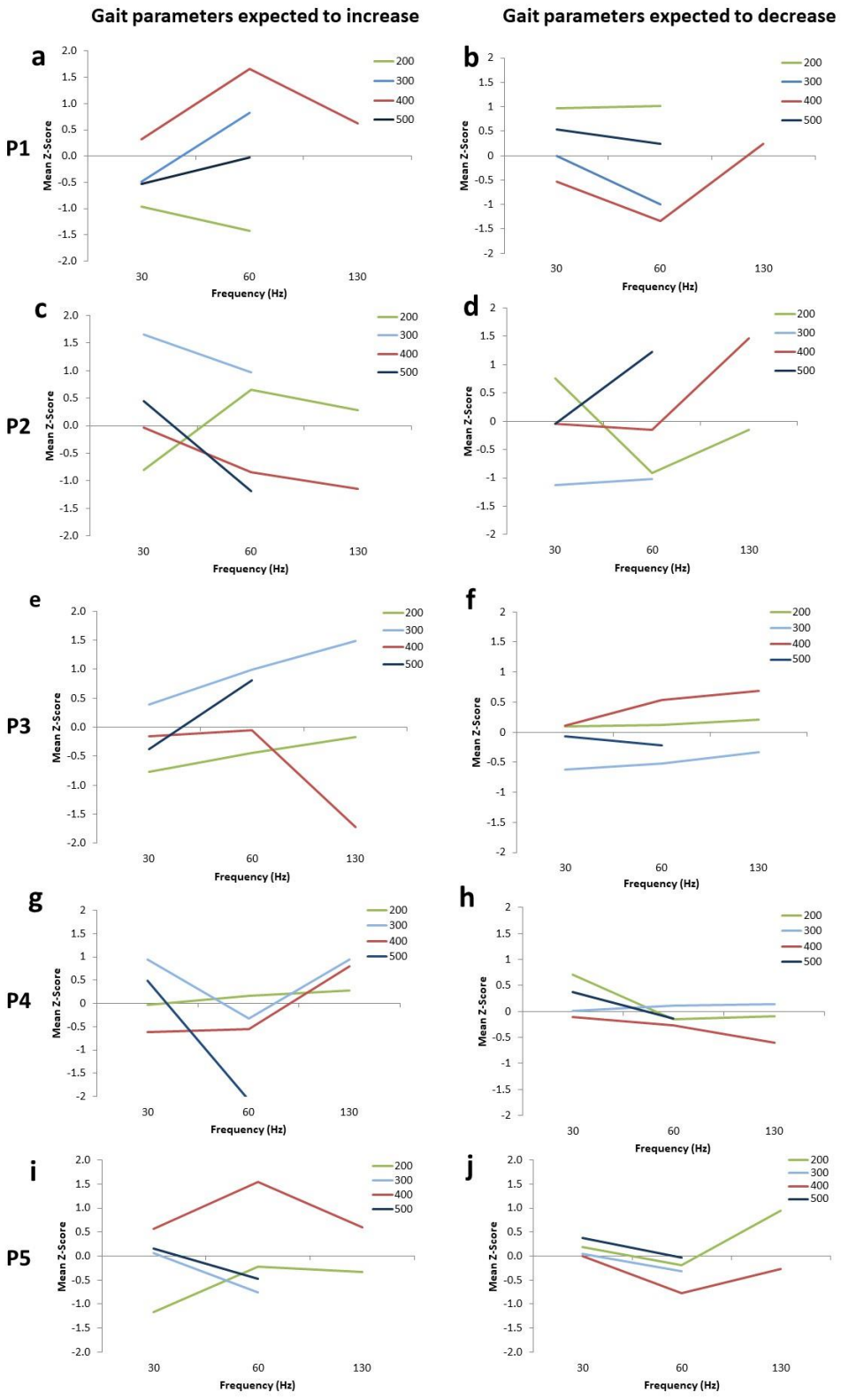
Gait parameters expected to increase
Gait parameters expected to decrease
a
b
c
d
e
f
g
h
i
j
P1
P2
P3
P4
P5
Mean Z-Score
Frequency (Hz)
30
60
130
200
300
400
500

Figure 4-3. Mean z scores plotted for gait measures expected to increase after SCS (left column) and for gait measures expected to decrease after SCS (right column) for each participant presented per row (P1 to P5).

The z scores for gait variables expected to increase were step length, stride velocity, swing %, and single support %, and these z scores were averaged for each SCS combination of pulse width and frequency tested per participant. The z scores expected to decrease were stride width, step time, gait cycle time, stance %, and double support %. The results shown are related to the best SCS setting tested between 1 and 4 months and at 6 months: participant 1, 400 ls/60 Hz; participant 2, 300 ls/30 Hz; participant 3, 300 ls/130 Hz; participant 4, 400 ls/130 Hz; participant 5, 400 ls/60 Hz. Each plotted line represents pulse width of SCS (green line, 200 microseconds; light blue line, 300 microseconds; red line, 400 microseconds; dark blue line, 500 microseconds) versus frequency tested (ranging from 30, 60, and 130 Hz). P1, participant 1; P2, participant 2; etc.

Improvements in spatiotemporal parameters were achieved, while participants remained on-medications, between 1-4-months (each participant tested on their best setting based on mean z-scores), and at 6-months with the SCS device turned on to each participant's best setting for 1-hr before testing compared to pre-operative measurements (Figure 4-4a).

Mean stride velocity statistically significantly improved (X^2_3=9.960; p=0.02) while on-stimulation by 54.4% (87.6±43.4cm/sec; median=103.6; p=0.01) between 1-4-months and by 29.4% (73.4±41.3cm/sec; median=84.0; p=0.05) while on-stimulation at 6-months compared to pre-operative (56.7±47.4cm/sec; median=63.2). Mean step length improved (X^2_3=5.160; p=0.16) by 44.4% between 1-4-months which was maintained at 6-months by 38.9% (38.3±13.8cm; median=43.8), compared to pre-operative (27.6±16.1cm; median=28.6). Percent swing (X^2_3=7.800; p=0.05) and percent single support (X^2_3=4.347; p=0.2) produced similar increasing trends by a mean change of 27.4% and 21.0% between 1-4-months and at 6-months, respectively, compared to pre-operative. Double support was reduced (X^2_3=3.000; p=0.4) by a mean change of 23.8% at 6-months. Slight improvements in step time and stance phase over the study course.

Substantial asymmetry of spatiotemporal parameters observed pre-operatively was reduced between 1-4-months after SCS, and while on-stimulation at 6-months (Figure 4-4b). Asymmetry for step time (X^2_3=2.265; p=0.5) and stride velocity (X^2_3=4.304; p=0.23)

improved by a mean change of 76.9% (5.0±3.1%; median=5.0) and 75.2% (1.8±1.9%; median=1.6), respectively at 6-months compared to pre-operative (21.8±17.5%; median=12.0 and 17.2±20.8%; median=7.2, respectively).

Variability of mean step length improved (X^2_3=6.120; p=0.1) by 42.5% (13.9±4.3%; median=15.2) between 1-4-months and was maintained at 6-months compared to pre-operative (24.2±5.7%; median=25.3), displayed in Figure 4-4c. Mean variability of stride velocity was improved (X^2_3=5.308; p=0.15) by 39.6% (16.9±10.4%; median=11.9) between 1-4-months and by 42.9% (16.0±6.5%;17.9) at 6-month compared to pre-operative (28.0±17.3%; median=26.9).

Mean number of FOG episodes (FOGs) captured over two trials across the gait-mat was significantly reduced (X^2_3=11.775; p=0.008) by a mean change of 93.2% from 14.8±15.4 FOGs (median=8.0) at pre-operative to 1.4±3.1 FOGs (median=0; p=0.01) between 1-4-months, and to 0.2±1.7 (median=0.0; p=0.007) FOGs on-stimulation at 6-months (Figure 4-4d). Mean duration of FOGs were reduced (X^2_3=6.220; p=0.1) by 85.5% from 4.1±1.8sec at pre-operative to 0.6±1.3sec at 1-4-months and by 38.5% (4.7±3.7sec) at 6-months. Mean timed-up (sit-to-stand) was significantly improved (X^2_3=8.385; p=0.04) by 50.3% (3.8±2.5sec; median=2.6; p=0.006) at 6-months compared to pre-operative (7.6±6.0sec; median=5.9), illustrated in Figure 4-4e.

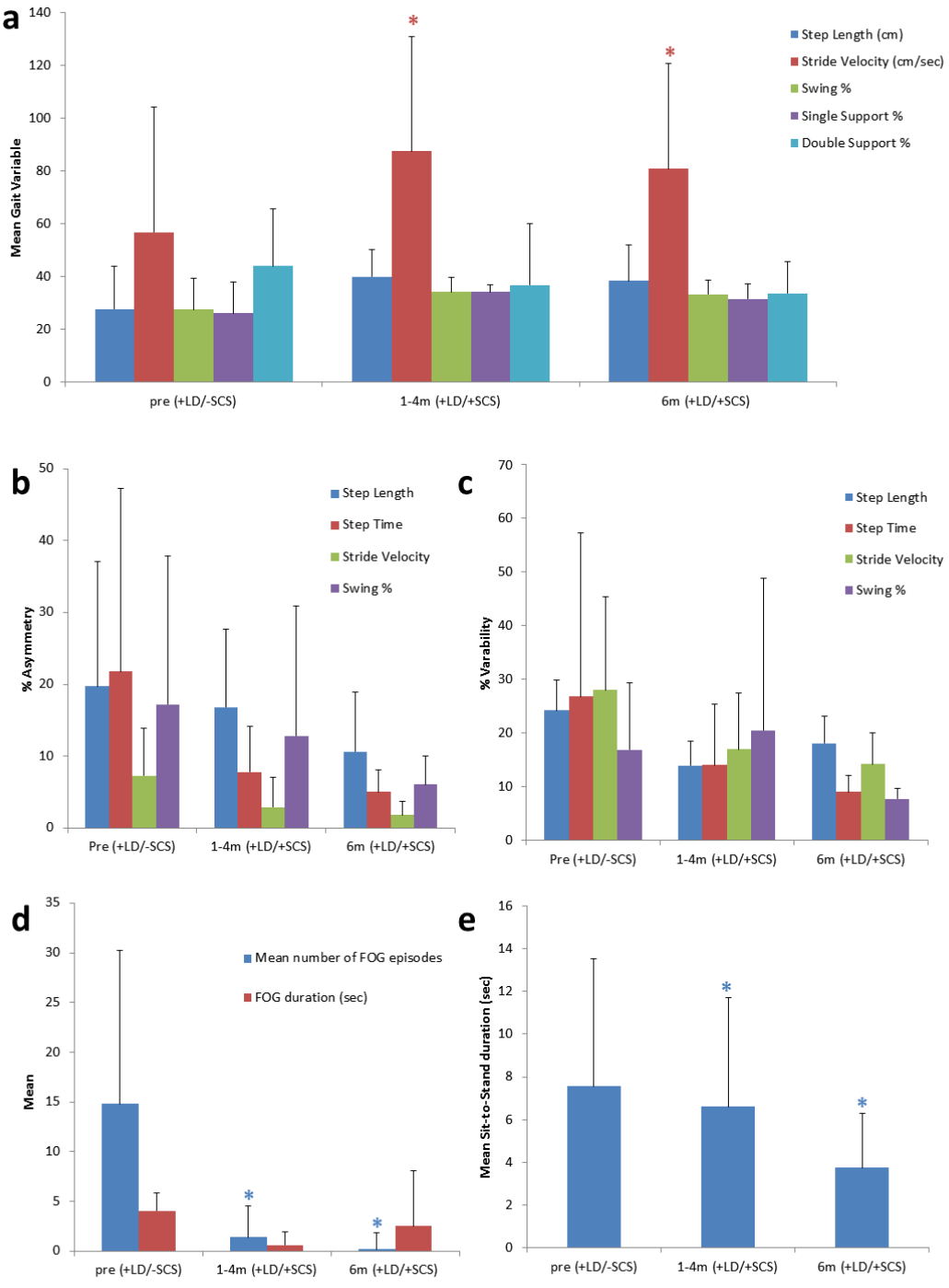

Figure 4-4. Participants improved in overall gait following 6 months of SCS intervention.

(a) Mean spatiotemporal gait measures of step length (blue), stride velocity (red), swing % phase (green), single support % phase (purple), and double support % phase (light blue) with standard deviations of all participants; (b) mean asymmetry and (c) mean

variability, represented by percentage of gait measures: step length (blue), step time (red), stride velocity (green), and swing % phase (purple) with standard deviations of all participants; (d) mean number of FOG episodes and duration per episode; and (e) mean duration of sit-to-stand with standard deviations of all participants illustrated. +LD/+SCS, on-mediation/on-stimulation, 1-4 m, 1 to 4 months after SCS; device set to each participant's best setting; 6m, 6 months after SCS. Asterisks represent statistical significance compared with preoperative (pre).

4.3.4 Long-term (3-year) update

Participants (N=4) continued to demonstrate a reduction in the number of FOG episodes during straight walking at 3-years compared to pre-SCS, and two participants did not freeze during the assessment (Table 4-3). Mean duration per FOG episode increased in two participants by 36.5%. Mean stride velocity remained increased in participant #2 by 202.4%, remained unchanged in participant #3 and was reduced in two participants by 26.3% at 3-years. Mean step length, swing phase and single support phase was increased by a mean 14.5% at 3-years. Step time variability was reduced by 34.9% in three participants. Mean step length, stride velocity and swing phase variability increased by a mean 29.9% in two participants and was unchanged in two participants.

Mean UPDRS-III score was reduced by 6.2% (Δ1.8 UPDRS points) at 3-years. UPDRS-III sub-scores for rigidity and axial symptoms were improved by 23.1% (Δ1.5 points) and 20.4% (Δ1.8 points), respectively, however bradykinesia sub-scores increased by 9.4% (Δ0.8 points). Mean FOG-Q and PDQ-8 scores were reduced by 18.3% (Δ3.8 points) and by 21.9% (Δ2.1 points), respectively, and ABC scale did not change.

Three participants required a battery replacement (Boston Scientific Precision Spectra). Two participants (#2,4) switched between their two best SCS settings as previously tested within the 6-month study time-point. Daily levodopa dose decreased for two participants by 250 and 400 mg due to bothersome levodopa-induced dyskinesias; dosages for adjunctive anti-parkinsonian medication were not adjusted.

Table 4-3. Participant demographics reported at the 3-year follow-up and their clinical scale scores and gait measures (mean and standard deviations) at pre-SCS and at 3-years of SCS use.

	Patient ID	1	2	3	4	Mean	SD
Pre-SCS / 3-year follow-up	Age	66	81	67	69	70.75	6.9
	Years with PD	17	21	18	11	16.75	4.2
	SCS setting (PW (μs)/Freq (Hz))	400/ 60	300/ 60	300/ 130	300/ 30		
	DLD (mg)	1500 / 1500	2000 / 2000	1000 / 750	900 / 500	1330 / 1262.5	441.0 / 619.3
	Total UPDRS-III Score (/108)[a]	23 / 22	29 / 25	21 / 18	39 / 40	28.0 / 26.2	8.1 / 9.6
	Rigidity (item#: 22) sub-scores (/20)	6 / 3	5 / 3	5 / 3	10 / 11	6.5 / 5	2.6 / 4.0
	Bradykinesia (items#: 23-26) sub-scores (/32)	5 / 8	5 / 7	7 / 4	15 / 16	8 / 8.7	4.9 / 5.1
	Axial (items#: 27-31) sub-scores (/20)	6 / 6	14 / 11	6 / 6	10 / 4	9 / 6.7	3.6 / 3.0
	ABC (%)	36 / 65.6	14.3 / 10.0	54 / 46.9	62 / 46.3	41.6 / 42.2	21.2 / 23.3
	FOG-Q (/24)	19 / 17	22 / 20	20 / 13	21 / 17	20.5 / 16.8	1.3 / 2.9
	PDQ-8 (/32)	10 / 8	10 / 3	11 / 14	3 / 5	8.5 / 7.5	3.7 / 4.8
	Number of FOGs	8 / 2	36 / 2	2 / 0	2 / 0	12 / 1.0	16.3 / 1.1
	Duration per FOG	5.2 / 7.9	5.2 / 6.3	3.4 / 0	1.1 / 0	3.7 / 3.5	2.0 / 4.1
	Stride velocity (cm/s)	63.2 / 48.4	8.4 / 25.4	114.2 / 114.0	88.9 / 63.0	68.6 / 62.7	45.2 / 37.5
	Step length (cm)	28.6 / 21.9	8.3 / 18.6	51.4 / 47.0	31.3 / 36.3	29.9 / 31.0	17.6 / 13.2
	Gait asymmetry (%)[b]	9.3 / 5.0	19.6 / 10.2	2.4 / 6.5	2.0 / 2.9	8.3 / 6.3	11.1 / 6.3
	Step time variability (%)	10.6 / 15.2	27.9 / 8.9	4.3 / 4.0	12.1 / 8.5	13.7 / 9.1	10.0 / 4.6

Abbreviations: ABC: Activities-specific balance confidence scale; DLD: Daily levodopa dose; FOG: Freezing of gait; FOG-Q: Freezing of gait questionnaire; Freq: frequency; MDS-UPDRS-

III: Unified Parkinson's Disease Rating scale motor scores; PDQ-8: Parkinson's disease questionnaire PW: Pulse width; SCS: Spinal cord stimulation.
[a] UPDRS-III scores represent participants rated while ON-levodopa (~1 hour after dose intake)
[b] Mean of stride velocity and swing phase asymmetry values

4.4 Discussion

This exploratory, open-label, pilot study investigated the therapeutic efficacy of mid-thoracic epidural SCS at different stimulation parameter combinations in five PD participants with significant gait dysfunction and FOG. To mimic previous clinical cases,[16,18-21] a similar range of pulse width and frequency combinations was tested in each of the 5 PD participants to determine which SCS settings best improved gait for each participant by using objective gait technology to measure changes in spatiotemporal gait parameters and FOG episodes over a 1-4 and 6-months follow-up duration. Overall, significant reduction in the number of FOG episodes was seen and sustained improvements in gait measurements were observed.

This is the first study to use objective gait technology to assess the efficacy of SCS for gait in advanced PD patients. As stride velocity, step length and swing phase are known to be reduced in PD,[22] this study reported improvements in stride velocity, step length and single and double support phases at the 1-4-months and 6-months follow-ups (Figure 4-4a). A mean 44.4% increase in step length was observed at 1-4 which was maintained at 38.8% improvement at the 6-month follow-up compared to pre-operative. A mean 54.4% and 42.4% increase in stride velocity was observed at 1-4 and 6-months, respectively. Single support % phase was improved by 30.4% and 20.8% at 1-4 and 6-months follow-up, respectively.

The number of FOG episodes captured on the gait-mat was significantly reduced after SCS at all time-points (Figure 4-4d). Shown in Figure 4e, improvement in timed-up duration (from sit to stand) by a mean change of 50.3% at 6-months was comparable to past studies reporting improvements by 63% at 6-months in previously DBS treated PD patients,[21] and by 27.8% and 35.3% at 3-months[17] and 24-months,[18] respectively in PD patients with pre-existing pain. Improved timed-up duration (time in seconds for a participant to arise from a chair to a standing position) suggests improved rate of force

production, enhanced postural stability and balance and reduction of general body bradykinesia.[31,32]

Reduction in asymmetry and variability of step length, step time, stride velocity and swing % phase over 6-month period of SCS use (Figure 4-4b). PD gait is known to be less rhythmic, asymmetric and lacking bilateral coordination due to the hypodopaminergic basal ganglia state, characteristics which are generally improved by administration of levodopa.[23] Observing reduced asymmetry and variability in gait suggests SCS plays a similar role to levodopa medication by improving bilateral gait coordination although the precise mechanism of SCS remains unclear. Previous non-human primate PD model and rodent PD model studies have proposed that SCS may suppress the aberrant beta-frequency synchronous cortico-striatal oscillations thereby restoring neural activity in the primary cortex and dorsolateral striatum to a state observed prior to spontaneous locomotion.[13-15,20]

Significant 32.3% and 33.5% improvements in mean UPDRS motor score were seen while on-stimulation at 4-months and 6-months after SCS surgery. These results were comparable to improvements previously reported in 18 patients and however the de Souza study including 4 PD participants previously treated with DBS demonstrated a greater 54.5% reduction in UPDRS motor score at 6-months.[18,20,21] The scores of ADLs were significantly improved by a mean change of 67.0% after 2.5-months continuing to 6-months, where past studies demonstrated only a 21% improvement in PD patients with chronic pain.[18] This study reported PDQ-8 and FOG-Q scores improved by 29.2% and 26.8%, respectively, at 6-months. However, de Souza *et al* demonstrated a significant 44.7% and 56.4% improvement in PDQ-39 and FOG-Q scores, respectively, at 6-months in STN-DBS patients.[21]

This study's mean baseline participant demographics including total UPDRS motor score (33.0 and 32.2 points), FOG-Q (17.7 and 20.5 points), disease duration (21.2 and 14.0 years), and mainly a small cohort of male participants, are comparable to de Souza and colleagues study from 2016, respectively.[21] In addition, the change in these clinical scores reported at 6-months is also comparable, as stated above. De Souza *et al* reported using

paddle electrodes totaling 32 contacts placed in the upper thoracic region where our study utilized cylindrical electrodes totaling 16 contacts placed in the mid thoracic area. Both studies tested participants under suprathreshold stimulation intensities as paresthesia sensations were the same regardless of high/low frequencies. De Souza *et al* concluded that a low pulse width (90μs) and a high frequency (300Hz) SCS setting combination produced the greatest effect for gait intervention and that a low frequency (60Hz) combined with a low pulse width (90μs) was largely ineffective.[21] Our study expands the knowledge regarding stimulating parameters demonstrating that high pulse width (300-400μs) combined with lower frequencies (30-130Hz) also produce similar efficacious gait improvements.

The study's gait analysis results were compared with control PD data from the literature. After 6-months of SCS, step length became comparable to PD patients on-medication without gait difficulties who had the disease for a shorter period of time; these PD patients produced a mean step length of 51.9cm.[33] Additionally, median stride velocity increased from 63.2cm/sec pre-operatively to 84.0cm/sec at 6-months after SCS, which is comparable to PD patients without significant gait dysfunction producing velocities of 93.5cm/sec.[33] SCS use reduced mean step time to 0.49sec while on-stimulation after 6-months of SCS which is comparable to age-matched healthy controls (0.54sec) and superior to PD patients without freezing or postural instability (0.57sec).[33]

The key longitudinal outcome of SCS was the reduction in FOG frequency in all participants and reflected in the FOG-Q; participant #2, originally wheelchair-bound in the home, now uses a walker daily. Temporal gait asymmetry improved indicating SCS may have a greater influence on the rhythmicity of gait.[34] Severity of rigidity and axial features (UPDRS-III) was reduced while two participants reduced their daily levodopa intake, suggestive of SCS effect on axial systems. The most optimal SCS parameters include long pulse widths and lower frequencies.[35]

Recent literature suggests SCS mediates its gait effects by modulating ascending afferents and long propriospinal fibers located next to the gray matter of the dorsal horn that

directly reach the brainstem, cerebellum, basal ganglia, and cortical areas such as the supplemental motor area.[35,36]

As this is an open-label study and stimulation intensity was subjectively reported by the participant, a placebo effect of stimulation-induced paresthesia could have been possible. To address this issue to some extent the participants were blinded to which SCS program was delivered and were given stimulation to result in a medium suprathreshold degree of paresthesia at all settings. Gait assessments were carried out at the same time of day for all visits to exclude wearing off medication states. As the study design focused on exploring different setting combinations, there are several limitations to the study. No repetition of SCS programs on separate days to avoid fatigue factor was done. Testing of SCS programs was done over 4 months which does not disregard time as a variable, as changes in gait measures regardless of SCS setting could be different between 1 and 4 months. Since the gait tasks were simply walking across the mat with no cognitive or other loads, learning effect on gait improvement was unlikely a reason for sustained effect of SCS. This is an exploratory study primarily demonstrating whether SCS could improve gait and assess potential individualization of the effects of specific stimulation pulse widths and frequencies on gait. Additionally, the high variability of the data was based on the baseline differences in gait symptomologies of the small cohort of patients (recruited participants with 10+ years of disease and ON-FOG presentation). Further studies will control for any SCS modulation by repeat testing of different SCS programs within well specified time periods. For example, acute effects of SCS could be examined by switching on the device only during a series of initial testing visits and left off when the patient returns home. The change in off/on medication response was not an objective of this study and thus was not explored as the study focus remained on understanding which variables of gait improve with SCS. Future studies will include off/on medication and off/on stimulation states at repeated measures over a longer period to investigate SCS plasticity and to address important questions about observing permanent changes in medication response, and improvements in other PD cardinal symptoms, such as bradykinesia.

This is the only study to date to quantitatively measure spatiotemporal parameter changes with SCS. The initial evidence up to 6-months demonstrates 300-400μs and frequencies 30-130Hz may be safe and possibly effective for reducing FOG frequency and improving gait dysfunction in advanced PD patients. This study also provided valuable insight to the longitudinal effects of SCS for FOG reduction, despite the limitations of a small sample size, open-label nature, and no falls or turning/initiation FOG reporting. The findings of this study require replication in a larger study cohort with significant dopaminergic-resistant FOG.

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Chapter 5

5 General discussion and conclusions

The research described in this thesis demonstrated the effect of SCS therapy for alleviating dopaminergic-resistant FOG and gait impairments in advanced PD participants and those with a form of atypical parkinsonism, PSP-RS. Objective gait and FOG assessments were conducted to enable individualization of SCS programming by determining which gait features and types of FOG (straight walking or 360-degree turning on the spot) respond the best to which SCS parameter combination for each participant. This method of neuromodulation programming contrasts past SCS for gait treatment studies as most small pilot studies used the same SCS program for all patients or reported a range of parameters used (see Table 1-1). It was observed that optimal SCS programming should be conducted within the first month post-surgery or prior to a patient commencing use of SCS daily to minimize the time variable, as performed in **Chapters 2 and 3**. Programming SCS while participants were using the device at home would require new baseline measurements at each programming visit, which was a limitation described in **Chapter 4**. Tonic, mid-thoracic SCS significantly reduced the frequency of FOG episodes while walking and increased spatiotemporal gait parameters including step length, and stride velocity while PD participants were ON-levodopa (**Chapter 4**). These gait and FOG improvements were long-lasting (up to 3-years) minimizing the likelihood of placebo effects, which can be difficult to blind participants to as paresthesias are felt throughout their lower limbs. However, placebo effect was minimized as all participants were blinded to the different tonic SCS settings tested and there were no defining trends within or between subjects when correlating changes in pulse width/frequency to gait outcome. Optimal SCS programs consisted of parameters with low frequencies combined with high pulse widths that supports the notion that the pattern of stimulation is important. A newer method of SCS programming that does not require suprathreshold paresthesias and that could be used to blind patients is burst stimulation. However, the effectiveness of burst stimulation for treating dopaminergic-resistant FOG in PD should be considered in larger future studies.

SCS therapy was explored in PSP-RS participants who characteristically have early onset of FOG and gait dysfunction with a limited to no response to dopaminergic replacement therapy. Lesions within the basal ganglia and cholinergic depletion in the PPN, which is central to receiving and regulating somatosensory information from the thalamus and cerebral cortex to locomotor generators in the spinal cord for gait execution, are pathological criteria of PSP-RS. **Chapter 3** demonstrated that all PSP-RS participants found improvements in FOG and gait measures with up to 6-months of therapy. Thereby, SCS may modulate non-dopaminergic pathways within the cortical-striatal-pallidal-PPN-pontomedullary reticular nuclei-spinal cord network,[1] such as stimulating or reactivating the cholinergic pathway required to overcome the pathological cause of PSP-RS symptomologies.[2] Thus, SCS may improve FOG and gait in a similar fashion for PD patients with dopaminergic-resistant axial symptoms.[3,4] However, 2 of the 3 PSP-RS participants had a loss of SCS response due to the fast progression of their symptoms, indicating that SCS may not produce a neuroprotective response, unlike the effects observed in studies with pre-clinical PD models.[5,6]

The theorized underlying mechanism of FOG involves multiple network systems such as cortical areas responsible for planning and execution of motor control (e.g. SMA, anterior cingulate cortex, dlFPC, pre-motor cortex, and orbitofrontal cortex). The disruption of cortical connectivity may further modulate striatal, STN, and pallidal output activities, as already observed in the parkinsonian state, and affect downstream networks.[7] The output activity of the PPN, a locomotor integration centre, and ponto-medullary is further reduced and affects feedback input originating from the peripheries and modulation of spinal central pattern generation centers (CPG). As the PPN is mainly composed of cholinergic neurons and is central to models of FOG,[8] dopaminergic replacement therapies lack effectiveness to alleviate FOG and axial disability due to their inability to modulate pathways involving the PPN.[9] Increasing PPN activity by targeting the PPN and GPi using DBS[4] has been associated with improvements in gait speed and alleviation of FOG.[10] **Chapter 2** of this thesis described the possible involvement of cortical and subcortical mechanisms accessible by SCS to alleviate FOG in PD participants. Modulation of the primary motor cortical areas representing the lower limbs (Cz), SMA (FC1, FC2), pre-frontal (F3, F4), and somatosensory (CPz, CP1, CP2) cortical areas were

significantly associated with the reduction of FOG following SCS therapy while participants were in the OFF-levodopa state. Thus, it is possible that impaired cortical and subcortical circuits contributing to FOG and to the reduced perception of sensory stimuli and execution of movement are more sensitive to SCS. SCS may change the activity of cortical input to the striatum reducing activity of basal ganglia inhibitory (GPi/SNr) efferents to the PPN, thereby possibly increasing PPN activity. The research described in **Chapter 2** also demonstrated that improvements in appendicular (upper limb) visual-motor performance by SCS was associated with changes in striatal dopaminergic innervation, but no relationship was observed between FOG and striatal dopaminergic innervation. This further supports the view that SCS modulates dopaminergic networks related with appendicular motor features and that axial motor features are related with non-dopaminergic pathways.[9]

The results of this thesis are promising given the significant unmet need for an effective FOG therapy, as there are currently no effective interventions for dopaminergic-resistant FOG, nor any disease modifying or neuroprotective strategies for parkinsonian syndromes. Further studies including a larger cohort of patients with dopaminergic-resistant FOG, exploration of the effect of different types of SCS programming (burst versus tonic stimulation) for FOG, and the use of proprioception (passive motion) assessments are required to increase the value of these promising therapeutic effects of SCS in PD and atypical parkinsonism. Advancements in wearable and objective technology over the past decade may be applied to monitor the quality of mobility for daily activities of living, to enable accurate assessment (reduced subjectivity and variability of clinical ratings) and to individualize programming of neuromodulation interventions.

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Appendices

Appendix A: Ethics Approvals

Western Research

Research Ethics

Western University Health Science Research Ethics Board
HSREB Full Board Initial Approval Notice

Principal Investigator: Dr. Mandar Jog
Department & Institution: Schulich School of Medicine and Dentistry\Clinical Neurological Sciences,London Health Sciences Centre

Review Type: Full Board
HSREB File Number: 107451
Study Title: Thoracic dorsal spinal cord stimulation for the treatment of gait and balance impairments in Parkinson disease

HSREB Initial Approval Date: January 22, 2016
HSREB Expiry Date: January 22, 2017

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Data Collection Form/Case Report Form	quality of life	2015/11/16
Data Collection Form/Case Report Form	global impression of change scale	2015/11/16
Data Collection Form/Case Report Form	Dyskinesia scale	2015/11/16
Data Collection Form/Case Report Form	UPDRS scale	2015/11/16
Data Collection Form/Case Report Form	berg scale	2015/11/16
Revised Letter of Information & Consent		2016/01/20
Revised Western University Protocol		2016/01/20

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

[redacted]
Ethics Officer, on behalf of Dr. Marcelo Kremenchutzky, HSREB Vice Chair

Ethics Officer to Contact for Further Information: Erika Basile ___ Nicole Kaniki ___ Grace Kelly ___ Mina Mekhail ___ Vikki Tran ___

This is an official document. Please retain the original in your files.

Western University, Research, Support Services Bldg., Rm. 5150
London, ON, Canada N6G 1G9 T [redacted] www.uwo.ca/research/ethics

Western Research

Date: 8 November 2018

To: Mandar Jog

Project ID: 107451

Study Title: Thoracic dorsal spinal cord stimulation for the treatment of gait and balance impairments in Parkinson disease

Application Type: HSREB Amendment Form

Review Type: Delegated

Full Board Reporting Date: 20November2018

Date Approval Issued: 08/Nov/2018 12:09

REB Approval Expiry Date: 22/Jan/2019

Dear Mandar Jog ,

The Western University Health Sciences Research Ethics Board (HSREB) has reviewed and approved the WREM application form for the amendment, as of the date noted above.

Documents Approved:

Document Name	Document Type	Document Date	Document Version
107451 - LOI SCS - 3.1_clean	Consent Form	07/Nov/2018	3.1
107451 - SCS ethics - 3.1_clean	Protocol	07/Nov/2018	3.1

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Nicola Geoghegan-Morphet, Ethics Officer on behalf of Dr. Philip Jones, HSREB Vice-Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Western Research

Date: 8 May 2019

To: Mandar Jog

Project ID: 107451

Study Title: Thoracic dorsal spinal cord stimulation for the treatment of gait and balance impairments in Parkinson disease

Application Type: HSREB Amendment Form

Review Type: Delegated

Full Board Reporting Date: 21May2019

Date Approval Issued: 08/May/2019 10:33

REB Approval Expiry Date: 22/Jan/2020

Dear Mandar Jog ,

The Western University Health Sciences Research Ethics Board (HSREB) has reviewed and approved the WREM application form for the amendment, as of the date noted above.

Documents Approved:

Document Name	Document Type	Document Date	Document Version
107451 - LOI SCS - 4.0	Consent Form	04/Apr/2019	4.0
107451 - SCS ethics - 4.0	Protocol	05/Apr/2019	4.0

Documents Acknowledged:

Document Name	Document Type	Document Date	Document Version
107451 SCS 4.0 revisions letter April-5-2019	Summary of Changes	05/Apr/2019	4.0

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Nicola Geoghegan-Morphet, Ethics Officer on behalf of Dr. Joseph Gilbert, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Western Research

Date: 25 October 2019

To: Mandar Jog

Project ID: 107451

Study Title: Thoracic dorsal spinal cord stimulation for the treatment of gait and balance impairments in Parkinson disease

Application Type: HSREB Amendment Form

Review Type: Delegated

Full Board Reporting Date: 05Nov2019

Date Approval Issued: 25/Oct/2019 09:21

REB Approval Expiry Date: 22/Jan/2020

Dear Mandar Jog ,

The Western University Health Sciences Research Ethics Board (HSREB) has reviewed and approved the WREM application form for the amendment, as of the date noted above.

Documents Approved:

Document Name	Document Type	Document Date	Document Version
107451 - LOI SCS - 5.0	Consent Form	18/Oct/2019	5.0
107451 - LOI SCS-DATscan- 5.0	Consent Form-optional	23/Oct/2019	5.0
107451 - SCS ethics - 5.0	Protocol	22/Oct/2019	5.0

Documents Acknowledged:

Document Name	Document Type	Document Date	Document Version
107451 SCS 5.0 revisions letter Oct-23-2019	Summary of Changes	23/Oct/2019	5.0

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Nicola Geoghegan-Morphet, Ethics Officer on behalf of Dr. Philip Jones, HSREB Vice-Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Appendix B: Letter of Information and Consent (most recent version)

Movement Disorders Program
339 Windermere Rd, A10-026
London, Ontario, Canada N6A 5A5
www.londonmdc.ca

Letter of Information and Consent

Study Title: Spinal cord stimulation for the treatment of gait and balance impairments in Parkinson disease

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

Introduction

We are inviting you to participate in our research project designed to assess the short-term and long-term effects of spinal cord stimulation (SCS) on mobility changes such as gait and posture. The use of SCS for treating abnormal mobility is entirely a clinical decision by your movement disorders neurologist (Dr. Mandar Jog) and by your neurosurgeon (Dr. Andrew Parrent). Recent studies have emerged showing the promise of SCS as a treatment for gait disorders, rigidity, and postural instability in parkinsonian patients. SCS is minimally-invasive and is routinely used to treat chronic pain. SCS consists of implanted electrodes on your spinal cord that can deliver electrical pulses. We hope to understand the effects of SCS on gait dysfunction and in the central nervous system pathways in parkinsonian syndromes by having you perform simple sitting and walking tasks and to undergo neurophysiological assessments. Your best SCS setting that provides you with the best possible alleviation of your symptoms will be determined within the first month following SCS surgery. This will be achieved by measuring your mobility in the laboratory over a series of defined programming SCS settings. We will be monitoring improvements in your mobility and changes in your central nervous system at 3-months, 6-months, and 12-months of SCS use. In addition, at 2, 3 and 4 years of using your SCS device at-home, we will reassess your mobility at each of these time-points.

Nature of the research project and tasks involved

We are looking to investigate short and long-term effects of SCS in a total of **50 persons diagnosed with parkinsonian syndrome** with significant gait difficulties who are unresponsive to your current medical management. You will be invited to participate from the Movement Disorders Clinic at London Health Sciences Centre (LHSC). You will be required to attend two study visits to capture baseline mobility and

neurophysiological measurements one-four weeks before your planned SCS surgery. Following your surgery, you will attend four study visits in the first month to establish which SCS setting(s) best improves your mobility. Starting one month following surgery, you will attend nine study visits over the course of 12 months to monitor your mobility and nervous system activity to fully understand the long-term effect of SCS. Thus, a total of 14 study visits over a 15-month duration will be conducted.

You will be required to bring your medications with you to each visit so that you may take them in accordance with your routine scheduled times. A movement disorders neurologist will screen for inclusion and exclusion criteria to ensure you meet the study's requirements. You are eligible for the study based on the following:
1) A diagnosis of clinically certain Parkinson's disease or a parkinsonian syndrome
2) You have severe gait disturbances, postural instability and/or freezing of gait, due to your PD
3) A history of frequent falls, gait and balance dysfunction and postural instability
4) You are stable (medically optimized) on your current treatment plan by the movement disorders neurologist (Dr. Jog) for at least 3 months before study recruitment
5) You are able to attend all clinic visits and assessments
6) You are able to perform walking tasks (under close supervision)
7) You have no dementia or psychiatric abnormalities on neuropsychological testing
8) You do not have secondary causes for your gait and mobility dysfunction, such as cerebrovascular disease (condition which affects blood circulation to the brain), normal pressure hydrocephalus (abnormal buildup of cerebrospinal fluid), peripheral neuropathy (peripheral nerve damage), and severe degenerative lower limb or back disease
9) You will complete the Montreal Cognitive Assessment (MoCA)
10) Therapeutic intervention by SCS for your gait and mobility dysfunction has been decided by both Dr. Mandar Jog (your neurologist) and Dr. Andrew Parrent (your functional neurosurgeon).

SCS intervention for gait and mobility dysfunction is not a standard of care. SCS standard of care for gait dysfunction will follow implantation and post-operative procedures similar to SCS implants for pain. Patients with SCS will attend 3 SCS programming study visits following surgery. Long-term clinic follow-up visits for patients with SCS will be conducted by Dr. Jog every 6 months or more frequently if necessary.

Pregnancy: If you are pregnant then you CANNOT BE IN THIS STUDY. Pregnancy screening will take place before study admission by the physician, Dr. Jog. A researcher will ask you about pregnancy at every study visit. Please notify the research team if you are presently pregnant or if you are attempting to become pregnant or if you become pregnant at any time during the course of the study.

***Other Muscle/Nerve diseases*:** If you have a disease called Myasthenia Gravis or Amyotrophic Lateral Sclerosis (ALS or Lou Gehrig's disease) then you CANNOT BE IN THIS STUDY. Please notify the research team if you have these conditions.

Summary of Tests and Procedures

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

At each study visit you will be asked to complete the following tasks, which are described in detail below. All explanations and/or questions pertaining to the study clinical scales and study tasks will be provided to you by the researcher during each visit.

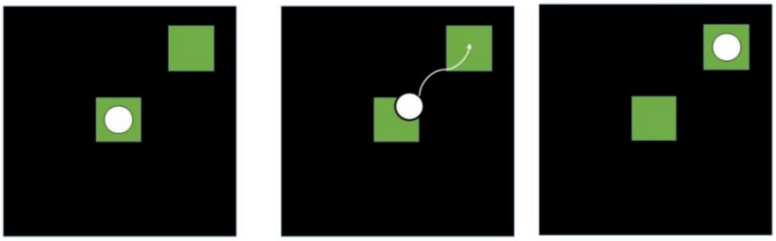
Visit 1: One-four weeks pre-operation:

- You will be required to arrive to the visit "off" dopamine therapy by withholding oral medications (levodopa/Sinemet, amantadine, pramipexole/Mirapex, and ropinirole/Requip) for at least 12 hours prior to the visit. This is denoted as the "OFF-drug" state.
- Whole-body mobility and gait assessments will be conducted and will take approximately 30 minutes to complete. You will be asked to complete simple seated and walking tasks while "OFF-drug". The same tasks will be conducted again one-hour after ingesting your oral medications, denoted as "ON-drug" state. We collect this data to understand your symptoms before your surgery and to understand changes in your mobility solely due to your oral medications. Mobility assessments will take 2 hours to complete including wait times.
- An electroencephalogram (EEG) assessment while you are seated, resting with eyes closed for 5 minutes will be conducted when you are in "OFF-drug" and "ON-drug" states. This will approximately take 30 minutes.
- Clinical rating scales for movement difficulties and other difficulties (depression etc.) will be adminstered and will take 30 minutes to complete:
    - Montreal Cognitive Assessment (MoCA)
        - MoCA is a brief 30-question test which assesses different types of cognitive abilities such as short-term memory and concentration which will be conducted only at this visit.
    - Unified Parkinson Disease Rating Scale (UPDRS)
        - UPDRS is a widely used measure of impairment and disability associated with Parkinson disease.
        - This is completed while "OFF-drug" and "ON-drug"
    - Activities-specific Balance Confidence (ABC) Scale
        - Rates the level of confidence in doing an activity without losing balance or becoming unsteady on a percentage 0% to 100% scale.
    - Parkinson's disease Questionnaire (PDQ)-8
        - Self-adminstered questionnaire rating aspects of functionality and well-being consisting of 8 items.
    - MATTIS Dementia rating scale
        - Assesses overall level of cognitive functioning.

Visit 2: One-four weeks pre-operation:

- You will be required to arrive to the visit “off” dopamine therapy by withholding oral medications (levodopa/Sinemet, amantadine, pramipexole/Mirapex, and ropinirole/Requip) for at least 12 hours. This is denoted as the “OFF-drug” state.
- Somatosensory evoked potentials (SSEP) testing will be conducted by Dr. Nicolle (Director of EMG laboratory and neuromuscular group) and will take 1 hour to complete.You will be seated comfortably during the assessment. Electrodes positioned over particular areas of your body record responses of an evoked potential caused by a physical stimulus (lower limb nerve stimulation). SSEP tests the pathway of the sensory nerves to the sensory areas of your brain.
- Transcranial magnetic stimulation (TMS) testing will be conducted following the SSEP testing and will take 2 hours to complete while you are “OFF-drug”. A one-hour wait time will be alloted after you ingest your oral medications, at which time the TMS protocol will be conducted again while you are “ON-drug”. Thus, a total of 2 hours is required to complete TMS protocols while you are “OFF-drug” and “ON-drug”.
    - You will be seated comfortably in a position with full muscle relaxation. A researcher will conduct several TMS protocols that allow us to measure sensory and motor performance in your brain. The researcher will demonstrate a few stimuli in the air or to your arm in order to familiarize you with stimulus.
    - TMS is carried out by placing a wire coil over the scalp. The pulses travel through the scalp and skull and cause small electrical currents in the outer part of the brain. The stimulation will cause light twitching of the muscles that are controlled by the part of the brain that is being stimulated. Electrical activity of muscles will be recorded with electrodes attached to the skin over the muscles. In addition to TMS, there will also be electrical stimulation of a nerve, specifically the peroneal nerve, in the lower limb.

The proprioception, target choice reaching task, will be conducted using the pictured device (figure below, left). Using the toggle on the device, you can move the cursor towards different targets that will be presented on the screen (figure below, right). Several rest breaks can be taken if you feel fatigued. Upper arms movements will be assessed using the KINARM (2nd image on the left). This will take approximately 1 hour to complete.



SCS implantation:
The procedure will be performed by functional neurosurgeons skilled at the procedure. SCS device will remain switched off for the first month following surgery in order to establish which SCS settings are best suited to alleviate your gait symptoms. The SCS device implanted will be provided in-kind by Boston Scientific from a product-only grant and no data will be shared with Boston Scientific.

Visit 3-5:1, 2, and 3 weeks post-operation:

- You will be required to arrive to the visit "ON-drug" indicating no medications will be withheld.
- Over the 3 study visits, spaced one week apart, each of the pre-determined 9 SCS settings will be assessed twice on different study visit days and at different times of the day. Each study visit will last approximately 6 hours including wait times.
- We will temporarily change your frequency and pulse width stimulation settings. Thus, a total of 6 SCS settings will be assessed at each visit. A 30-minute wait time is required for programming each SCS setting to allow stabilization of any behavioural responses to your SCS device. Thus, a total of 3 hours per visit will be allocated for rest.
- Mobility assessment, a similar set of seated and walking tasks performed in visit 1 (pre-operation), will be conducted for each SCS setting and will take approximately 30 minutes to complete. Thus, a total of 3 hours per visit will be required for the mobility assessments.
- At week 3 visit, we will show you which SCS settings provided the best improvements in your gait, from the mobility measures we collected from visits 3-5. We will instruct you how to use the SCS device at home.

Visits 6-14: 2 to 14 months post-operation:

- You will be brought back to the lab after 3-months, 6-months and 12-months of using SCS at home. At each time-point a total of three visits, with 1-2 days apart, will be required to fulfill the assessments planned and participants arrive "OFF-drug" for each visit. Thus, a total of 9 study visits over the course of 12-months will be required.

1. Visit 1 involves the neurophysiological assessments (TMS and SSEP). You will be required to leave your SCS device turned off for 24 hours prior to the visit. In addition, the proprioception (target reaching task) will be conducted following TMS assessment. This study visit will be conducted in a similar fashion to visit 2 (described above) and will last approximately 6 hours including wait times.

2. Visit 2 involves gait assessments and completion of clinical scales, including UPDRS assessments while "OFF-drug" and "ON-drug" states, will be conducted to study the effect of your oral medication (e.g. levodopa) while the SCS device is turned off. You will be required to leave your SCS turned off for at least 1 hour before this visit. An EEG assessment, similar to visit 1, while you are "OFF-drug" and "ON-drug" states will be conducted. This study visit will last approximately 3-4 hours including wait times.
3. Visit 3 involves gait assessments and completion of UPDRS to study the effect of levodopa medication while the SCS device is turned on. Two SCS settings will be assessed while "OFF-drug" and "ON-drug" states. This study visit will last approximately 6 hours including wait times.

Visits 15-17: 2, 3 and 4 years of using the SCS device in-home

- You will arrive at the lab "OFF-drug" and a reassessment of your mobility, ambulatory walking tasks across our gait carpet, while wearing the whole-body motion capture suit will be conducted to monitor the long-term effects of SCS.
- These tasks will be conducted while you are "ON-drug" during this visit. Clinical rating scales conducted in previous visits will also be repeated.
- This visit will last approximately 2-3 hours including wait times.

Motor Function:

During each visit, a researcher will complete the United Parkinson's Disease Rating Scale (UPDRS) while "OFF-drug" and "ON-drug" states will be completed at pre-operation and at 3-,6-, and 12-months of SCS use. This is the same assessment that your doctor completes with you during your routine clinic visit. It assesses the condition of your disease and the quality of your movements, including: stiffness, tremor, walking, activities of daily living, speech, etc. It is a non-invasive assessment and will take approximately 5-10 minutes to complete.

Whole-body Mobility Assessment:

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

Gait Measurements:

The GAITRite carpet will be used for gait measurements. It consists of a roll-up carpet with sensor pads used to measure functional ambulatory status. You will be required to walk on the walkway, so that the system can capture your walking patterns in various ways. We will guide you through a range of mobility tasks such as walking up and down the mat, sit to stand tasks and turning tasks. Mobility assessments (sitting and walking tasks) will take approximately 30 minutes to complete.

Video recording:

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

Benefits, risks and inconveniences

You may benefit directly from participation in this study as different SCS stimulation settings tested during study visits may provide you with the best clinical outcome. You may benefit by experiencing relief of your gait difficulties and SCS may improve the severity of your other PD symptoms, such as rigidity, balance, and tremor. As well, you may experience an improved quality of life, reduce your risk of falls, and reduce programming time.

You may not benefit directly from participation in this study though information obtained from this study may advance current knowledge of the effect of spinal cord stimulation for gait dysfunction in Parkinson's disease patients.

The potential side effects of the SCS surgery will have been explained to you by your doctors as part of your clinical treatment as surgical implantation of SCS is a routine procedure and is not part of the study.

During study visits, some individuals may be uncomfortable with being video taped. However, we will attempt to only record from the neck down in order to study your mobility and gait. Video recordings will only be used for data analysis purposes and all recorded files will be de-identified and stored in a secure location. Some individuals may be uncomfortable with having to change into a hospital gown.

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

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

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

Risks associated with transcranial magnetic stimulation

The procedure is non-invasive (does not involve skin penetration or use of needles). The stimulation will cause a sensation in the scalp, but most people who have undergone this

type of stimulation do not consider it unpleasant. Occasionally (in about 5% of magnetic stimulation studies), some subjects develop a headache which usually resolves spontaneously in a few hours or is relieved with simple analgesics (such as plain Tylenol). It is important to note that in very rare cases seizures have been induced in normal subjects using TMS stimulation at high rates of which are far beyond those used in this study. TMS has been used on thousands of individuals in North America and Europe since 1985 without any serious problems. TMS is not suitable for people with a cardiac pacemaker and central nervous system stimulators, since the safety of the TMS procedure has not been determined in this group of patients. Please inform the investigators if you have a cardiac pacemaker or other metal objects in your body as this is important for safety reasons.

The SSEP procedure is non-invasive and there are no known complications or risks to having an SSEP performed. The SSEP testing procedure is usually painless; the electrical impulses used as the stimulus are very small. Side effects from the procedure are very rate, though there is a chance you may have some minor skin irritation from the electrodes.

The EEG assessment is non-invasive as the cap contains the surface electrodes. Conductive gel is placed in the electrodes to ensure conductivity with your scalp. The gel is water-soluble, non-greasy, non-irritant, non-corrosive and is only used on healthy skin. There are no risks for EEG recordings.

There are no risk factors associated with the proprioception assessment. Fatigue may occur with concentrating on the tasks, but each task is very short (~5min) and there are plenty of breaks.

Data collection and use of information

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

The data from the study will be kept electronically and securely using the LHSC computer network. At all times, the data will be in the possession of one of the investigators of this study and will not be stored off-site. Only de-identified data may be shared with other researchers outside of the LHSC computer network.

For the purposes of contacting you to arrange the data collection sessions and linking your data from the multiple visits, we will keep a master list of all participants, securely used within the LHSC computer network. This list will contain your first name, telephone number, address, the dates you completed your sessions, and a number that we will assign to you that will also appear on your data recordings. Personal health information about you will be kept in a secure and confidential location for a minimum of 5 years. A list linking your study number with your name will be kept by the study doctor

in a secure place, separate from your study file. All data will be retained for 15 years, in accordance with LHSC policy.

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

Any use of this information for publication in scientific journals, health regulatory submissions, or presentation at professional conferences, will not contain any of your personal information that could be linked back to you or to your health information.

You will receive a copy of this information letter for your records.

Withdrawal from the study by the investigator

The investigator may decide to take you off the study if he feels your continued participation would impair your wellbeing.

Monetary compensation

You will not be paid for participation in this study. Parking will covered as we will provide you with an exit pass for each study visit.

Confidentiality

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

Representatives of the University of Western Ontario Health Sciences Research Ethics Board may look at the study records and at your personal health information to check that the information collected for the study is correct and to make sure the study followed proper laws and guidelines.

Voluntary participation

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

You will be able to withdraw from the study at any point in time. You may decide not to be in this study, or to be in the study now and then can change your mind later. You may leave the study at any time without affecting your current care status, employment status

or academic standing occupation. However, to protect the integrity of the study the data collected up to the point of your withdrawal will remain a part of the study.

Alternatives to study participation

The alternative to study participation is to continue on your current course of medication and any post-operative procedures and SCS programming clinic visits will be conducted under the direction of Dr. Jog.

Persons to Contact with Questions

For more information about this research study, or if you believe that you may have a research related injury or experienced any side effects as a result of participating in this study you may call Dr. Mandar Jog's research laboratory at [redacted]. If you have questions about the conduct of the study or your rights as a research participant, you may call the LHSC Patient Experience officer at [redacted] or access the online form at: https://apps.lhsc.on.ca/?q=forms/patient-experiencecontact-form .

You do not waive any legal rights by signing the consent form. You will receive a copy of the letter of information for your records.

PATIENT CONSENT FORM

STUDY TITLE

Spinal cord stimulation for the treatment of gait and balance impairments in Parkinson disease

STUDY DOCTOR

- Dr. Mandar Jog, MD
- Heather Russell (Dr. Jog's clinical nurse)

I have read the Letter of Information, have had the nature of the study explained to me and I agree to participate. All questions have been answered to my satisfaction.

Signature of Research Participant	Printed Name	Date

Signature of Investigator *not present during consent	Printed Name	Date

Signature of Person Obtaining Consent	Printed Name	Date

Appendix C: Letter of Information and Consent for DaTSCAN imaging

London Health Sciences Centre

Movement Disorders Program
339 Windermere Rd, A10-026
London, Ontario, Canada N6A 5A5
www.londonmdc.ca

Letter of Information and Consent

Study Title: Spinal cord stimulation for the treatment of gait and balance impairments in Parkinson disease
Subtitle: DaTSCAN imaging

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

Introduction

You are being invited to take part in this sub-study because you are a participant in the spinal cord stimulation (SCS) for treatment of gait and balance study. We are inviting 10 out of the 50 participants in the main study to have a DaTSCAN. You can continue in the main study without participating in this sub-study

A DaTSCAN involves a radioactive diagnostic agent which is used with a special camera to take pictures of the brain. In adult patients who have symptoms of Parkinson's disease, DaTSCAN is used along with other diagnostic tests to give us more information about your condition and will be used to explore whether SCS, the intervention you will be receiving in this study, causes changes to brain areas of interest.

How does DaTSCAN work?
When DaTSCAN is injected into a vein, it is carried around the body in the blood. It collects in a small area of your brain. The small amount of radioactivity can be detected from outside the body using a special camera that will take a picture, or scan, of your brain.

The scan will show if there are any changes in this area of your brain and will give your doctor more information about your condition.

Study funding

The DaTSCAN and imaging is funded by a research grant from GE Healthcare, which is the company that provides the radioactive diagnostic agent (ioflupane) and funds for Nuclear Medicine technician and using the imaging machine.

Nature of the research project and tasks involved

We are looking to investigate short and long-term effects of SCS in a total of **10 Parkinson's disease persons recruited and planned to be implanted with spinal cord stimulation (SCS)**. You will be invited to participate from the Movement Disorders Clinic at London Health Sciences Centre (LHSC).

You will be required to have a total of three DaTSCANs, before SCS surgery, and 6-months and 12-months following SCS use. The first DaTSCAN is conducted as per standard care for us to confirm your diagnosis. The two additional DaTSCANs that will happen at 6-months and 12-months will be done for research purposes to assess if there are changes in this area of your brain associated with the intervention you will be getting in the study (SCS). Thus, a total of 3 study visits over a 15-month duration will be conducted. These DaTSCANs will be conducted during the study visit involving the neurophysiological assessments, as outlined in the main letter of information for this study.

You will be required to bring your medications with you to each visit so that you may take them in accordance with your routine scheduled times. A movement disorders neurologist will screen for inclusion and exclusion criteria to ensure you meet the study's requirements. You are eligible for the DaTSCAN based on the following:

You are not eligible if:
- you are allergic to ioflupane or any of the other ingredients of DaTSCAN

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take DaTSCAN. Talk about any health conditions or problems you may have, including:
- Are breast-feeding, your doctor may delay the use of DaTSCAN, or ask you to stop breastfeeding. It is not known whether ioflupane(^{123}I) is passed into breast milk. As a precaution, you should not breast-feed your child for 3 days after DaTSCAN is given. Instead use formula feed for your child. Express your breast milk regularly and throw away any breast milk you have expressed. You will need to continue to do this for 3 days, until the radioactivity is no longer in your body.
- Have moderate or severe problems with your kidneys or liver

Other warnings you should know about:
DaTSCAN contains alcohol (ethanol) 5 % by volume. Each dose contains up to 197 mg alcohol
which is the amount contained in approximately 5 ml of beer or 2 ml of wine. The alcohol content of DaTSCAN may be harmful to patients who have alcoholism, liver disease, or epilepsy, and also in patients who are pregnant or breastfeeding. If you have concerns in this regard, discuss with your Doctor.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Some drugs may reduce the quality of the picture obtained with DaTSCAN. If you are taking any of the drugs listed below or any other drugs that may interfere with DaTSCAN, you may be asked to stop taking them for a short time before you receive DaTSCAN. Ask your doctor whether you can safely stop taking your medications.

The following may interfere with DaTSCAN:
• buproprion
• benzatropine
• mazindol
• sertraline
• methylphenidate
• phentermine
• amphetamine
• cocaine

Summary of Tests and Procedures

The research visits will require you to come to Dr. Mandar Jog's research facilities located at University Hospital, London, Ontario. A research coordinator will meet with you and bring you to Nuclear Medicine in order to begin the DaTSCAN process.

What are the ingredients in DaTSCAN?
• The active substance is ioflupane (^{123}I).
• The other ingredients are acetic acid, sodium acetate, ethanol and water for injections.

DaTSCAN comes in the following dosage forms:
DaTSCAN is available as a 2.5- or 5-ml solution containing 185 MBq ioflupane (^{123}I) or 370 MBq ioflupane (^{123}I), respectively.

DaTSCAN will be given to you by our Nuclear Medicine department, under the supervision of Dr. Jonathan Romsa. They should tell you anything you need to do for the safe use of this medicine. Your doctor will decide the dose that is best for you.

Before you receive DaTSCAN, your doctor will ask you to take some tablets or liquid that contain iodine, to help prevent radioactivity from building up in your thyroid gland. It is important that you take the tablets or liquid as the doctor tells you.

DaTSCAN is given to you as an injection, usually into a vein in your arm. Pictures of your brain will be taken 3 to 6 hours after the injection of DaTSCAN. During the wait time, a study researcher will be with you and will conduct other study assessments: mobility assessments, neurophysiological assessments and proprioception tasks (total time is ~3-4 hours including rest periods).

You should drink large glasses of water before and after you get your injection of DaTSCAN, and urinate frequently in the hours after your injection to reduce the amount of radioactivity in your bladder.

Benefits, risks and inconveniences

When DaTSCAN is used, you are exposed to small amounts of radioactivity. This exposure is less than some other types of X-ray investigation. Your doctor will always consider the possible risks and benefits of DaTSCAN.

Like all medicines, DaTSCAN can cause side effects, although not everybody gets them. These are not all the possible side effects you may feel when taking DaTSCAN. If you experience any side effects not listed here, contact your research coordinator [redacted] or our clinical nurse ([redacted]).

Common: may affect up to 1 in 10 people
• Headache
• Dizziness
• Nausea

Uncommon: may affect up to 1 in 100 people. You may experience the following uncommon side effects:
• Increased appetite
• Taste disturbance
• Dry mouth
• Vertigo
• A sensation like insects crawling over your skin (formication)
• Intense pain on injection. This has been reported among patients receiving DaTSCAN into a small vein

Not known: frequency cannot be estimated from the available data
Allergic reaction (hypersensitivity). Risk of an allergic reaction may occur during the 3-6 hours you are present at LHSC with a researcher.

Serious side effects and what to do about them			
Symptom/effect	Talk to your health professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Allergic reaction		✓	Yes

Data collection and use of information

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

The data from the study will be kept electronically and securely using the LHSC computer network. At all times, the data will be in the possession of one of the investigators of this study and will not be stored off-site. Only de-identified data may be shared with other researchers outside of the LHSC computer network.

For the purposes of contacting you to arrange the data collection sessions and linking your data from the multiple visits, we will keep a master list of all participants, securely used within the LHSC computer network. This list will contain your first name, telephone number, address, the dates you completed your sessions, and a number that we will assign to you that will also appear on your data recordings. Personal health information about you will be kept in a secure and confidential location for a minimum of 15 years. A list linking your study number with your name will be kept by the study doctor in a secure place, separate from your study file. All data will be retained for 15 years, in accordance with LHSC policy.

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

Any use of this information for publication in scientific journals, health regulatory submissions, or presentation at professional conferences, will not contain any of your personal information that could be linked back to you or to your health information.

You will receive a copy of this information letter for your records.

Withdrawal from the study by the investigator

The investigator may decide to take you off the study if he feels your continued participation would impair your wellbeing.

Monetary compensation

You will not be paid for participation in this study. Parking will covered as we will provide you with an exit pass for each study visit.

Confidentiality

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

Representatives of the University of Western Ontario Health Sciences Research Ethics Board and Lawson Institute Quality Assurance program (QAEP) may look at the study records and at your personal health information to check that the information collected for the study is correct and to make sure the study followed proper laws and guidelines.

Voluntary participation

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

You will be able to withdraw from the study at any point in time. You may decide not to be in this study, or to be in the study now and then can change your mind later. You may leave the study at any time without affecting your current care status, employment status or academic standing occupation. However, to protect the integrity of the study the data collected up to the point of your withdrawal will remain a part of the study.

Alternatives to study participation

The alternative to study participation is to continue your current course of medication and any post-operative procedures and SCS programming clinic visits will be conducted under the direction of Dr. Jog.

Persons to Contact with Questions

For more information about this research study, or if you believe that you may have a research related injury or experienced any side effects as a result of participating in this study you may call Dr. Mandar Jog's research laboratory at [redacted]. If you have questions about the conduct of the study or your rights as a research participant, you may call the LHSC Patient Experience officer at [redacted] or access the online form at: https://apps.lhsc.on.ca/?q=forms/patient-experiencecontact-form .

You do not waive any legal rights by signing the consent form. You will receive a copy of the letter of information for your records.

PATIENT CONSENT FORM

STUDY TITLE

Spinal cord stimulation for the treatment of gait and balance impairments in Parkinson disease

STUDY DOCTOR

- Dr. Mandar Jog, MD
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I have read the Letter of Information, have had the nature of the study explained to me and I agree to participate. All questions have been answered to my satisfaction.

Signature of Research Participant	Printed Name	Date

Signature of Investigator *not present during consent	Printed Name	Date

Signature of Person Obtaining Consent	Printed Name	Date

Appendix D: The Activities-specific Balance Confidence Scale

The Activities-specific Balance Confidence (ABC) Scale

For each of the following activities, please indicate your level of self-confidence by choosing a corresponding number from the following rating scale:

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

no confidence **completely confident**

"How confident are you that you will not lose your balance or become unsteady when you…

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

Appendix E: Freezing of gait questionnaire

Freezing of Gait Questionnaire (FOGQ)

1. ***During your worse state – Do you walk:_____***
   0 Normal
   1 Almost normally – somewhat slow
   2 Slow but fully independent
   3 Need assistance or walking aid
   4 Unable to walk

2. ***Are your gait difficulties affecting your daily activities and independence?_____***
   0 Normal
   1 Mildly
   2 Moderately
   3 Severely
   4 Unable to walk

3. ***Do you feel that your feet get glued to the floor while walking, making a turn or when trying to initiate walking (freezing)?_____***
   0 Never
   1 Very rarely – about once a month
   2 Rarely – about once a week
   3 Often – about once a day
   4 Always – whenever walking

4. ***How long is your longest freezing episode?***
   0 Never happened
   1 1 to 2 seconds
   2 3 to 10 seconds
   3 11 to 30 seconds
   4 Unable to walk for more than 30 seconds

5. ***How long is your typical start hesitation episode (freezing when initiating the first step)?***
   0 None
   1 Takes longer than 1 second to start walking
   2 Takes longer than 3 seconds to start walking
   3 Takes longer than 10 seconds to start walking
   4 Takes longer than 30 seconds to start walking

6. ***How long is your typical turning hesitation (freezing when turning)?***
   0 None
   1 Resume turning in 1 to 2 seconds
   2 Resume turning in 3 to 10 seconds
   3 Resume turning in 11 to 30 seconds
   4 Unable to resume turning for more than 30 seconds

Appendix F: Unified Parkinson's Disease Rating Scale

Unified Parkinson's Disease Rating Scale

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

III. Motor Examination

18. Speech
0 = Normal.
1 = Slight loss of expression, diction and/or volume.
2 = Monotone, slurred but understandable; moderately impaired.
3 = Marked impairment, difficult to understand.
4 = Unintelligible.

19. Facial Expression
0 = Normal.
1 = Minimal hypomimia, could be normal "Poker Face."
2 = Slight but definitely abnormal diminution of facial expression
3 = Moderate hypomimia; lips parted some of the time.
4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at Rest (head, upper and lower extremities)
0 = Absent.
1 = Slight and infrequently present.
2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
3 = Moderate in amplitude and present most of the time.
4 = Marked in amplitude and present most of the time.

21. Action or Postural Tremor of Hands
0 = Absent.
1 = Slight; present with action.
2 = Moderate in amplitude, present with action.
3 = Moderate in amplitude with posture holding as well as action.
4 = Marked in amplitude; interferes with feeding.

22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)
0 = Absent.
1 = Slight or detectable only when activated by mirror or other movements.
2 = Mild to moderate.
3 = Marked, but full range of motion easily achieved.
4 = Severe, range of motion achieved with difficulty.

23. Finger Taps (Patient taps thumb with index finger in rapid succession.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

24. Hand Movements (Patient opens and closes hands in rapid succesion.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

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

Unified Parkinson's Disease Rating Scale

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

26. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

27. Arising from Chair (Patient attempts to rise from a straightbacked chair, with arms folded across chest.)
0 = Normal.
1 = Slow; or may need more than one attempt.
2 = Pushes self up from arms of seat.
3 = Tends to fall back and may have to try more than one time, but can get up without help.
4 = Unable to arise without help.

28. Posture
0 = Normal erect.
1 = Not quite erect, slightly stooped posture; could be normal for older person.
2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
4 = Marked flexion with extreme abnormality of posture.

29. Gait
0 = Normal.
1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.
2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.
3 = Severe disturbance of gait, requiring assistance.
4 = Cannot walk at all, even with assistance.

30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.)
0 = Normal.
1 = Retropulsion, but recovers unaided.
2 = Absence of postural response; would fall if not caught by examiner.
3 = Very unstable, tends to lose balance spontaneously.
4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased arm swing, small amplitude, and poverty of movement in general.)
0 = None.
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.
2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.
3 = Moderate slowness, poverty or small amplitude of movement.
4 = Marked slowness, poverty or small amplitude of movement.

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

Unified Parkinson's Disease Data Form

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

Name _____ Unit Number _____

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

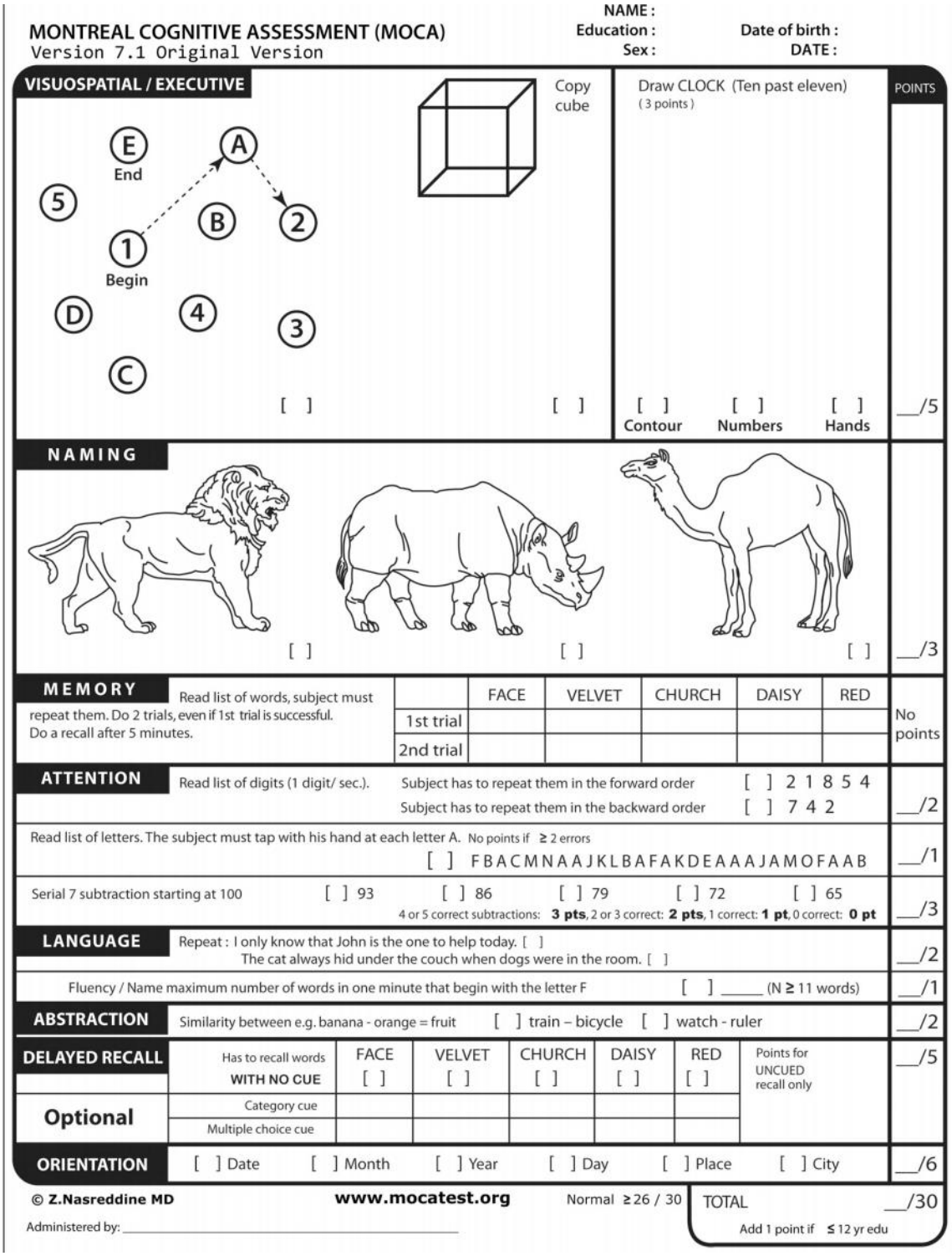
Unified Parkinson's Disease Data Form

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

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

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

Appendix G: Montreal Cognitive Assessment



MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

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

VISUOSPATIAL / EXECUTIVE — POINTS

Copy cube [ ] [ ]

Draw CLOCK (Ten past eleven) (3 points) [ ] Contour [ ] Numbers [ ] Hands __/5

NAMING [ ] [ ] [ ] __/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes. — No points

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

ATTENTION Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2 __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** __/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] __/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) __/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler __/2

DELAYED RECALL __/5

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

© Z.Nasreddine MD **www.mocatest.org** Normal ≥ 26 / 30

TOTAL __/30
Add 1 point if ≤ 12 yr edu

Administered by: _____

Appendix H: Global Impression of Change scale

Global Impression of Change Scale in Parkinson's Disease Symptoms and Mobility

Patient ID: _____ Date:_____

Visit: _____

Comparing your ability to walk with ease and confidence and your mobility from **today to since your LAST STUDY VISIT (Visit____)**, circle a number that best represents your impression of change in gait difficulties and if applicable festinating gait and freezing of gait:

Much worse **Worse** **No Change** **Better** **Much better**

-5 -4 -3 -2 -1 0 1 2 3 4 5

Comparing your ability to walk with ease and confidence and your mobility from **today to since your LAST STUDY VISIT (Visit____)**, circle a number that best represents your impression of change in balance and if applicable postural stability:

Much worse **Worse** **No Change** **Better** **Much better**

-5 -4 -3 -2 -1 0 1 2 3 4 5

Comparing your ability to walk with ease and confidence and your mobility from **today to since your LAST STUDY VISIT (Visit____)**, circle a number that best represents your impression of change in rigidity and bradykinesia symptoms:

Much worse **Worse** **No Change** **Better** **Much better**

-5 -4 -3 -2 -1 0 1 2 3 4 5

Comparing your ability to walk with ease and confidence and your mobility from **today to since your LAST STUDY VISIT (Visit____)**, circle a number that best represents your impression of change in tremor severity, duration and frequency:

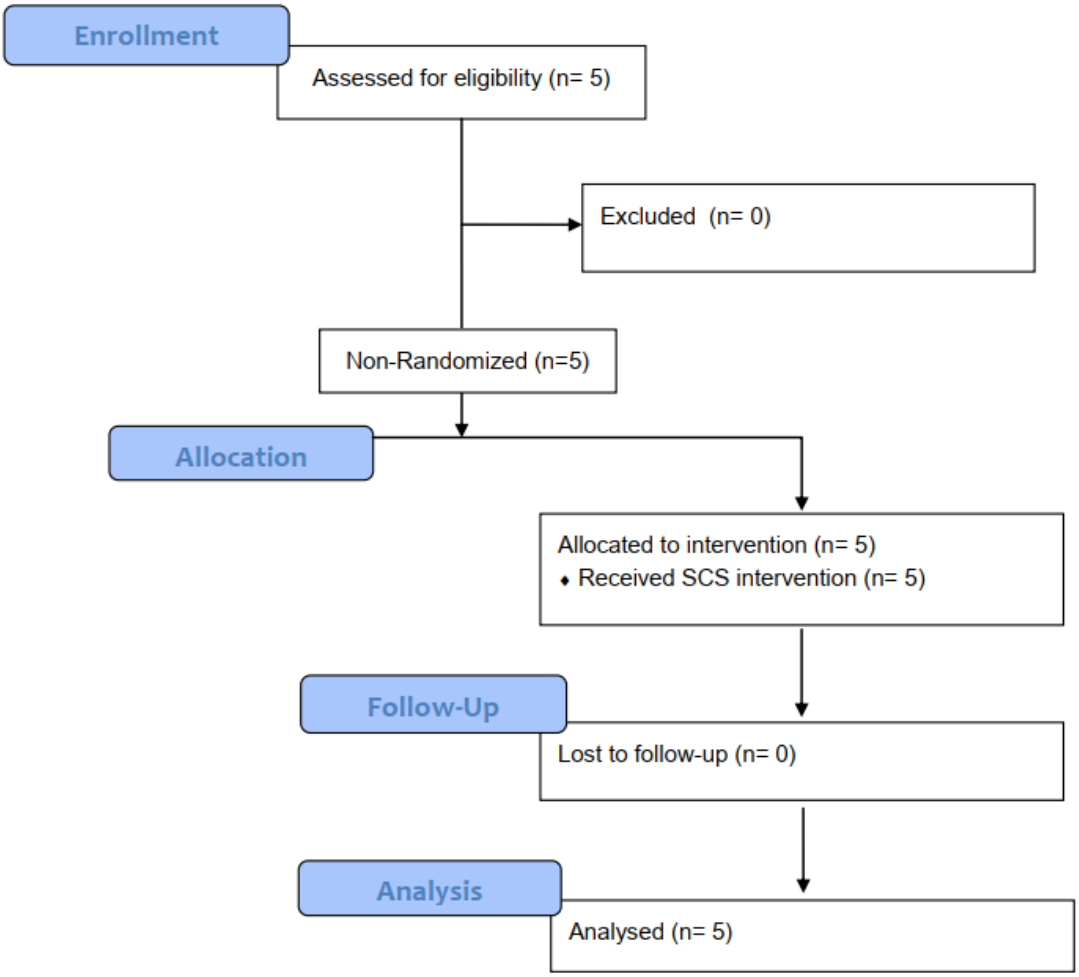
Much worse **Worse** **No Change** **Better** **Much better**

-5 -4 -3 -2 -1 0 1 2 3 4 5

Appendix I: Study design and analysis in a CONSORT flowchart

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram



Appendix J: Parkinson disease questionnaire (PDQ-8)

1. ***Had difficulty getting around in public?***
   - 0 Never
   - 1 Occasionally
   - 2 Sometimes
   - 3 Often
   - 4 Always

2. ***Had difficulty dressing yourself?***
   - 0 Never
   - 1 Occasionally
   - 2 Sometimes
   - 3 Often
   - 4 Always

3. ***Felt depressed?***
   - 0 Never
   - 1 Occasionally
   - 2 Sometimes
   - 3 Often
   - 4 Always

4. ***Felt embarrassed in public due to having Parkinson's disease?***
   - 0 Never
   - 1 Occasionally
   - 2 Sometimes
   - 3 Often
   - 4 Always

5. ***Had problems with your close personal relationships?***
   - 0 Never
   - 1 Occasionally
   - 2 Sometimes
   - 3 Often
   - 4 Always

6. ***Had problems with your concentration, e.g. when reading or watching TV?***
   - 0 Never
   - 1 Occasionally
   - 2 Sometimes
   - 3 Often

4 Always

7. Felt unable to communicate with people properly?

0 Never
1 Occasionally
2 Sometimes
3 Often
4 Always

8. Had painful muscle cramps or spasms?

0 Never
1 Occasionally
2 Sometimes
3 Often
4 Always

Curriculum Vitae

Name: Olivia Samotus

Post-secondary Education and Degrees:

The University of Western Ontario
London, Ontario, Canada
2014 – 2016 M.Sc. Neuroscience

University of Ottawa
Ottawa, Ontario, Canada
2008 – 2013 Hon. B.Sc. Spec. Biochemistry with Co-Op

Honours and Awards:

Parkinson Canada
Graduate Student Scholarship
2019-2021

Western Graduate Research
2014 – 2015, 2015 – 2016, 2016 – 2017, 2017 – 2018, 2018 – 2019, 2019 – 2020

Harold Brett Memorial Fellowship Award
2019

Ontario Centres of Excellence
TalentEdge Internship
2017-2019

Parkinson Society Southwestern Ontario
Graduate Student Research Program Award
2017 – 2019

Mitacs-Accelerate
Canada's Graduate Research Internship Program
2014 – 2015, 2015 – 2016, 2016 – 2018

University of Ottawa
Dean's Honours List
2010 – 2011

Related Work Experience

Teaching Assistant
The University of Western Ontario
2015 – 2021

Clinical Research Associate
London Health Sciences Centre
2013 – 2014

Peer-reviewed Publications:

1. Samotus O, Chen R, Jog M. Changes in cortical excitability and Parkinson tremor after botulinum toxin therapy. *Neurology*. 2021;97(14): e1413-e1424.
2. Samotus O, Lee J, Jog M. Developing a Consistent, Reproducible Botulinum Toxin Type A Dosing Method for Upper Limb Tremor by Kinematic Analysis. *Toxins*. 2021;13(4):264.
3. Samotus O, Parrent A, Jog M. Spinal cord stimulation therapy for gait dysfunction in progressive supranuclear palsy patients. *J Neurol*. 2021;268(3):989-996.
4. Samotus O, Parrent A, Jog M. Spinal Cord Stimulation Therapy for Gait Dysfunction in Two Corticobasal Syndrome Patients. *Can J Neurol Sci*. 2021;48(2):278-280.
5. Samotus O, Lee J, Jog M. Standardized algorithm for muscle selection and dosing of botulinum toxin for Parkinson tremor using kinematic analysis. *Ther Adv Neurol Disord*. 2020;13:1756286420954083.
6. Samotus O, Parrent A, Jog M. Long-term update of the effect of spinal cord stimulation in advanced Parkinson's disease patients. *Brain Stimul*. 2020;13(5):1196-1197.
7. Shahtalebi S, Atashzar F, Samotus O, Patel RV, Jog MS, Mohammadi A. PHTNet: Characterization and deep mining of involuntary hand tremor using recurrent neural network modelling – An ultimate solution. *Nature Sci Rep*. 2020;10(1):2195.
8. Samotus O, Lee J, Jog M. Bilateral upper limb treatment of essential tremor by kinematically –guided botulinum toxin type A injections. *Toxins (Basel)*. 2019;11(2).pii:E125.
9. Samotus O, Jog M. Reply to: Spinal cord stimulation for gait dysfunction in Parkinson's disease: Essential questions to discuss. *Mov Disord*. 2018;33(11):1829-1930.
10. Samotus O, Lee J, Jog M. Transitioning from unilateral to bilateral upper limb therapy for Parkinson's disease and essential tremor: case series. *Toxins (Basel)*. 2018;10(10).Pii:E394.
11. Samotus O, Lee J, Jog M. Personalized botulinum toxin type A therapy for cervical dystonia based on kinematic guidance. *J Neurol*. 2018;256(6):1269-1278.
12. Samotus O, Parrent A, Jog M. Spinal cord stimulation for gait dysfunction in advanced Parkinson disease patients. *Mov Disord*. 2018;33(5):783-792.
13. Samotus O, Kumar N, Rizek P, Jog M. Botulinum toxin type A injections as monotherapy for upper limb essential tremor using kinematics. *Can J Neurol Sci*. 2018;45(1):11-22.
14. Samotus O, Lee J, Jog M. Long-term tremor therapy for Parkinson and Essential tremor with sensor-guided botulinum toxin type A injections. *PLoS ONE*. 2017; 12(6):e0178670.
15. Atashzar SF, Shahbazi M, Ward C, Samotus O, Delrobaei M, Rahimi F, Lee J, Jackman M, Jog M, Patel R. Haptic Feedback Manipulation During Botulinum Toxin Injection Therapy for Focal Hand Dystonia Patients: A Possible New Assistive Strategy. *IEEE Trans Haptics.* 2016;9(4):523-535.
16. Samotus O, Rahimi F, Lee J, Jog M. Functional ability improved in Essential tremor by incobotulinumtoxinA injections using kinematically determined biomechanical patterns – A new future. *PLoS ONE*. 2016;11(4):e0153739.

17. Atashzar FS, Shahbazi M, Samotus O, Tavakoli M, Jog M, Patel RV. Characterization of Upper-limb involuntary movements in pathological tremor patients: application to design of an augmented haptic rehabilitation system. *IEEE Journal of Selected Topics in Signal Processing.* 2016;10(5):888-903.
18. Rahimi F*, Samotus O*, Lee J, Jog M. Effective Management of Upper Limb Parkinsonian Tremor by IncobotulinumtoxinA Injections Using Sensor-based Biomechanical Patterns. *Tremor Other Hyperkinet Mov (N Y).* 2015;5:348. *** co-authors.***

Conference/Abstract Publications:

1. Samotus O., Parrent A., Jog M. Effects of spinal cord stimulation on mobility and cortical activity in Parkinson's disease patients with severe gait dysfunction and ON-freezing. Accepted symposium presentation at ISPGR World Congress 2019 June.
2. Samotus O., Alamos M., Parrent A., Jog M. Spinal cord stimulation improves gait and modulates cortical activity in parkinsonian patients unresponsive to dopaminergic medication. Accepted abstract to ISPGR World Congress 2019 June.
3. Samotus O., Parrent A., Jog M. Investigating the therapeutic and transcortical effects of spinal cord stimulation for gait dysfunction in Parkinson's disease and cortical-basal degeneration patients. Accepted to 2nd PAS-MDS Conference. 2018 June 22-24th, Miami, Florida, USA. ***Selected for guided poster tour and selected as best abstract**
4. Samotus O., Parrent A., Jog M. Investigating the therapeutic and transcortical effects of spinal cord stimulation for gait dysfunction in Parkinson's disease and cortical-basal degeneration patients. Submitted to Freezing of Gait Conference. 2018 June 6-8th, Leuven, Belgium. ***Topic selected for keynote address**
5. Samotus O., Kumar N., Memar S., Parrent A., Jog M. Spinal cord stimulation reduces freezing of gait episodes and improves gait in advanced Parkinson's disease patients. Submitted to the 21st International Parkinson and Movement Disorder Society (MDS). 2017 June 8-10th, Vancouver, BC, Canada. ***Selected for: Best abstract, a guided poster tour, Blue Ribbons Highlights Talk**
6. Samotus O., Kumar N., Memar S., Parrent A., Jog M. Spinal cord stimulation reduces freezing of gait episodes and improves gait in advanced Parkinson's disease patients. Submitted to the 13th INS World Congress Neuromodulation, Edinburgh, Scotland. 2017 May 30th. ***Selected for Oral Presentation**
7. Samotus O., Kumar N., Memar S., Parrent A., Jog M. Spinal cord stimulation reduces freezing of gait episodes and improves gait in advanced Parkinson's disease patients. Submitted to the 5th Minnesota Neuromodulation Symposium. 2017 April 14-15th. ***Recipient of a Travel award ($1,650)**, ***Selected for Poster Highlight talk**
8. Samotus O., Kumar N., Memar S., Parrent A., Jog M. Spinal cord stimulation reduces freezing of gait episodes and improves gait in advanced Parkinson's disease patients. Submitted to the CNS Departmental Research Day. 2017 April 11th. ***Won Best abstract award and prize ($200)**

9. Samotus O., Kumar N., Memar S., Parrent A., Jog M. Spinal cord stimulation reduces freezing of gait episodes and improves gait in advanced Parkinson's disease patients. Submitted to the London Health Research Day. 2017 March.
10. Samotus O., Moradi H., Jog M. Individualized botulinum toxin type A therapy of bilateral upper limb essential tremor by multi-sensor kinematic technology. Poster accepted for presentation at the 20th MDS conference in Berlin, Germany. June 21, 2016.
11. Samotus O., Moradi H., Jog M. Personalized botulinum toxin type A therapy for bilateral upper limb essential tremor using multi-sensor kinematic technology. Poster presented at the Canadian Association of Neuroscience in Toronto. May 29 to June 1, 2016.
12. Samotus O., Moradi H., Jog M. Kinematic measures of bilateral upper limb essential tremor personalize botulinum toxin type A therapy. Poster presented at the Western University Resident Research Day Conference in London, Ontario. May 2016.
13. Samotus O., Moradi H., Jog M. Personalized botulinum toxin type A therapy for bilateral upper limb essential tremor using multi-sensor kinematic technology. Poster presented at the CNS departmental research day at the Bellamere Winery. April 26, 2016.
14. Samotus O., Moradi H., Lee J., Rahimi F., Jog M. Function improved in essential tremor by incobotulinumtoxinA injection patterns using upper limb biomechanical characterization. Presented at the 45th International Society of Neuroscience Conference. October 19, 2015.
15. Samotus O., Moradi H., Rahimi F., Jog M. Multi-sensor based biomechanical characterization of cervical dystonia determines optimal onabotulinumtoxinA treatment parameters. Presented at the 45th International Society of Neuroscience Conference. October 20, 2015.
16. Samotus O., Lee J., Rahimi F., Jog M. Longitudinal kinematic characterization of upper limb essential tremor to effectively guide incobotulinumtoxinA treatment. Presented at the 19th International Parkinson and Movement Disorder Society. June 18, 2015.
17. Samotus O., Lee J., Rahimi F., Jog M. Upper limb kinematics guides longitudinal, incobotulinumtoxinA therapy of Parkinson disease tremor. Presented at the 19th International Parkinson and Movement Disorder Society. June 18, 2015.
18. Samotus O., Vafadar H., Rahimi F., Jog M. Kinematic biomechanical characterization guides incobotulinumtoxinA treatment in cervical dystonia patients. Presented at the 19th International Parkinson and Movement Disorder Society. June 18, 2015.
19. Samotus O., Lee J., Rahimi R., Jog M. Kinematic characterization of upper limb essential tremor effectively guides longitudinal focal therapy. Presented at the 12th INS International Neuromodulation World Congress in Montreal, Quebec, Canada. June 9, 2015.
20. Samotus O., Lee J., Rahimi R., Jog M. Multi-sensor kinematic guidance for treatment of Parkinson disease tremor by incobotulinumtoxinA injections. Presented at the 12th INS International Neuromodulation World Congress in Montreal, Quebec, Canada. June 9, 2015.

21. Samotus O., Moradi H., Jog M. Sensor-based kinematics effectively guides onabotulinumtoxinA injections in cervical dystonia. Presented at the 12th INS International Neuromodulation World Congress in Montreal, Quebec, Canada. June 9, 2015.
22. Samotus O., Moradi H., Rahimi F., Jog M. Kinematic characterization successfully guides onabotulinumtoxinA treatment in cervical dystonia patients. Presented at the London Health Research Day. April 1, 2015. Poster #154
23. Samotus O., Lee J., Rahimi F., Jog M. Longitudinal kinematic characterization of upper limb essential tremor to effectively guide incobotulinumtoxinA treatment. Presented at the London Health Research Day. April 1, 2015. Poster #148
24. Samotus O., Lee J., Rahimi F., Jog M. Upper limb kinematics guides longitudinal, incobotulinumtoxinA therapy of Parkinson disease tremor. Presented at the London Health Research Day. April 1, 2015. Poster #131
25. Samotus O., Vafadar H., Rahimi F., Lee J., Jackman M., Jog M. Kinematic motion sensors objectively characterize neck movements in cervical dystonia. Presented at the 44th Society of Neuroscience Conference Washington, DC, USA. 2014 November. Poster#:47.12.
26. Lee J., Rahimi F., Samotus O., Jackman M., Jog M. Kinematic assessments effectively guide longitudinal treatment of Parkinson disease tremor. Presented at the 44th Society of Neuroscience Conference Washington, DC, USA. 2014 November.
27. Samotus O., Rahimi F., Lee J., Jackman M., Jog MS. Characterization of essential tremor by kinematic assessments in the upper limb. Presented at the 44th Society of Neuroscience Conference Washington, DC, USA. 2014 November. Poster#697.18.
28. Samotus O., Vafadar H., Rahimi F., Lee J., Jackman M., Jog M. Kinematic motion sensors objectively characterize neck movements in cervical dystonia. Presented at the IEEE EMBS Brain Grand Challenge Conference Washington, DC, USA. 2014 November.
29. Lee J., Rahimi F., Samotus O., Jackman M., Jog M. Kinematic assessments effectively guide longitudinal treatment of Parkinson disease tremor. Presented at the IEEE EMBS Brain Grand Challenge Conference Washington, DC, USA. 2014 November.
30. Samotus O., Rahimi F., Lee J., Jackman M., Jog MS. Characterization of essential tremor by kinematic assessments in the upper limb. Presented at the IEEE EMBS Brain Grand Challenge Conference Washington, DC, USA. 2014 November.
31. Rahimi F., Samotus O., Lee J., Jackman M., Jog MS. Kinematic Assessments Effectively Guide Botulinum Neurotoxin Type A Injections For Essential Tremor Treatment. Poster accepted for presentation at the 18th International Congress of Parkinson's Disease and Movement Disorders, Stockholm, Sweden, 2014 June.
32. Lee J, Rahimi F, Samotus O, Jackman M, Jog MS. Effective Long-term Upper-Limb Tremor Treatment in Parkinson Disease Patients. Poster accepted for presentation at the 18th International Congress of Parkinson's Disease and Movement Disorders, Stockholm, Sweden, 2014 June.
33. Samotus O., Rahimi F., Lee J., Jackman M., Jog MS. Objective kinematic assessment of torticollis using motion sensors. Poster accepted for presentation at

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34. Samotus O., Rahimi F., Lee J., Jackman M., Jog MS. Objective kinematic assessment of torticollis using motion sensors. Poster accepted for presentation at the Canadian Association for Neuroscience, Montreal, Canada, 2014 May.
35. Lee J., Rahimi F., Samotus O., Jackman M., Jog MS. Effective Long-term Upper-Limb Tremor Treatment in Parkinson Disease Patients. Poster accepted for presentation at the Canadian Association for Neuroscience, Montreal, Canada, 2014 May.
36. Rahimi F., Samotus O., Lee J., Jackman M., Jog MS. Kinematic Assessment Effectively Guide Botulinum Neurotoxin Type A Injections for Essential Tremor Treatment. Poster accepted for presentation at the Canadian Association for Neuroscience, Montreal, Canada, 2014 May.
37. Samotus O., Rahimi F., Lee J., Jog MS. Kinematic Assessment Effectively Guide Botulinum Neurotoxin Type A Injections for Essential Tremor Treatment. Poster accepted to be presented at the 44th American Academy of Neurology, Philadelphia, PA, 2014 April.